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TOPIC OF INTEREST - "ANTIMICROBIALS - I"

GENERAL ARTICLE

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ANTIMICROBIALS - I

OVERVIEW OF ANTIBIOTICS

Dhanya Dharmapalan

Abstract: *Antibiotics are used for treating bacterial infections. They are classified based on origin (synthetic or natural), mechanism of action, type of action (bacteriostatic or bactericidal) and spectrum (narrow or broad). Majority of antibiotics used in clinical practice such as cephalosporins, carbapenems, fluoroquinolones have broad spectrum of activity. Broad spectrum antibiotics have disadvantages of alteration of host microbiome and selection of resistance. To overcome the problem of antibiotic resistance, antibiotic surveillance and antibiotic stewardship measures were recognized as a policy by the World health Organization, as a component of which a new classification of antibiotics called as Access, Watch, Reserve (AWaRe) was introduced. This classification helps in guiding the selection of antibiotic and prevention of their abuse and overuse.*

Keywords: *Antibiotics, Spectrum, Access Watch Reserve Classification.*

Antibiotics are the principal tools used for treating bacterial infections. They can be classified in many ways, based on: a) origin (natural/synthetic) b) mechanism of action c) type of action (bacteriostatic/bactericidal) d) spectrum of activity (narrow spectrum /broad spectrum). Widespread antibiotic use is one of the main reasons for development of antibiotic resistance, which is recognized as a global public health crisis. For the purpose of antibiotic surveillance and to support stewardship activities at policy level, the World Health Organisation in 2017 introduced a new classification of antibiotics, termed Access, Watch, Reserve (AWaRe) classification which was updated in 2019.[1] This article provides an overview of antibiotics, including their classification, spectrum and mechanism of action.

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I. Classification based on origin

Antibiotics can be of natural origin or synthetic. For example, penicillin is a natural antibiotic derived from fungus *Penicillium chrysogenum by fermentation*. When natural products are chemically altered, these are called semi-synthetic, for example aminopenicillins. Most of the newer antibiotics currently undergoing trial are synthetic antibiotics which are chemically synthesized based on the structure of the natural products.[2]

II. Classification based on target in the bacterial cell

Antibiotics have different mechanism of action based on the structure/function of bacterial cell which they target, such as cell wall/cell membrane, ribosomes, nucleic acid and metabolic pathways (Box 1).

a) Cell wall

Bacteria synthesize cell wall which provides rigidity to the cell due to its peptidoglycan composition. Bacteria which are identified as Gram negative on Gram staining have an additional outer membrane which is rich in lipopolysaccharides which confers more resistance to antibiotics effective against Gram positive bacteria which act by inhibition of cell wall synthesis.

Beta-lactam antibiotics are the most widely used antibiotics in this group. This class derives its name due to

Box 1. Classification based on target in bacterial cell

1. Cell wall: Beta-lactam antibiotics such as penicillins, cephalosporins, carbapenems, monobactams and beta-lactamase inhibitors.

2. Cell membrane: Polymyxins, vancomycin and teicoplanin

3. Ribosomes: a) *30S ribosome inhibitors* - *Aminoglycosides,* tetracyclines *b) 50S subunit inhibitors* - Macrolides, clindamycin, oxazolidinone like linezolid, chloramphenicol

4. Nucleic acids: Fluoroquinolones

5. Folic acid metabolic pathway: Trimethoprim and sulphonamides

the presence of highly reactive 3-carbon and 1-nitrogen ring called beta-lactam ring.[2] These are classified as penicillins, cephalosporins, carbapenems, monobactams and beta-lactamase inhibitors. The mechanism of resistance of bacteria to agents belonging to this class is mostly by production of the beta lactamase enzyme by the bacteria, which destroys the beta-lactam ring. Alteration of penicillin-binding protein site (PBP) or reducing penetration of target site are other mechanisms of resistance to this class.

Penicillins are further classified as natural, penicillinase resistant penicillins, aminopenicillins and ureidopenicillins (Table I).

Cephalosporins are resistant to beta lactamases and are classified into 5 generations[3] (Table II). These differ in their coverage of Gram positive and Gram negative bacteria, with first generation cephalosporins possessing strong activity against Gram positive bacteria with a narrow spectrum while third generation cephalosporins have better activity against Gram negative bacteria and are broad spectrum antibiotics.

Aztreonam (IV) is a monobactam which has action only against aerobic Gram-negative organisms but no activity against Gram-positive bacteria or anaerobes.

Beta-lactamase inhibitors inactivate the hydrolysing action of the beta-lactamases and are further classified as first generation beta-lactamase inhibitors like clavulanic acid, sulbactam, tazobactam and newer inhibitors like avibactam and vaborbactam. These are co-administered with the beta lactam antibiotics in drug resistant infections. These inhibitors can overcome extended spectrum beta-lactamase produced by *Enterobacteriaceae* family, *Hemophilus influenzae*, *Pseudomonas aeruginosa* and also have activity against anaerobes. Amoxicillin-clavulanic acid is used in treating upper and lower respiratory tract infections, skin infections, and urinary tract infections. Ampicillin-sulbactam is used to treat skin and intra-abdominal infections. Sulbactam has additional activity against *Acinetobacter baumanii*. Piperacillin-tazobactum, with cefaperazone-sulbacatam being used as a second line agent to treat pneumonia and intra-abdominal infections. Piperacillin-tazobactam has relatively good activity against *Pseudomonas* and is also called an anti pseudomonal penicillin. Beta lactam / beta-lactamase inhibitors cross the blood brain barrier sub-optimally and hence should not be used in treating meningitis.

Carbapenems use outer member proteins (OMP), also called as porins to enter Gram negative bacteria and have a much wider spectrum of activity than penicillins, cephalosporins and beta-lactam-beta lactamase inhibitors. These should be reserved for critically ill children. Examples of this group are meropenem, imipenem, doripenem and ertapenem. Imipenem and doripenem have slightly more Gram positive activity.[4] Ertapenem has relatively less activity against *Pseudomonas aeruginosa* while meropenem is less potent than imipenem or doripenem against *Acinetobacter baumanni*. These are usually used in combination with other antibiotics to treat multidrug resistant infections. Bacteria like *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii* become resistant to carbapenems by production of carbapenemases, efflux pumps and mutations that target porins and PBPs.

Table I. Classification of penicillins

Categories of penicillin	Examples and routes	Use
Natural Penicillins	Crystalline penicillin (IV), benzathine penicillin (IM), penicillin V (PO)	Group A *streptococcus* species, diphtheria, tetanus, syphilis
Penicillinase resistant penicillins	Cloxacillin ((IV/PO), nafcillin (IV), dicloxacillin (PO), flucloxacillin (IV/PO)	Methicillin sensitive *Staphylococcus aureus*
Aminopenicillins	Ampicillin (IV/PO), amoxicillin (PO)	Respiratory pathogens like *Streptococcus pneumonia, H influenza B, Moraxella cattarhalis.* Ampicillin acts against *Listeria, Enterococcus fecalis*
Ureidopenicillins	Piperacillin (IV)	(Used in combination with beta-lactamase inhibitor) *Pseudomonas aeruginosa*

Table II. Classification of cephalosporins

Class	Examples and routes	Use
First generation	Cefazolin (IV), cephalexin (PO), cefadroxil (PO)	Gram positive bacteria like *Staphylococcus aureus* and *Streptococci spp*. Limited Gram negative action. Mostly used in uncomplicated skin and soft tissue infections, respiratory infections, bone infections. Cefazolin is used as surgical prophylaxis and for prophylaxis against urinary tract infection (UTI)
Second generation	Cefuroxime (IV/PO) cefoxitin (IV), cefotetan (IV)	Used in respiratory infections like pneumonia due to relatively increased activity against Gram negative bacteria
Third generation	Cefotaxime (IV), ceftazidime (IV), cefdinir (PO), ceftriaxone (IV), cefpodoxime (PO) and cefixime (PO).	Used in community acquired pneumonia, UTI, intra- abdominal infections, enteric fever. Parenteral 3rd generation cephalosporins cross blood brain barrier and are used in meningitis. Ceftazidime has better activity against *Pseudomonas aeruginosa*
Fourth generation	Cefipime (IV)	Has good activity against Gram positive (including MSSA) and Gram negative bacteria. Used in serious systemic infections which are multidrug resistant
Fifth generation	Ceftaroline (IV)	Has both Gram positive action (including MRSA and *Enterococcus fecalis*) and Gram negative except *Pseudomonas aeruginosa*). Also covers *Listeria monocytogenes*. FDA approved, for use in drug resistant community acquired bacterial pneumonia and acute skin and soft tissue infections where first line agents have failed.

b) Cell membrane

Polymyxins bind with lipopolysaccharides and cause disruption of the membrane phospholipids. Polymyxin E or colistin is an inactive drug which gets concerted to active form in blood. Polymyxin B is an active compound and less nephrotoxic than colistin. Both these drugs are used for treatment of multidrug resistant Gram negative infections. Polymyxins have no action against Gram positive bacteria and anaerobes. Among *Enterobacteriacae, Proteus spp., Providencia spp., Morganella morganii* and *Serratia marcescens* are intrinsically resistant to polymixins. *Burkholderia epacian* complex and *Burkholderia pseudomallei* are also resistant to polymyxins.[5]

Vancomycin and teicoplanin are glycopeptides which act on the cell membrane. Vancomycin is an important antibiotic for Methicillin resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* infections. Teicoplanin has better tolerability than vancomycin due to less nephrotoxicity and less 'red man syndrome' effect.

c) Ribosomes

Proteins are synthesized by ribosomes. Each ribosome is formed by i) small (30S) and ii) large (50S) subunits.

i*) 30S ribosome inhibitors*

Aminoglycosides, derived from actinomycetes, inhibit protein synthesis by binding to the A-site on the 16S ribosomal RNA of the 30S ribosome. The first aminoglycoside, streptomycin was isolated from *Streptomyces griseus*, followed by neomycin (*S. fradiae*), kanamycin (*S. kanamyceticus*), gentamicin (*Micromonospora purpurea*), netilmicin (derived from sisomicin), tobramycin *(S. tenebrarius*) and amikacin (derived from kanamycin).[6] Aminoglycosides are active against both Gram positives like *staphylococci* and Gram negative organisms like *enterobacterales* and *Pseudomonas aeruginosa*. They do not cover *streptococci, enterococci* (without synergistic combination with beta lactam antibiotics) and anaerobes. They are commonly used in intra-abdominal infections, urinary tract infections and

infective endocarditis. Aminoglycosides like amikacin, kanamycin are also used in treatment of multidrug resistant tuberculosis. Inhalation of tobramycin is used in patients with cystic fibrosis. Aminoglycosides are both nephrotoxic and ototoxic. Resistance against these agents occurs by aminoglycoside modifying enzymes, target site mutation and efflux. Plazomycin is a new aminoglycoside which has received FDA approval for treating complicated urinary tract infections in adults.

Tetracyclines are considered first generation, doxycycline and minocycline represent second generation and tigecycline, third generation. Tetracyclines inhibit the 30S ribosomal subunit. These are used in treating atypical infections like rickettsial infections, leptospirosis, amoebiasis, actinomycosis, nocardiosis, brucellosis, melioidosis, chlamydial infections and *Mycoplasma pneumoniae*. These also have activity against *Staphylococcus aureus*.[7]

ii) 50S subunit inhibitors

Macrolides have an important role in community acquired infections. Azithromycin has broader spectrum of activity and longer half-life than erythromycin. These are effective in mycoplasma infections and enteric fever.

Clindamycin is a lincosamide which has strong activity against streptococcal and staphylococcal infections. Clindamycin in addition has antitoxin effect and anaerobic action.

Chloramphenicol is a broad spectrum antibiotic, however its clinical role is limited by its serious adverse effects of gray baby syndrome and severe bone marrow suppression.

Oxazolidinones like linezolid act by interfering with protein synthesis by binding to the P site of the 50S ribosome. It is bactericidal against *streptococci* but bacteriostatic against *staphylococci* and *enterococci*.

d) Nucleic acids

Fluoroquinolones inhibit DNA synthesis by interacting with the related enzymes DNA gyrase and topoisomerase IV.[8] Nalidixic acid belongs to first generation fluroquinolones. Resistance to nalidixic acid is considered a surrogate marker for resistance against fluoroquinolones. The second generation quinolones like norfloxacin, ofloxacin and ciprofloxacin have broader antimicrobial coverage including *Pseudomonas aeruginosa* among Gram negative bacteria and *Staphylococcus aureus* among Gram positive bacteria excluding streptococcus species and few atypical organisms. They have clinical utility in urinary tract infections, dysentery and soft tissue infections. Levofloxacin and moxifloxacin have broader antibiotic coverage including both penicillin sensitive and penicillin resistant *Streptococcus pneumoniae* and atypical pathogens *like Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella pneumophila*. Moxifloxacin also additionally has good activity against anerobes.[9] These are clinically useful in lower respiratory tract infections but should be reserved for use in multidrug resistant TB.

Metronidazole causes rapid inhibition of DNA replication. It has very good activity against gram-negative anaerobic bacteria, such as *Bacillus fragilis* and Gram-positive anaerobic bacteria, such as *Clostridium difficile.*[10] It is drug of choice for infections which require anaerobic coverage. It also has anti-parasitic activity and is used against protozoa like amoebiasis, trichomonas vaginilis and giardiasis.

Rifampicin specifically inhibits bacterial RNA polymerase, the enzyme which is responsible for DNA transcription. It is a crucial part of the first line drug regimen for tuberculosis. Rifampicin monotherapy can cause rapid development of resistance. Non mycobacterial uses are in combination regimens for severe biofilm related bone infections due to *Staphylococci,* brucellosis and drug resistant *Streptococcus pneumonia* meningitis.[11] However, due to its potential to develop resistance, its use should be preferably limited for treatment of tuberculous infections.

e) Folic acid metabolic pathway

Trimethoprim and sulphonamide inhibit folate acid synthesis at different levels and have synergistic action. This combination is used to manage urinary tract infections, enteric fever, *pneumocystis jirovecii* pneumonia, toxoplasmosis, brucellosis and shigellosis.

III. Classification based on type of action and spectrum of antibacterial activity

a) Bacteriostatic or bactericidal: Antibiotics which kill the bacteria are called bactericidal whereas those which inhibit the growth of bacteria are called bacteriostatic. Typically, bactericidal action is exerted by attacking the cell wall structure of the bacteria. Examples are penicillins, cloxacillin, carbapenems, polymyxin and vancomycin. Aminoglycosides and fluoroquinolones also have bactericidal effect though the mechanism of action is different. The bacteriostatic antibiotics usually act to inhibit protein or folate synthesis. Examples are macrolides, linezolid, doxycycline, tigecycline and chloramphenicol. Some antibiotics which are classified as bacteriostatic can behave as bactericidal in higher serum concentrations.

Recent evidence suggest a similar efficacy for bacteriostatic and bactericidal antibiotics in treating infections, including skin and soft tissue infections, pneumonia, non-endocarditis bloodstream infections, intra-abdominal infections, and genital infections.[12]

b) Narrow spectrum or broad spectrum

Penicillin is a narrow spectrum antibiotic due to its limited activity against certain Gram positive bacteria. Majority of antibiotics used in clinical practice such as cephalosporins, carbapenems, fluoroquinolones have broad spectrum of activity. Narrow spectrum antibiotics should always be chosen over broad spectrum antibiotics whenever causative infection is identified. Broad spectrum antibiotics have disadvantages of selection of resistance and alteration of host microbiome.[13]

IV. AWaRe Classification of antibiotic based on threshold of resistance

With the aim of improving antimicrobial stewardship practices, the World Health Organization classified antibiotics into three main categories - Access, Watch and Reserve (AWaRe). This classification is based on the threshold of the antibiotic for development of resistance. AWaRe classification is the latest metric proposed for antimicrobial stewardship. a) Antibiotics which have lowest potential for developing resistance such as amoxicillin, co-amoxiclav, first generation cephalosporins, cotrimoxazole are grouped under 'Access' category.

b) Antibiotics which have high threshold for developing resistance such as second, third and fourth generation cephalosporins, macrolides, fluoroquinolone, vancomycin, piperacillin-tazobactam, etc. have been grouped under 'Watch'.

c) Antibiotics such as colistin, tigecycline, daptomycin, linezolid, etc. which should be used as last resort antibiotics when no other option is available, are listed under 'Reserve' category.

It has been recommended to improve use of antibiotics from the 'Access' category as first and second line agents for common infections.

Conclusion

Different modes of classifications of antibiotics help gain insight into the way they act on bacteria and their clinical utility. In addition, being aware of their mechanisms of action and their clinical spectrum, serve to prioritise those antibiotics which should be encouraged as first and second line, for better stewardship practices.

Points to Remember

- ***First generation cephalosporins have narrow spectrum and possess strong activity against Gram positive bacteria.***
- ***Beta lactam / beta-lactamase inhibitors cross the blood brain barrier sub-optimally and hence should not be used in treating meningitis.***
- ***Moxifloxacin and Levofloxacin should be reserved for use in multidrug resistant TB.***
- ***Recent evidence suggest a similar efficacy for bacteriostatic and bactericidal antibiotics in treating infections.***
- ***Narrow spectrum antibiotics should always be chosen over broad spectrum antibiotics whenever causative infection is identified.***
- ***AWaRe classification of antibiotics by the WHO comprises of three categories - Access, Watch and Reserve, mainly based on the antibiotic resistance threshold.***
- ***Antibiotic use as first and second line agents for common infections, needs to be improved from the 'Access' category of AWaRe Classification.***

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CLIPPINGS

Hydrocortisone to Improve Survival without Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia is a prevalent complication after extremely preterm birth. Inflammation with mechanical ventilation may contribute to its development. Whether hydrocortisone treatment after the second postnatal week can improve survival without bronchopulmonary dysplasia and without adverse neurodevelopmental effects is unknown.

A trial was conducted involving infants with a gestational age of less than 30 weeks and who had been intubated for at least 7 days at 14 to 28 days. Infants were randomly assigned to receive either hydrocortisone (4 mg per kilogram of body weight per day tapered over a period of 10 days) or placebo. Mandatory extubation thresholds were specified. The primary efficacy outcome was survival without moderate or severe bronchopulmonary dysplasia at 36 weeks of postmenstrual age, and the primary safety outcome was survival without moderate or severe neurodevelopmental impairment at 22 to 26 months of corrected age.

800 infants were enrolled (mean [±SD] birth weight, 715±167 g; mean gestational age, 24.9±1.5 weeks). Survival without moderate or severe bronchopulmonary dysplasia at 36 weeks occurred in 66 of 398 infants (16.6%) in the hydrocortisone group and in 53 of 402 (13.2%) in the placebo group. Two-year outcomes were known for 91.0% of the infants. Survival without moderate or severe neurodevelopmental impairment occurred in 132 of 358 infants (36.9%) in the hydrocortisone group and in 134 of 359 (37.3%) in the placebo group. Hypertension that was treated with medication occurred more frequently with hydrocortisone than with placebo (4.3% vs. 1.0%). Other adverse events were similar in the two groups.

In this trial involving preterm infants, hydrocortisone treatment starting on postnatal day 14 to 28, survival without moderate or severe neurodevelopmental impairment did not differ substantially between the group treated with hydrocortisone and the placebo group.

Watterberg KL, Walsh MC, Li L, Chawla S, D'Angio CT, Goldberg RN, et al. Hydrocortisone to Improve Survival without Bronchopulmonary Dysplasia. N Eng J Med 2022; 386(12):1121-1131.

ANTIMICROBIALS - I

PHARMACODYNAMICS AND PHARMACOKINETICS OF ANTIMICROBIAL THERAPY - CLINICAL APPLICATION

***Bhupendra Kumar Gupta**
****Sudhir Mishra***

Abstract: *Emergence of antimicrobial resistance and poor clinical outcome consequently, are mostly because of inappropriate drug choice and suboptimal dosing. Strategies for better clinical outcomes include selection of an appropriate antibiotic and optimization of antimicrobial dosing regimen. Hence, one must primarily understand the antimicrobial pharmacodynamics and pharmacokinetics of a particular drug to decide on the dosing regimen. Pharmacodynamics denotes the mechanism of action of the drug such as a drug's molecular, biochemical and physiologic effects. Pharmacokinetics deals with absorption, distribution, metabolism and excretion of the drug simplified and abbreviated as ADME.*

Keywords: *Pharmacodynamics, Pharmacokinetics, Minimal inhibitory concentration, Antimicrobial resistance.*

The goal of antimicrobial therapy is to eradicate the microorganism. Many factors must be considered in choosing the appropriate antimicrobial agent for treating a particular infection which includes, the infecting agent, antimicrobial susceptibility, the site of infection, host factors such as immune status, organ function and other preexisting diseases. Once an antimicrobial agent has been selected, principles of pharmacokinetics (PK) and pharmacodynamics (PD) determine the optimal dosing regimen.

Pharmacokinetics refers to the disposition of drugs in the body. It deals with absorption, distribution, metabolism and elimination of a drug, which means it is the study of what the body physiology does to the drug. PK principles can be used to maintain appropriate concentration of antibiotics. PD of antimicrobial agent in fact, determines the effect of the drug depending upon its concentration at the site of action.

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Pharmacokinetics

Absorption: Most antimicrobial drugs are administered either by intravenous (IV) or per oral (PO) routes. Absorption is described by the drug's bioavailability, which is defined as the percentage of a drug's dose that reaches the systemic circulation. Bioavailability of antimicrobial in intravenous route is 100%. The peak plasma drug level is determined by the rate of IV infusion, volume of distribution and its rate of elimination. Bioavailability of antimicrobial in PO route depends on absorption, which in turn depends on solubility of drug, first pass metabolism, volume of distribution (Vd), protein binding and its rate of elimination.[1,2] The area under the curve (AUC) of the plasma concentration of a drug versus time curve is a pharmacokinetic measure which indicates the exposure of the microbe to a drug during the whole duration of dosing interval (Fig.1). AUC denotes the extent of absorption of the antimicrobial. T Max denotes the time to reach the maximum concentration of antimicrobial. C max denotes maximum concentration of antimicrobial which can be obtained. MIC is the minimum concentration of the drug which prevents visible growth of the microbe.

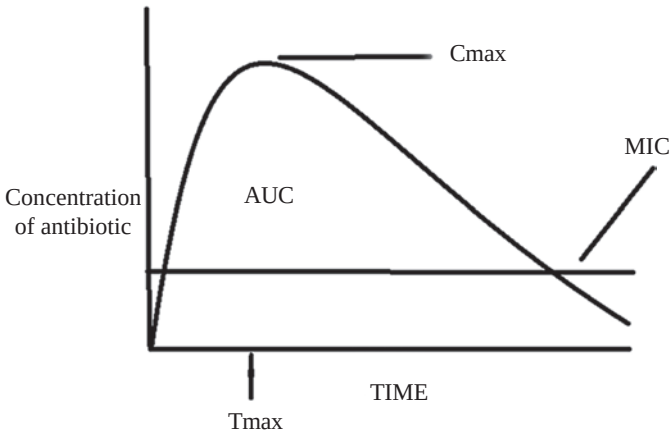

Fig.1. Graphical representation of PK, PD indices, AUC, C max, T max and minimum inhibitory concentration (MIC)

Distribution: Distribution is the process by which the drug diffuses from intravascular space to various tissues. This is determined by volume of distribution (Vd) which is the volume that would be required to contain the administered dose if that dose was evenly distributed at the concentration measured in plasma. If more amount of drug is entering the tissue, then Vd will be high and vice-a-versa.

Metabolism and elimination: Antimicrobial metabolism and elimination vary with age. The cytochrome P-450 (CYP) enzyme system is the most important system for antimicrobial metabolism.[3] Some important drug interactions can occur if they are metabolised by the cytochrome P-450 system. Erythromycin, clarithromycin and ketoconazole are cytochrome P-450 system inhibitors and rifampicin and nevirapine are CYP enzyme inducers. When antimicrobials are prescribed, other medications which the patient is taking must be taken into consideration to avoid any possible drug interaction. A common drug interaction encountered is that which occurs between macrolides and corticosteroids in relation to PK properties. Macrolide, particularly clarithromycin is a CYP3A4 inhibitor which decreases the metabolism of corticosteroids and increases plasma concentration of the drug leading on to toxicity. Rifamipicin is a CYP enzyme inducers. Concomittant administration of rifampicin and valproic acid leads to decreased efficacy of valproic acid.[4]

Antimicrobials are primarily eliminated via bile or urine. The rate of elimination of an antimicrobial depends on its half life. The half-life ($t_{½}$) of a drug is defined as the time it takes for the amount of a drug's active substance in the body to reduce by half. This depends on how the body processes and eliminate the drug. Half life helps to estimate the time required for plasma concentrations to reach

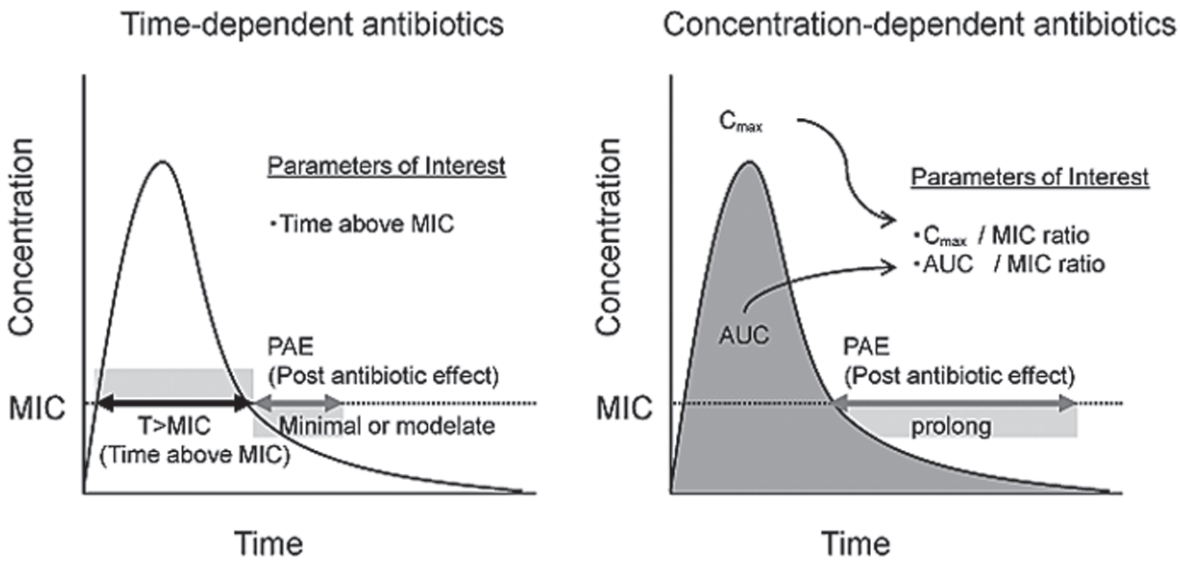

Fig.2. PK-PD characteristics of antimicrobial drugs

Left: *Time-dependent antibiotics (beta-lactams, including penicillins and penems, glycopeptides, linezolid, macrolides, etc.). The time that the concentration of a drug remains above the MIC (T > MIC) is the PK-PD index correlating with efficacy. The post-antibiotic effect (PAE) can be variable (macrolides), minimal (betalactams, including penicillins and carbapenems), or moderate (glycopeptides, linezolid).*

Right: *Concentration-dependent antibiotics (aminoglycosides, fluoroquinolones). The peak concentration/minimum inhibitory concentration (C_{max}/MIC) ratio and/or the area under the concentration-time curve at 24 h/MIC (AUC_{0-24}/MIC) ratio are the best PK-PD modeling and simulation correlating with efficacy. Moreover, there is a prolonged post-antibiotic effect with the concentration-dependent antibiotics.*

(Source: PK-PD characteristics of antimicrobial drugs. https://www.omicsonline.org/articles-images/JBB-S2-002-g002.html. Accessed on 16.01.2022).

steady-state after starting a dosing regimen and also to determine the dosing intervals. For e.g if the half-life is longer than expected, as shown by drug accumulation the dosing interval can be extended, rather than than decreasing the dose. Steady state of antimicrobial concentration is achieved by four to five half life. If Cmax and trough level of antimicrobial measured at steady state then patient specific half life and Vd can be calculated from two serum levels of antimicrobial.

Pharmacodynamics

Phamacodynamics of antimicrobial agent deals with interaction between the drug concentration at the site of action and antimicrobial effect and hence minimal inhibitory concentration (MIC) of antimicrobial is used to choose an antimicrobial regimen. MIC is also affected by local factors such as pH and oxygen concentration at the tissue level.[5]

Antimicrobial agents have been classified as concentration dependent antibiotic and time dependent antibiotic based upon the influence of drug concentration on microbial killing.[6] Antibiotics which are concentration dependent are aminoglycosides, fluroquinolones and metronidazole.[7,8] Efficacy of concentration dependent antibiotics are associated with area under the serum concentration time curve (AUC) in comparison with MIC (AUC:MIC ratio) and peak serum concentration in comparison to MIC (C max:MIC ratio) (Fig.2).

Time dependent antimicrobials are β-lactam antibiotic and vancomycin where killing of microorganism is primarily time dependent and efficacy is increased when the duration of drug concentration above the MIC is maximized.[9] Some antimicrobial efficacy is also influencd by post antibiotic effect. The post antibiotic effect is persistent suppresion of microorganism regrowth after brief exposure to an antimicrobial agent.[10] Antimicrobial agent showing post antibiotic effect are aminogycosides, fluroquinolones, macrolides, clindamycin and tetracyclines.

Some antimicrobial agent's efficacy is also influenced by synergistic properties. The synergy between two antimicrobial agents is a phenomenon in which two antimicrobial agents exihibit enhanced antimicrobial

Table I. Antimicrobial dose adjustment based on estimated GFR in mL/min/1.73m²

Antimicrobial	GFR 30-50	GFR 10-29	< 10
Amikacin	5-7.5 mg/kg q 12-18 h	5-7.5 mg/kg q 24 h	5-7.5 mg/kg48-72 h
Ampicilin	No change	25 % of normal	15% of normal
Amoxicillin	No change	10-20 mg/kg/dose q12h	10-20 mg/kg/dose q 24h
Azithromycin	No change	No change	No change
Capsofungin	No change	No change	No change
Co-amoxiclav	No change	Increase interval q 12 h	Increase interval q 24 h
Cefepime	50 mg/kg/dose q 24 h	50 mg/kg/dose q 24 h	50mg/kg/dose q 48 h
Cefixime	No change	Reduce daily dose by 25%	Reduce daily dose by 50%
Ceftriaxone	No change	No change	Reduce daily dose by 25-50%
Cefaperazone-sulbactam	No change	50% dose of sulbactam	25% dose of sulbactam
Ciprofloxacin	No change	Reduce daily dose by 50%	Reduce daily dose by 75%
Fluconazole	Reduce dose by 50%	Reduce dose by 50%	Reduce dose by 75%
Linezolid	No change	No change	No change
Metronidazole	No change	No change	Reduce daily dose by 50%
Meropenem	10-20 mg/kg q 12 h	10-20 mg/kg q 12 h	10-20 mg/kg q 24 h
Netilmicin	2 mg/kg q 12 h	2 mg/kg q 12 h	2 mg/kg q 24-48 h
Piperacillin tazobactam	Reduce 30% q 6 h	Reduce 30% q 8 h	Reduce 30% q 8 h
Vancomycin	10 mgkg q 12 h	10 mg/kg q 24 h	10 mg/kgq 48-72 h

Table II. Age and value of K

Preterm neonate upto 1 yr	0.33
Full term neonate upto 1 yr	0.45
1-12 yrs	0.55
13-17 yrs Male	0.55
13-17 yrs Female	0.7

Table III. Antimicrobial agents needing dose reduction/avoidance in liver disease

Drugs to be avoided	Dose reduction needed
Erythromycin	Chloramphenicol
Pyrizinamide	Metronidazole
Tetracycline	Clindamycin
Nalidixic acid	Isoniazid
Pefloxacin	Rifampicin

Table IV. PK and PD properties of commonly used antimicrobial agents

Antimicrobial agent	Clearance	Type of killing	Post antibiotic effect	Dosing
Penicillin	Renal	Time dependent	Minimal	High frequency and Prolonged infusion
Cephalosporin	Renal	Time depedent	No	High frequency and Prolonged infusion
Vancomycin	Renal	Time dependent	No	High frequency and Prolonged infusion
Carbapenam	Renal	Time dependent	Minimal	High frequency and Prolonged infusion
Tetracycline	Hepatic, Renal	Time dependent	Minimal	High frequency and Prolonged Infusion
Macrolide	Renal	Time dependent	Variable	Variable
Linezolid	Renal	Time dependent	Minimal	High frequency and Prolonged infusion
Clindamycin	Hepatic, Renal	Time dependent	Minimal	High frequency and Prolonged infusion
Chloramphenicol	Hepatic, Renal	Time dependent	No	High frequency and Frequent infusion
Fluroquinolones	Renal	Concentration dependent	Prolonged	High dose Low frequency
Aminoglycoside	Renal	Concentration dependent	Prolonged	High dose Low frequency

- *Goal in time dependent antimicrobial agent is to maximize duration of exposure of antimicrobial. Suitable dosing regimen for this is high frequency (TID/QID dosing) and prolong infusion (Over 1-4 Hours)*
- *Goal in Concentration dependent antimicrobial agent is to maximize concentration of antimicrobial. Suitable dosing regimen for this is high dose (maximum dose) and low frequency (OD/ BD dosing)*

Table V. Site specific infection and modification in dosing regimen

Infection site	PK alteration	Change in dosing regimen
CNS	Impaired permeability	Maximum dose and increase duration of therapy
Bone and joint	Impaired permeability	Increase dose and duration of therapy
Lung	Impaired permability	Increase dose
Blood	Expanded Vd, increase clearance	Provision of loading dose and increase frequency

properties when combined. Combination of sulfonamide with an inhibitor of dihydrofolate reductase (trimethoprim or pyrimethamine) provides synergistic activity because of sequential inhibition of folate synthesis.[11]

Clinical application of PK and PD

Hydrophilic antimicrobial agents (e.g. β-lactam, aminoglycoside) have relatively small volume of disribution and mostly excreted by kidneys. Lipophilic antimicrobial agent (e.g. quinolones, macrolides, tigycycline, capsofungin) have large volume of distribution and mostly undergo hepatic metabolism and elimination.[12,13]

In patients with change in renal clerance such as in acute kidney injury, renal clearance of predominantly renally excreted antimicrobial agent (e.g. β-lactam aminoglycosides) is significantly decreased. The dose of antimicrobials excreted through the kidneys is adjusted based on estimated GFR which is calculated by Schwartz formula (Table I).[14,15,16]

Estimated Glomerular Filtration Rate [eGFR(mL/min/1.73m^2)] = Kx Length in cm / Sr Creatinine, where K is a constant which is age dependent (Table II).

Lipophilic antimicrobial agents which are cleared by the liver are recommended to be administered at reduced doses in patients with Child-Pugh class C (decompensated) liver failure as per Child-Pugh-Turcotte score designed to predict mortality in cirrhosis patients) (Table III).[17,18] Aminoglycosides, fluroquinolones, metronidazole and amphotericin are concentration dependent antimicrobials wherein the efficacy is associated with high AUC:MIC and Cmax: MIC ratio. Administration of large doses at longer time intervals are more effective in killing the susceptible microorganism. This approach may minimise the emergence of resistant mutants by obtaining high peak concentration of antimicrobials and also can achieve good organism killing rate by producing adequate AUC:MIC ratio. Aminoglycosides and fluroquinolones also have post antibiotic effect. These properties of aminoglycosides are the rationale for using single daily dosing. β-lactam and vancomycin are time dependent antibiotics and these antibiotics have no post antibiotic effect. These antibiotics show maximum efficacy when the antibiotic concentration at the site of infection exceeds MIC of the organism for most of the dosing interval. For these antimicrobials frequent administration can be used to maximize the efficacy (Table IV).

Most site of infections are extravascular and treatment of site specific infection depends on entry of antimicrobial agent from the blood stream into interstitial and sometimes into intracellular fluid. This depends on tissue related factor such as perfusion to tissue, surface area of the tissue vascular bed and specialised vascular bed features such as blood brain barrier and drug related factor such as lipid solubility, plasma protein binding and drug PK.[5] Relationship of antimicrobial PK properties and site specific infection treatment strategies are summarised in Table V.

Conclusion

Once an antimicrobial agent has been chosen for a particular infection, the dose must be selected appropriately to achieve maximal efficacy and at the same time avoiding adverse effects. Designing the ideal dosing regimen for a patient depends on the appropriate application of patient specific PK and PD principles. The components included in the PK principle are absorption, distribution, metabolism and elimination and factors included in PD principles are concentration dependent killing, time dependent killing, post antibiotic effect and synergism.

Points to Remember

- ***Antimicrobial therapy for the treatment of infection not only require appropriate choice of antimicrobial agent but also appropriate dosing regimen, route and duration. To decide this, site of infection, type of bacteria and age of patients are other important variables.***

- ***Dose optimization of antimicrobial agent requires understanding of pharmacokinetic and pharmacodynamic properties.***
- ***Antimicrobial efficacy of concentration dependent antimicrobial agents (e.g. aminoglycoside, quinolones) depends on the peak concentration (C max) to MIC ratio.***
- ***Antimicrobial efficacy of time dependent antimicrobial agents (e.g. β-lactam, vancomycin) depends on the percentage of time that free plasma concentration of antimicrobial agent is maintained above MIC.***
- ***Dose adjustment is required in certain situations, renal impairment being the most important of them.***

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NEWS AND NOTES

ANTIMICROBIALS - I

SIDE EFFECTS OF ANTIMICROBIALS AND PREVENTIVE STRATEGIES

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****Santhosh Kumar A**

Abstract: *Antibiotics though life-saving drugs, may have side effects varying in severity from trivial to life-threatening. The side effects include local irritant effects, systemic toxicity, drug hypersensitivity reactions, drug interactions and intestinal dysbiosis. Intestinal dysbiosis has widespread and long lasting effects in a person including the risk of development of diseases with immunological basis, including asthma, allergic diseases and diabetes mellitus. Antibiotics are considered as societal drugs, their side effects are not restricted only to the treated individual as their use is an important modifiable factor that can result in the development of drug resistant bacteria and therapeutic failure.*

Keywords: *Side effects, Drug resistance, Antimicrobial stewardship programme, Drug hypersensitivity reactions, Drug interactions, Intestinal dysbiosis.*

Antimicrobials are one of the most widely prescribed class of drugs across all age groups.[1] Unlike other classes of drugs, the side effects of antimicrobials may not be confined to the person who uses the drug as their use will affect the health of the society, through development of antimicrobial resistance.

Side effects of antimicrobials can be divided into two groups

1. Side effects that affect the treated individual
2. Development of antimicrobial resistance which affects the community

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Box 1. Side effects of the antimicrobials

i. Drug toxicity:
   a. Local irritation
   b. Organ specific systemic toxicity: Hematological, gastrointestinal, hepatic, renal, neurological, cardiac, pulmonary, musculoskeletal, metabolic and skin

ii. Hypersensitivity reactions

iii. Drug to drug interactions

iv. Super infections: Due to multiplication of commensals

v. Destruction of gut microbiota

Side effects that affect the treated individual

They are listed out in the Box 1.

i. Drug toxicity

Drug toxicity can be local irritant effect or systemic toxicity

a. Local irritation: Gastrointestinal irritation is the most common adverse effect of orally administered antibiotics.[1] They can cause nausea, vomiting, diarrhea and abdominal discomfort. Practically all oral antimicrobials are irritants, especially erythromycin, tetracyclines and chloramphenicol. Intravenously administered drugs can cause thrombophlebitis.

b. Systemic toxicity (organ specific): Antimicrobials exhibit characteristic systemic toxicity. Antibiotics can produce side effects affecting different organ systems in the body. These toxic effects can occur on exposure to a particular class of antibiotic or, it could be specific to the individual antibiotic.[2] The following is a detailed discussion of toxicity affecting different organ systems.

1. Hematological side effects

1a. Bone marrow suppression: It is more common with prolonged use of antibiotics (two weeks or longer). The incidence of bone marrow suppression ranges between 5-34% depending on the antibiotic and duration of

Table I. Different mechanisms of antibiotic induced hemolysis

Mechanism	Process of hemolysis	Causative antibiotics
Drug dependent immune hemolysis: hapten mechanism	Drug adheres to RBC membrane, antibody directed to drug leads to hemolysis	Penicillins, cephalosporins
Ternary complex (A complex formed between two substrate molecules and an enzyme)	Ternary complex including drug, RBC membrane antigen and antibody recognizing both	Quinine, quinidine
Autoantibody	Induce true autoantibody to RBC membrane, hemolysis can continue even after stopping the drug	Cephalosporin
Oxidant injury to RBC	Hemolysis in patients with G6PD deficiency	Sulfonamides, cotrimoxazole, quinolones, nalidixic acid, nitrofurantoin, dapsone, chloramphenicol, antimalarials like primaquine and chloroquine

treatment and can present as anemia and/or neutropenia and/or thrombocytopenia.[3] Azidothymidine (AZT-zidovudine), chloramphenicol, cotrimoxazole, dapsone and linezolid very frequently cause bone marrow suppression. Bone marrow suppression can rarely occur following other classes of antibiotics including beta lactam antibiotics, tetracycline, methicillin, amphotericin, chloroquine and pyrimethamine.

1b. Hemolytic anemia: Antibiotics can induce hemolytic anemia through immune mediated or non-immune mediated destruction of RBCs. Table I shows the different mechanisms of antibiotic induced hemolysis.

1c. Immune mediated platelet dysfunction: High dose penicillin can cause platelet dysfunction.

2. Gastrointestinal (GI) side effects

2a. Antibiotic associated diarrhea: Antibiotic-associated diarrhea is defined as diarrhea occurring within 2 hours to 2 months after starting antibiotic.[4,5] Antibiotic associated diarrhea is described in 11% of children for whom antibiotics are prescribed.[4] It could be *Clostridium difficile* diarrhea or non-*Clostridium difficile* diarrhea.

Clostridium difficile diarrhea: *Clostridium difficile* is a Gram-positive, spore forming, non-invasive bacterium. *C. difficile* colonizes the intestine after disruption of the normal intestinal flora. *C. difficile* is being recognized as an important pathogen associated with antibiotic induced diarrhea in children[6]. Clindamycin, tigecycline, cephalosporins and quinolones are the most common antibiotics associated with *Clostridium difficile* infection (CDI).[7] Clinical presentation of *C. difficile* diarrhea ranges from mild watery diarrhea to pseudomembranous colitis. CDI is defined as acute onset of diarrhea with documented toxigenic *C. difficile* or its toxin and no other cause for diarrhea[3,8] Treatment of CDI in children depends on the severity of the disease (Box 2).[7]

Box 2. Severity of CDI

- *Mild to moderate disease:* diarrhea (<6 stools/day) without signs of systemic toxicity or fever
- *Severe colitis:* frequent diarrhea (>6 stools/day) with severe abdominal pain, leukocytosis and fever
- *Fulminant colitis:* complete ileus or toxic megacolon associated with hypotension and rising lactic acid levels.[7]

Non *Clostridium difficile* diarrhea: Usually presents as mild to moderate diarrhea. This could be due to overgrowth of pathogens following destruction of normal flora by the antibiotics or changes in the carbohydrates and bile acids metabolism in the gut resulting in osmotic diarrhea. Some antibiotics like erythromycin and amoxicillin-clavulanate increase gastrointestinal motility. Majority of these patients responds to discontinuation of antibiotics and administration of probiotics, such as *Lactobacillus rhamnosus GG* and *S boulardii.*

Table II. Nephrotoxicity of antibiotics

Type of nephrotoxicity	Drugs causing nephrotoxicity
Acute kidney injury	Aminoglycosides, acyclovir, amphotericin B, vancomycin
Renal vasculitis	Isoniazid, penicillins, sulfonamides
Nephrogenic diabetes insipidus	Amphotericin B, demeclocycline
Fanconi syndrome	Aminoglycosides, outdated tetracyclines
Renal tubular dysfunction	Amphotericin B
Acute interstitial nephritis	Colistin, gentamicin, kanamycin, penicillins (especially methicillin), cephalosporins, rifampicin, sulfonamides, ciprofloxacin, tetracyclines, vancomycin, erythromycin, daptomycin, acyclovir
Acute tubular necrosis	Aminoglycosides
Obstructive uropathy	Sulfonamides, acyclovir
Urine discoloration	Rifampicin, nitrofurantoin, metronidazole

2b. Acute pancreatitis: Metronidazole and tetracycline are rarely associated with drug induced pancreatitis.

2c. Hepatic side effects: Drug induced hepatitis may be dose dependent or idiosyncratic. Antibiotics are implicated in idiosyncratic liver injury. Among the first line antituberculous drugs, isoniazid, rifampicin and pyrazinamide are hepatotoxic. Tetracyclines can lead to micro-vesicular steatosis. Erythromycin, especially the estolate form produces cholestasis. Ceftriaxone use is associated with biliary sludge. Clavulanic acid is another drug, which is hepatotoxic.

3. Nephrotoxicity

Table II shows the different types of nephrotoxicity and the causal antibiotics.

Aminoglycosides usually produce non oliguric renal failure. It is characterized by slow rise in serum creatinine and decrease in the ability of kidneys to concentrate urine, due to proximal renal tubular damage. Nephrotoxicity depends on the trough level of aminoglycosides. Hence giving the drug in frequent divided doses will potentiate the nephrotoxicity.[9] Nephrotoxicity of aminoglycosides is potentiated in hypovolemia, use of radiographic contrast and concomitant use of other nephrotoxic drugs like non steroidal anti inflammatory drugs(NSAIDs), ACE inhibitors, amphotericin and cisplatin.[9] Aminoglycosides should be avoided in children with pre-existing renal diseases. Aminoglycoside induced nephrotoxicity is usually reversible. Appropriate selection of patient, restricting the use of aminoglycosides to those infections which are resistant to other drugs and giving the drug as once daily dose will decrease the incidence of aminoglycoside induced nephrotoxicity.

Vancomycin produce reversible nephrotoxicity in less than 5% of patients treated with the drug. Vancomycin nephrotoxicity is associated with trough level of >15 mg/L.[9] Concurrent use of aminoglycosides enhances nephrotoxicity.

Amphotericin B is associated with different types of nephrotoxicity (see Table II). One of the frequent effects is loss of renal concentrating capacity leading to dehydration and loss of electrolyte like sodium, potassium and magnesium through urine leading to severe electrolyte disturbances. Spironolactone can reduce amphotericin induced tubular dysfunction.

4. Neurological side effects

Beta lactams and quinolones are the antibiotics most frequently implicated with neurotoxicity.[10] Other antibiotics that can produce neurotoxicity include aminoglycosides, tetracyclines, clindamycin, erythromycin, polymyxins, ethambutol, isoniazid, quinolones and chloramphenicol.[10]

4a. Encephalopathy and seizures: The major cause for penicillin induced encephalopathy is proposed to be the inhibitory effect on GABA transmission, due to structural similarity of the beta lactam ring with GABA.[10] Thiazolidone ring and side chain length also potentiate epileptogenic activity. All the four generations of cephalosporins can cause neurotoxicity through a similar mechanism. The neurotoxicity of beta lactams include lethargy, psychosis, confusion, disorientation, seizures, encephalopathy, asterixis, myoclonus and

chorea-athetosis.[10] Presence of CNS infections and renal insufficiency potentiate the neurotoxicity of beta lactams. Isoniazid and cycloserine can produce psychosis and seizures. Imepenem-cilastin can also induce seizures.

The neurological side effects of quinolones include headache, seizures, delirium, encephalopathy, orofacial dyskinesia, psychosis, Tourette like syndrome and extrapyramidal manifestations.[10] These effects are dose dependent and suggested to be due to activation of excitatory NMDA receptors. The chemical structure of quinolones also plays a role in the degree of neurotoxicity. The occurrence of quinolone related neurotoxicity is as follows:norfloxacin>ciproflocacin>ofloxacin> levofloxacin.[10] Macrolides, especially clarithromycin can produce both CNS depression (confusion, stupor) and excitation (agitation, insomnia, delirium, psychosis).

4b. Peripheral neuropathy: Isoniazid and linezolid are associated with peripheral neuropathy. Pyridoxine is prescribed for preventing the neurotoxic effects of INH including peripheral neuropathy. Linezolid induced peripheral neuropathy occurs when the drug is used for more than 4 weeks, when used for treatment of multi drug resistance (MDR) tuberculosis. Linezolid induced peripheral neuropathy is painful and irreversible. Long term use of metronidazole can produce cerebellar signs, optic neuropathy and peripheral neuropathy due to axonal swelling secondary to metronidazole induced vasogenic edema. These effects are completely reversible on drug discontinuation.[10] Dapsone is rarely associated with pure motor neuropathy.

4c. Neuromuscular blockade: Aminoglycosides have curare like action and can cause reversible neuro paralysis. Neurotoxicity is potentiated by use of skeletal muscle relaxants and hypomagnesemia.[11] Polymyxins are another group of drugs which can produce neuromuscular blockade. Prolonged depolarization due to depletion of calcium and direct interaction with neurons due to high lipid content are the proposed mechanism of polymyxin induced neuromuscular blockade. Macrolides, especially clarithromycin also produce neuromuscular blockade.[10] These drugs should be avoided in patients with muscular diseases.

4d. Blindness: Optic neuritis and blindness are well described with ethambutol. Patients above 6 years on ethambutol treatment should undergo periodic assessment of visual field. Linezolid is also associated with optic neuropathy and visual loss. Mitochondrial toxicity is the proposed mechanism of linezolid induced optic neuropathy.

4e. Ototoxicity: Ototoxicity can occur in up to 10% of patients treated with aminoglycosides. Ototoxicity has been reported even after the use of ear drops containing aminoglycosides. There are two types of ototoxicity. Amikacin and kanamycin affect cochlea leading to deafness. Streptomycin and gentamicin are mainly vestibulotoxic.[12] Higher serum drug levels and prolonged use are determinants of ototoxicity. They produce irreversible high tone hearing loss. The hearing loss can occur even after a latency of 6 months. Hence all patients on prolonged aminoglycoside treatment have to be followed up with serial audiograms.

Vancomycin can also produce ototoxicity, especially if it is combined with other ototoxic drugs. Ototoxicity of vancomycin is related to high trough levels, more than 40 mg/L.

4f. Benign intracranial hypertension: Nalidixic acid and outdated tetracyclines can lead to benign increase in intracranial pressure. It can manifest as bulging fontanelle in infants or irritability and vomiting in older children.

5. Cardiac side effects

Prolonged QT interval: Macrolides, especially clarithromycin can produce prolonged QT interval. Concurrent use of drugs like cisapride, pimozide, terfenadine and astemizole is contraindicated with clarithromycin. Clarithromycin increases the blood levels of these drugs and these drugs also prolong QT interval. Hence, concurrent use of these drugs with clarithromycin increases the risk of polymorphic ventricular tachycardia. Clarithromycin and azithromycin can also potentiate the cardiac toxicity of digoxin and class 1 antiarrhythmic drugs.

6. Pulmonary side effects

6a. Acute pulmonary reaction: Daptomycin can cause acute eosinophilic pneumonia. Use of higher dose and prolonged duration of treatment are associated with higher incidence of acute eosinophilic pneumonia.[9] It will be difficult to differentiate daptomycin induced acute eosinophilic pneumonia from hospital acquired pneumonia, as both have similar symptomatology. Daptomycin is inactivated by surfactant, hence not effective for pneumonia. Nitrofurantoin can also cause acute hypersensitivity pneumonitis. Amphotericin B and sulfonamides can rarely produce pulmonary reactions like interstitial pneumonitis.[13]

6b. Chronic pulmonary reaction: Nitrofurantoin causes chemical pneumonitis, pulmonary fibrosis and bronchiolitis obliterans.

Table III. Drug hypersensitivity reactions

Drug hypersensitivity reactions[14]		
Reaction	**Presentation**	**Examples of antibiotics**
A. Antibody mediated reactions		
IgE mediated Type 1	Urticaria, angioedema, bronchospasm, anaphylaxis Onset: typically <1 hour, but may be up to 6 hours	Penicillins, cephalosporins
IgG mediated Type 2	Hemolytic anemia, thrombocytopenia, vasculitis Onset: < 72 hrs, but can be up to 15 days	Penicillins, cephalosporins, sulfonamides, dapsone, rifampicin
Serum sickness like reaction Type 3	Fever, rash, arthralgia Onset : 1-3 weeks	Penicillin, amoxicillin, cefaclor, cotrimoxazole
B. Cell mediated reactions		
1. Primarily single organ disease		
Acute interstitial nephritis	Acute kidney injury, rash, WBC casts in urine, eosinophiluria, blood eosinophilia Onset: 3 days - 4 weeks	Nafcillin, oxacillin, fluoroquinolones, rifampicin
Drug induced liver injury	Usually presents with hepatitis/ transaminitis, rash is rare Onset: 5 days to 12 weeks (typically > 4 weeks)	Amoxicillin-clavulanate, flucloxacillin, rifampin, cotrimoxazole, nevirapine, efavirenz, nitrofurantoin,
2. Isolated cutaneous disease		
Maculopapular rash	Maculopapular rash, eosinophilia Onset: days to weeks	Amoxicillin, sulfonamides
Fixed drug eruption	Erythematous and edematous plaques with round shape, occur at same site Onset: days to weeks	Sulfonamides, vancomycin
Contact dermatitis	Erythema and edema with vesicles Onset: days to weeks	Ampicillin, bacitracin
3. Systemic or multisystem diseases		
DRESS syndrome	Fever, rash, eosinophilia, lymphadenopathy, organ involvement Onset: 2-6 weeks	Vancomycin, rifampicin, sulfonamides, dapsone, beta-lactam antibiotics
Steven Johnson syndrome (SJS) & toxic epidermal necrolysis (TEN)	Rash with desquamation, mucositis, fever SJS: < 10% BSA SJS/TEN overlap: 10-30%BSA TEN: >30% BSA Onset: 4 days-4 weeks	Cotrimoxazole, nevirapine, anti TB drugs, macrolides, quinolones
Acute generalized exanthematous pustulosis	Acute pustular eruptions with fever, facial edema, neutrophilia, oral involvement in 25% Onset: < 48 hours	Aminopenicillin, other betalactams piperacillin, ceftazidime and meropenem, clindamycin, fluoroquinolones, sulfonamides

BSA- Body surface area, SJS - Steven Johnson Syndrome, TEN - Toxic epidermal necrolysis

7. Miscellaneous side effects

7a. Musculoskeletal problems: Quinolones are implicated in tendonitis and arthritis. Rupture of tendon is also described. Cotrimoxazole is associated with flare up of rheumatoid arthritis. Myalgia and elevated CPK levels can occur with use of daptomycin. It can rarely lead to rhabdomyolysis. Muscle involvement usually starts in the first week of treatment. The drug should be discontinued if CPK levels rise above 10 times the normal value or symptoms of myopathy develop.

7b. Skin discoloration: Photosensitivity reactions can occur with quinolones, dapsone.

7c. Rash: In addition to the hypersensitivity reactions, betalactam antibiotics, especially ampicillin and amoxicillin can induce rash in patients with Epstein Barr virus infection.

7d. Redman Syndrome: Redman syndrome is associated with rapid infusion of vancomycin. Rapid infusion of vancomycin will lead to release of histamine from mast cells. This leads to acute onset of generalized rash with itching and hypotension. It is not an allergic reaction and does not warrant discontinuation of vancomycin.

7e. Metabolic side effects: Lactic acidosis can occur on prolonged treatment with linezolid. This is due to mitochondrial toxicity.

ii. Hypersensitivity reactions

Antibiotics are the commonest cause of severe life threatening allergic drug reactions including anaphylaxis, organ specific reactions and severe cutaneous reactions.[14] See Table III for the different types of drug hypersensitivity reactions.

Anaphylaxis: Antibiotics are implicated in 35-66% cases of drug induced anaphylaxis.[15] Beta lactam antibiotics penicillins (most frequently amoxicillin), cephalosporins and non-beta lactam antibiotics like fluoroquinolones, macrolides, sulfonamides and tetracyclines may cause anaphylaxis.[15]

DRESS syndrome (Drug rash with eosinophilia and systemic symptoms): It is a severe idiosyncratic multisystem reaction to drug characterized by fever, rash, lymphadenopathy, hematological abnormalities (thrombocytopenia, eosinophilia) and systemic involvement in the form of hepatitis, pericarditis, interstitial nephritis or pneumonitis.[16] It usually occurs 2-6 weeks after starting the drug. Beta lactam antibiotics, aminoglycosides, fluoroquinolones, macrolides dapsone, anti-tuberculous drugs and antiretroviral drugs are examples of antimicrobials associated with DRESS syndrome.[17]

Serum sickness: Fever, rash and arthralgia occur 1-3 weeks after drug intake. Penicillin, amoxicillin, cefaclor and co-trimoxazole are examples of some antimicrobials that can induce serum sickness.

iii. Drug to drug interactions

Induction/ inhibition of hepatic enzymes: Macrolide antibiotics can inhibit CYP3A4 enzymes - Erythromycin > clarithromycin >azithromycin. Inhibition of CYP3A4 enzyme system will lead to increased blood levels of certain drugs, such as benzodiazepines (midazolam, alprazolam) carbamazepine, cyclosporine, tacrolimus, cisapride, statins, pimozide, warfarin and theophylline. Itraconazole may increase macrolide levels, whereas rifampin, rifabutin, carbamazepine and phenytoin may decrease macrolide levels by stimulation of hepatic metabolism.

Linezolid has MAO inhibitory activity. Hence, linezolid can induce serotonin syndrome in patients on tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) like fluoxetine. Adrenergic drugs like adrenaline, dopamine, noradrenaline, phenylpropanolamine and ephedrine should not be combined with linezolid.

iv. Superinfections

Superinfections can occur due to multiplication of commensals. Oral candidiasis due to suppression of the normal oral flora is very common following antibiotic use. *C. difficile* diarrhea is described earlier. Exposure to vancomycin and streptomycin increases susceptibility to *Salmonella typhimurium*. Antibiotic induced destruction of the gut microbiota can affect digestion and release of sugar and bile acids. These nutrients favor the growth of pathological bacteria like *S. typhimurium* and *C. difficile*. Antibiotics also enhance bacterial translocation out of gut, which can lead to blood stream infection.

v. Intestinal dysbiosis

Antibiotics can affect the intestinal microbiota, which can have both short term and long term effects. The common effects are

a. Decreased diversity of the gut microbiota.
b. Increase in population of proteobacteria including Enterobacteriaceae.
c. Enhanced expression of antibiotic resistance genes by the intestinal bacteria.[18]

Table IV. Adverse effects of specific antimicrobials[9]

Drug	Common side effects	Serious side effects
Penicillins	Nausea, vomiting, diarrhea, rash, urticaria, pain at injection site, IV-thrombophlebitis. Amoxicillin and ampicillin can induce rash in patients with infectious mononucleosis. Candidiasis	Anaphylaxis, Jarisch-Hexheimer reaction - occurs in syphilitic patient. Drug induced anemia, serum sickness, *C. difficile* infection
Amoxicillin - clavulanic acid	Same as amoxicillin Headache	Drug induced hepatitis More chance of *C. difficile* infection than amoxicillin
Aztreonam	GI disturbances, mouth ulcers, altered taste, skin rash	GI bleeding, thrombocytopenia, neutropenia, eosinophilia, hepatitis
First and second generation cephalosporins	GI disturbances, skin rash, headache, dizziness, paresthesia, prolonged prothrombin time	Serum sickness, hemolysis, hematological toxicity, *C. difficile* infection
Ceftriaxone	Biliary sludge and reversible pseudolithiasis, can bind albumin and cause displacement of bilirubin. (hence not used in neonates), drug fever, drug rash, candidiasis	Anaphylaxis,transient rise in liver enzymes, hemolytic anemia, neutropenia, thrombocytopenia
Cefepime	GI disturbances, rash, fever, phlebitis, headache	Anaphylaxis,transient rise in liver enzymes, increased risk of seizures in children treated with higher doses
Cefoperazone	Disulfiram like reactions	Hypoprothrombinemia and coagulopathy (hence avoid in patients likely to have vitamin K deficiency).
Piperacillin - tazobactam	Has high sodium content, false positive galactomannan test for Aspergillosis	Risk of hypokalemia in patients with low potassium reserve - on diuretics or cytotoxic drugs, elevation of liver enzymes
Meropenem	Drug rash	Anaphylaxis - If the patient has history of penicillin / beta lactam hypersensitivity carbapenems should be used with caution, thrombocytosis, transient raise in liver enzymes
Imipenem- cilastatin	Discoloration of urine, nausea, vomiting, diarrhea	Anaphylaxis,oliguria, anuria, acute kidney injury, neurotoxicity - seizures can occur (hence avoid in patients with meningitis and those with higher risk for seizures), transient raise in liver enzymes, thrombocytosis, eosinophilia, neutropenia

Drug	Common side effects	Serious side effects
Linezolid	GI symptoms- diarrhea, nausea, vomiting, reversible tongue discoloration, candida infection	Reversible thrombocytopenia, neutropenia and anemia on prolonged use, peripheral neuropathy, optic neuritis and visual loss. Serotonin syndrome in patients on SSRI, lactic acidosis on prolonged use
Aminoglycosides	Allergic reactions and rashes are very rare	Nephrotoxicity - non oliguric renal failure, ototoxicity - can occur in 10% of patients, neuromuscular blockade - curare like effect and reversible paralysis
Erythromycin	GI symptoms - nausea, vomiting, diarrhea, abdominal cramps, skin rash, inducible clindamycin resistance	Erythromycin estolate can cause cholestatic hepatitis, conduction abnormalities, reversible hearing loss
Azithromycin Clarithromycin	Nausea, vomiting, diarrhea, abdominal cramps, headache, dizziness, IV azithromycin - pain at injection site	Transient increase in transaminases, QT interval prolongation – especially if given with other drugs which prolong QT, clarithromycin can produce mania
Quinolones	Well tolerated, mild GI symptoms – nausea, vomiting, diarrhea, abdominal cramps, headache, dizziness, sleep disorders, rash and allergic reactions, photosensitivity, drug fever. Nalidixic acid - increased intracranial pressure	Cartilage toxicity, arthropathy, tendonitis and tendon rupture *C. difficile* infection, hallucination, delirium, seizures - due to action on GABA and NMDA receptors QT prolongation, serum sickness, anaphylactoid reactions, hypoglycemia and hyperglycemia in diabetic patients, hemolysis in G6PD deficiency, leukopenia, eosinophilia
Glycopeptides Vancomycin and Teicoplanin	Vancomycin can produce red man syndrome when rapidly infused, drug fever, rash, thrombophlebitis	Nephrotoxicity - vancomycin is more nephrotoxic than teicoplanin, ototoxicity - tinnitus, vertigo, deafness, thrombocytopenia, neutropenia, eosinophilia, abnormal liver function tests
Daptomycin	Nausea, constipation, injection site reactions	Elevated CPK, rhabdomyolysis, acute eosinophilic pneumonia, acute interstitial nephritis, elevation of transaminases

Drug	Common side effects	Serious side effects
Tigecycline	Nausea, vomiting, permanent discoloration of teeth in children below 8 years	Thrombocytopenia, anemia, hyperbilirubinemia, transaminitis, hypoproteinemia, prolongation of PT and aPTT, pancreatitis, photo sensitivity, pseudo tumor cerebri Hepatic failure can occur rarely
Minocycline	Nausea, vomiting, injection site reactions, permanent discoloration of teeth in children below 8 years	Thrombocytopenia, anemia, hyperbilirubinemia,transaminitis, nephrotoxicity,pancreatitis, photo sensitivity, pseudo tumor cerebri, tinnitus, decreased hearing, teratogenic- avoid in pregnancy
Colistin and polymyxin B	GI disturbances Aerolsolized colistin: sore throat, cough, bronchospasm, chest tightness, bronchodilators before colistin nebulization may be beneficial.	Nephrotoxicity: hematuria, oliguria, proteinuria and acute renal failure Neurotoxicity: dizziness, weakness, paresthesia, vertigo, visual disturbances, rarely neuromuscular blockade can lead to respiratory paralysis,ototoxicity, hypersensitivity reactions
Fosfomycin	GI symptoms, injection site reactions	Headache, dizziness, weakness, back pain, vaginitis, alteration in liver enzyme, hypokalemia, hypernatremia, hypertension, heart failure
Cotrimoxazole	Nausea, vomiting, epigastric pain, crystalluria	Hematuria, anuria, hypersensitivity reactions, hepatitis, hemolysis in G6PD deficiency, neutropenia, can displace bilirubin from albumin and precipitate kernicterus in preterm newborns
Metronidazole	Metallic taste, anorexia, nausea, abdominal cramps, headache, glossitis, dryness of mouth, dizziness, urine discoloration, thrombophlebitis, rash	Chest pain, palpitations, rarely acute pancreatitis, mutagenic and carcinogenic in laboratory animals
Amphotericin B	Infusion related reactions - headache, myalgia, dyspnea, tachypnea	Nephrotoxicity, increase in urea, creatinine, loss of concentrating capacity of tubules leading to hyponatremia, hypokalemia, hypomagnesemia, anemia, elevated liver enzymes
Fluconazole	Gastrointestinal disturbances, headache	Transient transaminitis, skin rash, liver failure very rarely reported
Itraconazole	Gastrointestinal disturbances, hypertriglyceridemia, hypokalemia	Elevated liver enzymes, rash, pruritus

Table V. Strategies to prevent/limit side effects of antibiotics

Side effect	Preventive strategies
Drug resistance	Follow rational antibiotic prescribing practices Avoid unnecessary/ just-in- case antibiotics Prescribe right drug, at right time, for the right patient for right duration Follow guidelines and local antibiogram. Follow Access, Watch, Reserve (AWaRe) antibiotic groups (WHO 2019 AWaRe Classification Antibiotics. WHO/EMP/IAU/ 2009.11) Send cultures before starting antibiotics in presumed bacterial infections De-escalate after 48-72 hours Limit duration and spectrum of drugs used for surgical prophylaxis
Drug hypersensitivity	Elicit proper history of prior antibiotics use and history suggestive of drug hypersensitivity. Avoid drugs with history of reliable drug reaction
Drug – drug interactions	Avoid combinations of drugs that interact and potentiate each other's toxicity. Combination of clarithromycin with terbenafine, pimozide, astemazole to be avoided, as clarithromycin increases the blood level of these drugs and all these drugs can independently prolong QTc. Avoid combination of linezolid with selective serotonin reuptake inhibitors (SSRIs) like fluoxetine and adrenergic drugs
Nephrotoxicity	Avoid combining drugs with potential for nephrotoxicity. Aminoglycosides to be avoided in volume depleted conditions. Single daily dose decreases nephrotoxicity of aminoglycosides
Drug induced liver injury	Clinical and lab monitoring of patients on hepatotoxic drugs like ATT. Stopping all hepatotoxic drugs if DILI occurs. Reintroduce drugs (ATT) one by one once LFT normalizes. Avoid offending drug if LFT worsens
Other systemic toxicity	Clinicians to be aware of the toxicity of the antibiotics. Monitor (clinical and lab) for early features of systemic toxicity and discontinue drugs. Systemic toxicity is more frequent with longer duration of treatment. Avoid combining drugs with similar systemic toxicity
Redman syndrome	Vancomycin to be given as a slow infusion over one hour
Antibiotic induced diarrhea	Use of probiotics in otherwise healthy children when on antibiotics *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii* are examples Be on the lookout for *C. difficile* diarrhea. Start treatment if suspected
Rash in IMN	Avoid ampicillin and amoxicillin in suspected cases of IMN
Hemolysis in G6PD deficiency	Avoid oxidant drugs like chloroquine, primaquine, cotrimoxazole, dapsone, nitrofurantoin etc. in patients with G6PD deficiency
Vitamin K deficiency	Supplement vitamin K weekly for all patients on prolonged antibiotic treatment
Tubular dysfunction due to amphotericin B	Monitor for dehydration. Check serum electrolytes level, especially serum Na, K and Mg. Supplement if needed. Spironolactone may prevent amphotericin induced hypokalemia
Bronchospasm due to Colistin nebulization	Salbutamol nebulization prior to colistin nebulization
INH neurotoxicity	Pyridoxine 10 mg/day to be prescribed with INH

IMN (infectious mononucleosis) INH (isoniazid) DILI (drug induced liver injury)

Suppression of the vitamin producing normal gut microbiota can lead to vitamin K deficiency, leading to increase in prothrombin time and bleeding tendency. Change in the metabolic functions of the microbiota can affect digestion and alter the efficiency of nutrient extraction from food.[19]

The changes in the gut microbiota or intestinal dysbiosis is a pro-inflammatory condition which can persist for a long duration. The persistence of inflammation can modulate the immune function and can lead to immunologically mediated diseases in later life. Use of antimicrobials during childhood is associated with increased risk of asthma, allergy, type 1 diabetes mellitus and inflammatory bowel diseases.[19] Persistence of inflammation is also associated with development of metabolic syndrome and obesity.[18,19] Gut microbiota also has influence on development of central nervous system, which can have lasting effects on neurocognitive functions. Studies have shown that prevalence of attention deficit hyperactivity disorder (ADHD) and depression is higher in children who were exposed to antibiotics during infancy.[20]

Drug resistance which affects the community

Use of antibiotics is the most important factor responsible for the development of antibiotic resistance. Exposure to antibiotics favors elevated and long term expression of antibiotic resistance genes in the bacteria.[18] The development of resistance by an organism (which was originally sensitive) after exposure to an antimicrobial agent is known as acquired resistance.

The bacteria can acquire resistance through mutation and gene transfer. Mutation is a stable and heritable genetic change that occur in an organism. Gene transfer is the process of acquisition of genetic materials containing resistance genes through the process of conjugation, transduction or transformation. Even though mutation and gene transfer are not induced by exposure to antimicrobials, antimicrobials can exert selection pressure and favor the growth of the drug resistant bacteria. The following are the resistance mechanisms of the bacteria.

Drug tolerance: Bacteria can acquire drug tolerance through alteration in the binding site for the drug (e.g. alteration in penicillin binding protein of *S. pneumoniae*) or acquiring alternate pathways for metabolism.

Drug impermeability: Many antibiotics gain entry into the organism through specific channels in the cell wall, formed by proteins called 'porins'. Some will need specific transport mechanisms. Bacteria can lose these channels and transport mechanisms, thus decreasing the drug concentration inside the cells, e.g. penicillin resistant *gonococci*, chloroquine resistant *P. falciparum.*

Drug efflux: Some bacteria have inducible efflux proteins in their cell wall, which will actively pump out the drug. e.g. erythromycin and fluoroquinolone resistance.

Drug inactivation: Some resistant bacteria produce enzymes which inactivate the drug e.g. beta lactamase produced by staphylococcus and gram negative bacilli, chloramphenicol acetyl transferase produced by *H. influenza* and *S. typhi*.

Cross resistance: Acquisition of resistance to one antimicrobial can confer resistance to another antimicrobial, to which the organism was not exposed, e.g. resistance to erythromycin, can confer resistance to clindamycin.

Antibiotics have also shown to increase the transmissibility of organism and facilitate carrier state.[21] Beta lactam antibiotics can increase the alpha-toxin production by *Staphylococcus aureus* and hence enhance its virulence.

Hospitals act as ideal environment for spread of organisms, as there is a constant exchange of organisms between patients and staff.[21] The antibiotic susceptible organisms on the patient's body will be replaced by the resistant organisms, soon after hospitalization. Antibiotic administration exerts further pressure, selecting the growth of hospital organisms, which may be resistant to multiple antibiotics.

Table IV shows the adverse effects of commonly used antibiotics.

Strategies to prevent or limit the side effects: Even though the side effects of antibiotics cannot be completely avoided, it can be prevented / decreased in majority of cases, if the clinician considers patient characteristics also while prescribing the antibiotics. When prescribing antibiotics with predictable toxicity, measures have to be taken for preventing these by monitoring for side effects (clinical and lab), restricting the duration or giving antidotes, e.g. pyridoxine with INH, folinic acid with sulfa-pyrimethamine, vitamin K with prolonged courses of antibiotics. Rational antibiotic prescription practices and antibiotic stewardship programs are the only measures to curtail the rapidly increasing menace of drug resistance. Table V shows the preventive strategies that can be taken to decrease side effects of antibiotics.

Points to Remember

- ***The side effects of antibiotics are not restricted to the person who consumed the drug, the effect also extends to the society by the development of drug resistance.***
- ***Systemic side effect can affect every organ system leading to serious consequences.***
- ***Though hypersensitivity reactions are rare, sometimes they may be life threatening.***
- ***Inappropriate use of antibiotics is the major cause for development of drug resistance which will lead to deleterious consequences in the individual and the society at large.***
- ***Antibiotics are lifesaving drugs and side effects are unavoidable. But there are strategies to prevent or limit the side effects.***
- ***Rational antibiotic prescription practices and antibiotic stewardship programs are the only measures to curtail the rapidly increasing menace of drug resistance.***

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ANTIMICROBIALS - I

ANTIMICROBIALS FOR PERINATAL AND NEONATAL INFECTIONS

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Abstract: *Antimicrobials are the most commonly used therapeutics in the neonatal intensive care units, as neonatal sepsis is the third leading cause of neonatal mortality. The signs of neonatal sepsis are non-specific and accurate diagnostic tests are not available immediately. With dynamic neonatal pharmacokinetics, attention to the dose and frequency of the antimicrobials are important. With increasing antibiotic resistance, the search for an ideal empiric antibiotic is still on. This review will include the antimicrobials most commonly used in the management of perinatal and neonatal infections.*

Keywords: *Neonatal sepsis, Management, Infection, Perinatal infection.*

Neonatal sepsis is the third leading cause of neonatal mortality, contributing to 13% of overall neonatal mortality. Antimicrobials are the most commonly used therapeutics in the neonatal intensive care units (NICU) with antibiotic exposure in 1.6% to 42.5% of live births.[1] With the triple challenge of a) non-specific signs of neonatal sepsis, b) lack of accurate, timely, low cost diagnostic tools for sepsis and c) the high morbidity and mortality associated with neonatal sepsis, up to 89% of infants admitted in the NICUs in low and middle income countries (LMICs) may be exposed to antibiotics.[2] In addition to antibiotics given directly to the neonates, perinatal antibiotic exposure includes in utero exposure to maternal intrapartum antibiotic prophylaxis, whether for group B streptococcus (GBS) colonization or concern for maternal chorioamnionitis. Antimicrobials most commonly used in the management of perinatal and neonatal infections will be discussed.

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Early and late onset neonatal sepsis

National Institute of Child Health and Human Development (NICHD) Neonatal Network defines early onset sepsis (EOS) by the onset of signs/symptoms and an associated positive culture at or before 72 hours of life. EOS occurs in utero from either a transplacental transmission or ascending bacteria following rupture of membranes. Choice of antimicrobial for empiric therapy is based on the population epidemiology of EOS, whereas definitive therapy is targeted to the specific culture and sensitivity reports. The most common organisms associated with EOS are *Streptococcus agalactiae* (GBS) and *Escherichia coli* in developed nations.

The incidence of neonatal late-onset sepsis (LOS) is inversely related to the degree of maturity. LOS is associated with the postnatal nosocomial or community environment, with the peak incidence reported to be between the 10th and 22nd day of life. The incidence of LOS has increased in parallel with the improved survival of premature infants, especially in those with very low birth weight (VLBW), indicating the role of hospitalisation and life-sustaining medical devices in the pathogenesis of neonatal LOS.[3] Epidemiological data on very low birth weight infants shows that the predominant pathogens of neonatal LOS are coagulase-negative *staphylococci* (CONS), followed by Gram-negative bacilli and fungi.

However, this distinction of pathogens between early and late onset sepsis is not seen in India. According to the Delhi Neonatal Infection Study (DeNIS) study,the most common organisms implicated in neonatal sepsis were *Acinetobacter spp*, *Klebsiella spp* and *E.coli*.[4] The pathogen mix in EOS did not differ from that of LOS. High rates of multidrug resistance were observed in *Acinetobacter spp* (Acinetobacter several species-181/222, 82%), *Klebsiella spp* (91/169, 54%) and *Escherichia coli* (52/137, 38%) isolates. Polymicrobial infections were rare.[5] In Low and Low Middle Income Countries (LMICs), in addition to *Coagulase-negative staphylococci* (CoNS), *E coli, Klebsiella, Candida, Enterococcus, Pseudomonas* are important etiological agents.

Choice of antibiotics in neonatal sepsis

The blood culture is the gold standard for diagnosis of neonatal sepsis and guides the choice of antibiotics. Although it is preferable to obtain cultures before the initiation of antimicrobial therapy to optimise recovery of organisms, antimicrobial therapy administration should not be unduly delayed for specimen collection in severely ill neonates in septic shock. In neonates, sepsis is a potentially life-threatening clinical emergency that demands prompt diagnosis and treatment. Hence, empiric antibiotic therapy should be provided to neonates with suspected sepsis. The selection of empiric antibiotic therapy should be based on the unit-specific antibiotic policy. Empiric antibiotic treatment varies between NICUs and countries and there are currently no consensus guidelines on the choice of empiric antibiotics.[6]

Empiric treatment for sepsis involves the administration of broad-spectrum antibiotics with the goal of covering the most likely causative pathogens, until culture results are available. Traditionally, a combination of a B-lactam aminopenicillin such as ampicillin or amoxicillin and an aminoglycoside is used, most commonly ampicillin and gentamicin.[7] This combination provides adequate coverage for most common Gram-positive pathogens including GBS, *Streptococcus viridans*, *Enterococcus* spp and *Listeria monocytogenes*, as well as *E coli* and other Gram-negative bacteria. The range of organisms causing LOS includes Gram positive and Gram negative bacteria as well as fungi. As bacterial infections predominate, empiric antibiotic regimens focus on cover for both Gram positive and Gram negative bacterial infection. An ideal choice of antimicrobial agents is one that covers the most common pathogens without providing selection pressure for antibiotic resistance.[8] The World Health Organization (WHO) has recommended a relatively narrow spectrum β lactam (e.g. amoxicillin, benzylpenicillin, or if at risk of staphylococcal infections, cloxacillin) in combination with gentamicin as first line empirical treatment of neonatal sepsis with cefotaxime/ceftriaxone as second line.[9] An open-label, cluster-randomized trial among 283 neonates with suspected EOS, compared regimens of gentamicin combined with either ampicillin or penicillin and found no difference in treatment failure.[10] A combination of antibiotics might have the advantages of synergistic effect, broadening the spectrum of antibiotic coverage and suppressing the development of antibiotic resistance in subpopulations of microbes.

However, there has been an increased use of alternative protocols using a cephalosporin (most commonly cefotaxime) or a glycopeptide (most commonly vancomycin) as a first line option to treat especially late onset sepsis, due to increased resistance among the most common pathogen such as coagulase-negative staphylococci.[11,12] Guidelines may differ due to local antibiotic resistance of the most common pathogens or whether the empirical regimen is supposed to cover the common but low virulence coagulase-negative staphylococci for LOS.[13] Vancomycin is often considered if staphylococcal infection is suspected.[14] Third-generation or fourth-generation cephalosporin drugs are reserved for suspected Gram-negative meningitis.[6] Infections due to extended-spectrum β-lactamase producing Gram-negative bacilli require treatment with carbapenems, such as meropenem. The recent Cochrane meta-analysis on antibiotic regimen for early and late onset sepsis could not choose one antibiotic regimen being more superior to another.[15,16]

Choosing empiric antibiotics

Blood culture is the gold standard. But even with advances in technique, it takes 36 to 72 hours. Hence, it is imperative to start antibiotic treatment empirically. The choice of empiric antibiotics should be ideally unit specific. Each NICU should formulate its own antibiotic policy based on i) type of pathogen , ii) antibiotic sensitivity pattern - antibiogram data and iii) suspected site of infection - meninges, bones, heart

Type of pathogen: In India, the common pathogens causing both early and late onset neonatal sepsis are Klebsiella, *E coli*, Acinetobacter, Staphylococci and coagulase negative Staphylococci. In addition to this knowledge, each NICU must maintain local data on the common organisms cultured from infants in their NICU. The first line empiric antibiotics must cover these common organisms.

The antibiotic sensitivity pattern*:* The antibiotic sensitivity pattern of the common organisms over the past 6 months to 12 months must be noted. The empiric first line antibiotics must have at least 60-70% coverage for the three most commonly isolated organisms from the unit. The first line antibiotic must be of narrow spectrum. It is usually combined with an aminoglycoside for its synergistic effect. Avoid using a third generation cephalosporin as the first line of empiric therapy. Antibiotics that do not promote antibiotic resistance such as piperacillin tazobactum are preferred. Considering that 83-94% of infants treated with antibiotics have negative cultures in recent times, single drug amikacin has been used in NICU to reduce the antibiotic exposure.[17] Empiric monotherapy with amikacin did not result in higher incidence of treatment failure in neonates at risk for EOS as compared with piperacillin-tazobactum.[17]

The second line of empiric therapy must include antibiotics that cover 80% of the isolated organisms from the NICU. Common second line therapies are piperacillin-tazobactum and vancomycin, cefoperazone - sulbactam and vancomycin. Carbapenems such as meropenem should be reserved for culture positive sepsis. However, meropenem does not cover methicillin resistant staphylococcus aureus (MRSA) and vancomycin can be part of the second line empiric therapy if the incidence of MRSA in the unit is high.

Suspected site of infection

a. Meningitis: If there is a suspicion of meningitis, use antibiotics that cover the common pathogens such as Klebsiella and *E coli* and also that have good penetration into the central nervous system. Cefotaxime is a good choice but ampicillin should be added if there is suspicion of Listeria. Culture positive meningitis especially if complicated may warrant the use of meropenem. All antibiotics should be given in meningitic doses.

b. Bone and joint infections: The empiric choice for bone and joint infections should cover staphylococcus and Gram negative organisms. Cloxacillin with aminoglycoside is a good choice. If MRSA is suspected, clindamycin or vancomycin should be considered. Linezolid can be an alternative and has the advantage of easy switch to oral route. The duration of therapy for bone and joint infection is prolonged.

c. Urinary tract infections: A combination of ampicillin and aminoglycoside covers the most common organism i.e. *E coli.*

Duration of treatment

The duration of treatment depends on culture positivity and site of the infection. In addition, resolution of symptoms is needed for discontinuation of treatment (Table I).

Table I. Duration of antibiotic therapy

Duration of antibiotic therapy	
Culture negative sepsis	
Suspect sepsis	48-72 hours
Probable sepsis	5-7 days
Culture positive sepsis	
No meningitis	10-14 days
Meningitis	21 days
Bone or joint infection	6 weeks

Route of antibiotic administration

When bacterial infection is probable or proven, parenteral antibiotics are usually the first choice. Occasionally, when problems with intravenous (IV) access occur, or when hospital referral is not possible, as in low-and-middle-income countries (LMICs), newborns are treated with oral antibiotics.[18] While oral administration is not usually considered at present in neonates, several pharmacological and efficacy studies have been performed with different types of antibiotics. In general, adequate serum levels according to the MICs of relevant pathogens, can be achieved after oral administration in neonates. The efficacy studies showed equal relapse rates and good tolerance of oral therapy compared with IV therapy without reporting an increase in side effects. Moreover, in two studies, oral administration led to a shorter stay in hospital and also higher number of exclusively breastfed infants. In LMICs, mortality rates have decreased through the introduction of home-based therapy when referral is not possible and simplified antibiotic regimens with an oral switch have shown efficacy similar to that of standard intramuscular (IM) therapy.[18] Early switch to oral antibiotics after a short course of IV antibiotics could be promising in term neonates with a probable bacterial infection. The common antibiotics used in the neonatal period are given in Table II.

Antibiotic choice when hospitalization is not possible

Antibiotics are routinely prescribed as inpatient therapy. However, hospitalization is not always feasible. A meta-analysis of five large studies of community based antibiotic delivery in LMICs for neonatal potentially serious bacterial infection (PSBI) in Africa and Asia, including 125,134 infants has shown that the neonatal mortality is reduced (typical risk ratio RR 0 .82; 95% confidence interval 0.68 to 0.99). A combination of oral amoxicillin (7 days) and injectable gentamicin (2-5 days) did not increase mortality when compared to the standard treatment of using only injectable antibiotics.[19,20]

Adverse effects

A 2017 systematic review examined serious adverse outcomes such as necrotizing enterocolitis (NEC), invasive fungal infections (IFI) and death in the neonatal period associated with antibiotic exposure early in life.[21] It showed prolonged duration of antibiotic exposure in uninfected preterm infants is associated with an increased risk of developing NEC later in the neonatal period. Previous exposure to third-generation cephalosporins or

Table II. Common antibiotics used in NICU

Name	Category	Mode of action	Organisms covered by the antibiotic	Dose (for term neonates)	Adverse effects
Ampicillin	Amino-penicillin	Inhibit penicillin binding proteins (PBPs)	*Strep. viridans*, *Enterococci*, *ListeriaPneumococci*, G*onococci*, *Meningococci.*	25-50 mg/kg/dose	Diarrhea, rash, elevations of serum aminotransferase and creatinine, mild eosinophilia
Penicillin G	Beta lactam	Inhibit penicillin binding proteins (PBPs)	*Primarily Gram-positive bacteria, Streptococci (except viridans*, group D or *Enterococci)* are highly sensitive	50,000 units/kg	Local irritancy and direct toxicity, hypersensitivity
Piperacillin	Ureidopenicillin	Inhibit penicillin binding proteins (PBPs)	*Pseudomonas, Klebsiella*, many *Enterobacteriaceae* and some *Bacteroides*	50-100 mg/kg	Diarrhea, local reaction, abscess, infection, bloody diarrhea, pharyngitis, constipation and elevated liver enzyme
Gentamicin*	Aminoglycoside	Binds to the bacterial 30s ribosomal subunit and inhibit bacterial protein synthesis	Gram-negative bacilli, including *E. coli, Klebsiellapneumoniae, Enterobacter, H. influenzae, Proteus,Serratia* and *Pseudomonas aeruginosa*	4 mg/kg	Ototoxicity, nephrotoxicity
Amikacin*	Aminoglycoside	Binds to the bacterial 30s ribosomal subunit and inhibit bacterial protein synthesis	Wide spectrum of activity, including many organisms resistant to other aminoglycosides however, relatively higher doses are needed for *Pseudomonas, Proteus* and *S.aureus* infections.	15 mg/kg	Ototoxicity, nephrotoxicity
Cefotaxime	3rd generation cephalosporin	Binds to different PBPs thanthose which bind penicillins	Aerobic Gram-negative as well as some Gram positive bacteria, but is not active on anaerobes (particularly *Bact. fragilis*), *S. aureus* and *Pseudomonas aeruginosa*	50 mg/kg	Rash, diarrhoea moderate or transient rise in liver enzymes
Ceftazidime	3rd generation cephalosporin	Binds to different PBPs thanthose which bind penicillins	High activity against *Pseudomonas aeruginosa.* activity against *Enterobacteriaceae* is similar to that of cefotaxime	30 mg/kg	Neutropenia, thrombocytopenia, rise in plasma transaminases and blood urea
Meropenem	Carbapenem	Binds to penicillin-binding proteins (PBPs) involved in the biosynthesis of mucopeptides	Both Gram-positive and Gram negative bacteria, aerobes as well as anaerobes; somewhat more potent on Gram-negative aerobes, especially *Pseudomonas aeruginosa* but less potent on Gram-positive cocci.	20 mg/kg for meningitis 40mg/kg	Thrombophlebitis, thrombocytosis, eosinophilia and elevation of hepatic enzyme concentrations

Name	Category	Mode of action	Organisms covered by the antibiotic	Dose (for term neonates)	Adverse effects
Vancomycin	Glycopeptide	Inhibits transpeptidation by binding to D-alanyl -D-alanine residues of the bacterial cell wall.	MRSA, *Strep. viridans*, *Enterococcus* and *Cl.difficile*. Bactericidal action is exerted only on Gram-positive cocci, *Neisseria*, C*lostridia* and diphtheroids	10 mg/kg For meningitis 15 mg/kg	Concentration-dependent nerve deafness, kidney damage. Skin allergy and fall in BP during IV injection can occur

**Frequency Q 24 h; others are Q 12 h 0-7 days and Q 8 h > 7 days.*

carbapenems is associated with an increased risk of developing IFI. Prolonged duration of empirical antibiotic therapy without any proven infection is also associated with increased all-cause mortality in preterm infants.

AWaRe antibiotics

To address the rapidly emerging crisis of antimicrobial resistance, the WHO Essential Medicines List (EML) Working Group in 2017 has classified the antibiotics into three groups: Access, Watch and Reserve (Table III), collectively known as AWaRe classification with traffic light colour codes. Each country has a target of 60% of total antibiotic consumption from the access group.[22] In India, the current use of access category of antimicrobials in neonates is < 50 percent.

Potential antibiotics for multidrug resistant bacteria

With increasing multidrug resistance (95%, 80% and 60% resistance rates to amoxicillin, ceftriaxone and gentamicin, respectively) in Gram negative bacteria causing neonatal sepsis, the current WHO recommended empirical regimen needs an alternative. The Global Antibiotic Research and Development Partnership (GARDP) aims to determine a regimen for empiric management of neonatal sepsis in LMICs.[24] The criteria for the new antimicrobial selection include

i. Antimicrobial should be inexpensive to manufacture (i.e. off patent)

ii. Clinically relevant activity against multidrug-resistant bacteria, particularly Gram-negative bacteria with gentamicin resistance or extended-spectrum β-lactamases and methicillin-resistant Gram positive organisms

iii. Licensed for use in neonatal infection by a stringent regulatory authority (e.g. the European Medicines Agency); or extensive experience of use in the neonatal context where no licence exists.

iv. Limited toxicity

Five antibiotics have been identified that fulfil these criteria (Table IV). The neonatal pharmacokinetics are well characterized for most, with cefepime and flomoxef needing some additional data.

Table III. AWaRe classification of antibiotics[23]

	Category	Description	Examples
	Access	Narrow spectrum antibiotics recommended as first and second choice for most common clinical infection syndromes	Aminoglycosides - amikacin, Gentamicin Penicillins - Amoxicillin/clavulanic-acid, Ampicillin/sulbactum, First gen.cephalosporins
	Watch	Broader spectrum antibiotic classes corresponding to the highest priority agents on list of critically important antimicrobial drugs for human medicine	Aminoglycosides - netilmicin, tobramycin, Penicillins - piperacillin Macrolides - azithromycin, erythromycin Fluoroquinolones- 2nd, 3rd and 4th gen cephalosporins Meropenem Vancomycin
	Reserve	Last resort antibiotics for targeted use in multidrug-resistant infections	Aztreonam, colistin, daptomycin, linezolid, tigecycline, polymyxin, tedizolid, plazomicin

Table IV. Candidate drugs for new empiric therapy for neonatal sepsis

Characteristic	Amikacin	Tobramycin	Fosfomycin	Flomoxef	Cefepime
Category	Aminoglycoside	Aminoglycoside	Phosphoric acidic derivative	Beta lactam	4th generation cephalosporin
Molecular target	16S ribosomal subunit	16S ribosomal subunit	MurA (Fosfomycin acts by inactivating this enzyme) an essential enzyme by inactivation	Penicillin binding proteins	Penicillin binding proteins
Spectrum of activity	Gram negative bacteria including *Pseudomonas*, some activity against S*taphylococci*	Gram negative bacteria including *Pseudomonas*, some activity against S*taphylococci*	*Enterobacterales*, *Pseudomonas*, *Streptococci* and *Staphylococci*	*Enterobacterales*, *Streptococci* and *Staphylococci*	*Enterobacterales*, *Pseudomonas*, *Streptococci* and *Staphylococci*
Important efficacy gap	*Streptococci*	*Streptococci* and gentamicin resistant GN bacteria with cross reactive AMEs.	*Acinetobacter*, *Listeria*, GN bacteria with chromosomal Fos A	AmpCBeta lactamase like ESBL producing GN bacteria, *Enterococci*, *Pseudomonas*, *Acinetobacter*	*Enterococci*, anaerobes, potentially non class C ESBL producing GN bacteria
Characterization of neonatal pharmaco-kinetics	++	++	++	++	+
Significant toxicities	Dose dependent nephro toxicity, non dose dependent ototoxicity, neuromuscular blockade (rare)	Dose dependent nephro toxicity, Non dose dependent ototoxicity, neuromuscular blockade (rare)	Sodium overload, hypokalemia	Pneumonitis (rare)	Neurotoxicity (rare)
CSF: Plasma partition	0.103	Undefined	0.32	0.05	0.05-0.34

AME aminoglycoside modifying enzymes, ESBL - extended spectrum beta lactamase, GN - gram negative, PBP penicillin binding protein, ++ substantial data available, + some data available

Antifungal therapy

With increasing survival of preterm infants, fungal infections are common in the NICU. Prophylaxis with nystatin and fluconazole have been found to be useful[25] but may not be relevant in the Indian context where fungal infections with candida species inherently resistant to fluconazole are common.[26] Fluconazole is the first line of therapy for ease of administration both intravenously and orally.[27] However, amphotericin B is often indicated in resistant cases and complicated infections. Micafungin is also closely studied. Voriconazole, capsofungin are used

in cases resistant to amphotericin B. The duration of therapy must be at least one week after the blood culture is sterile (usually 14-28 days).

Antiviral therapy

Cytomegalovirus is the most common cause of congenital infection. Treatment with valganciclovir is well tolerated and improves outcome. A recent randomized controlled trial has shown that a prolonged course of 6 months compared to 6 weeks improved hearing and neurodevelopmental outcomes including better language and receptive communication.[28] Valganciclovir is well tolerated and mild neutropenia was the only significant side effect.

Neonatal herpes simplex infection is rare but devastating. Acyclovir intravenously on suspicion, PCR based rapid diagnosis and use of suppressive oral acyclovir therapy after completing the course of IV acyclovir has improved outcomes.

Nonpolio enteroviruses and parechoviruses are more frequently diagnosed with PCR based tests. These infections may mimic severe sepsis. Though the current therapy is only supportive, therapy with pleconaril has shown promising data. Further evaluation for use in neonates with suspected infections are warranted.[25]

Conclusion

Neonatal sepsis, the third leading cause of neonatal mortality globally, warrants prompt diagnosis and treatment. With increasing antibiotic resistance, the search for the ideal empiric therapy for neonatal sepsis continues.

Points to Remember

- ***Antimicrobials are the most frequently used therapeutic agents in neonates.***
- ***Empiric antibiotic therapy for neonatal sepsis should be based on local antibiograms.***
- ***Empiric therapy should be of sufficiently narrow spectrum and from the "Access category" of "WHO AWaRe antibiotics".***
- ***Antifungal and antiviral therapy are warranted in a select group of neonates.***

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CLIPPINGS

Comorbidities associated with hospitalization among adolescents with symptomatic COVID-19.

By evaluating the relationship between comorbidities and hospitalization among US adolescents 12- 17 years old with symptomatic COVID-19, the researchers aimed to identify subgroups likely to benefit from monoclonal antibody and antiviral therapy. Comorbidities assessed included obesity, chronic kidney disease, diabetes, immunosuppressive disease or treatment, sickle cell disease, heart disease, neurologic disease/neurodevelopmental disorders, and pulmonary disease (excluding patients with mild asthma). These children were part of the Pediatric COVID-19 U.S. registry, a multicenter retrospective cohort of US pediatric patients with COVID-19.

1877 patients met inclusion criteria, of whom 284 (15%) were hospitalized within 28 days of COVID-19 diagnosis. Multivariable logistic regression was used to determine race/ethnicity-adjusted associations between comorbidities and hospitalization. The following comorbidities were independently associated with increased odds of hospitalization: sickle cell disease, immunocompromising conditions, obesity, diabetes, neurologic disease and pulmonary disease (excluding mild asthma). They concluded that adolescents with acute COVID-19 and these comorbidities should be prioritized for consideration of therapy to avert hospitalization. Heart disease and chronic kidney disease were not independently associated with hospitalization.

Dubois MM, Campbell JI, Savage TJ, Lamb GS, Nakamura MM on behalf of the Pediatric COVID-19 U.S. Registry. J Pediatr. February 2022. DOI:https://doi.org/10.1016/j.jpeds.2022.02.048

ANTIMICROBIALS - I

CHOICE OF ANTI-STAPHYLOCOCCAL THERAPY

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Abstract: *Staphylococcus aureus is considered to be the most virulent amongst all staphylococci. It is known to elude antimicrobial therapy by adopting various strategies posing therapeutic dilemmas for clinicians, particularly in intensive care settings. The coagulase negative staphylococci like S. Hemolyticus, S. Saprophyticus, S. Epidermidis are relatively less pathogenic unless indwelling devices are present. When complicated or invasive S. aureus infection is suspected, blood culture and culture of sample from potential source are essential before starting empirical treatment due to the increased prevalence of methicillin resistant staphylococcus aureus. Disruption of skin, immune compromised conditions, malnutrition, burns, scabies or post varicella lesions are more prone for S. aureus infections.*

Keywords: *Staphylococcus aureus, Methicillin sensitive staphylococcus aureus, Methicillin resistant staphylococcus aureus, Coagulase negative staphylococcus.*

Staphylococcus aureus (coagulase positive) species is considered to be the most virulent amongst all species of staphylococcus. It has the ability to acquire and integrate the accessory genetic elements conferring its virulence. Apart from being responsible for many health care and community acquired infections, it is also known to elude antimicrobial therapy by adopting various strategies, posing a therapeutic dilemma for the clinician. *S. aureus* (SA) strain resistant to B-lactam antibiotics, known as methicillin resistant staphylococcus aureus (MRSA) is one such example.

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Methicillin-susceptible S. aureus (MSSA) is the isolate with an oxacillin minimum inhibitory concentration (MIC) ≤2 mcg/mL whereas methicillin-resistant S. aureus (MRSA) is the isolate with an oxacillin MIC >4 mcg/mL.

Coagulase negative staphylococci (CoNS) like *S. hemolyticus, S. saprophyticus and S. epiderdimis* are relatively less pathogenic unless indwelling devices like catheters or shunt tubes are present.

Clinical spectrum

SA with its locally invasive, tissue destructive and distal toxin producing property has a multi systemic reach to every organ or tissue in the body. Common spectrum of the clinical disorders is depicted in Table I.

In addition to this, the toxin mediated syndromes associated with SA infection are staphylococcal scalded skin syndrome (SSSS), toxic shock syndrome, staphylococcal food poisoning or even a severe sepsis syndrome.

The antibiotic of choice for treating SA infection will depend on host factors like age of the child, presence of

Table I. Disease spectrum caused by S. aureus

System	Disease spectrum
Skin and soft tissue	Impetigo, abscess, cellulitis, furuncle, necrotizing fasciitis, pyomyositis, etc.
Pulmonary	Pneumonia, empyema, lung abscess, etc.
Musculoskeletal	Osteomyelitis, septic arthritis, etc.
CNS	Meningitis, brain abscess, subdural empyema, shunt infections
CVS	Suppurative thrombophlebitis, endocarditis
Abdomen	Intra-abdominal or liver abscess
Ophthalmology /ENT	Conjunctivitis, endophthalmitis, sinusitis, otitis externa, etc.

immunodeficiency, site and severity of infection as well as the prevalence of MRSA in the community.

It is essential to draw samples of blood or samples from the source for cultures prior to antibiotics except in uncomplicated skin infections. MSSA or MRSA can cause severe disease even in immunocompetent children and staphylococci can be readily grown in liquid and solid media.[1]

Surface culture should be avoided as it reflects contamination and apart from food poisoning which results from ingestion of preformed enterotoxin, all the other infections typically begin with colonization, rates of which can vary from 25-50%.[2]

When to suspect a staphylococcal infection?

Disruption of intact skin is essential for development of staphylococcal infections. Presence of eczema, scabies, burns or a past varicella lesion, corticosteroid therapy, malnutrition, immunocompromise, prematurity and low socioeconomic strata increase the likelihood of SA infections. Similarly, a child with influenza or measles is predisposed to secondary staphylococcal infection. Immunodeficiency disorders like Chediak Higashi/Wiskott-Aldrich syndromes/ chronic granulomatous disease/HIV/ cystic fibrosis (chronic infections) can cause recurrent staphylococcal infection.

MSSA and MRSA

Historically, hospital acquired MRSA infections (HA-MRSA) included ventilator associated pneumonia, surgical site infections or blood stream infections, whereas community acquired MRSA (CA-MRSA) was associated with skin and soft tissue infections. Over the past few years the distinction between the two have become minimal. MRSA can be both hospital acquired and community acquired. However, some centres have noticed that 88% of MRSA isolates in pediatric intensive care unit (PICU) were CA.[3] Currently the risk factors like recent hospitalization/surgery, presence of devices or indwelling catheters, residence in a long-term care facility, IV drug administration, dialysis, prolonged antibiotic therapy are common for both CA-MRSA and HA-MRSA. Even MSSA has become a healthcare-associated pathogen in some settings. Unfortunately, CA-MSSA and CA-MRSA cannot be differentiated on clinical grounds.[4]

Staphylococci exert virulence through many toxins, with alpha-hemolysin[5] leading the list resulting in hemolysis of erythrocytes, release of cytokines and skin necrosis. Also important is the panton-valentine leucocidin (PVL) which acts by activation of granulocytes causing severe inflammatory reactions and should be thought of when dealing with severe skin infections as well as necrotizing pneumonia.[6,7]

For MSSA infections, B-lactam antibiotics are the drugs of choice. The first generation cephalosporins like cefazolin (parenteral) and cephalexin (oral) have better anti staphylococcal activity than the later generation cephalosporins and even preferred over vancomycin which is less bactericidal than cloxacillin in the treatment of MSSA. Even treatment failure and relapse rates with vancomycin are more in MSSA infection. But vancomycin is the preferred drug when the child has type 1 allergic reaction to betalactum (BL) antibiotics. Third generation cephalosporins, carbapenems, co amoxiclav and other beta lactam/BL inhibitor (BL/BLI) combinations also have anti MSSA activity. However, the drug of choice for MSSA meningitis is cloxacillin or flucloxacillin - 200 mg/kg/day in 4 divided doses. Cefazolin is used with good efficacy for all other sites of MSSA infection other than CNS infection. Ceftriaxone (100 mg/kg/day in 2 divided doses) may have to be used for CNS infection due to MSSA, if cloxacillin is not available.

Local prevalence of MSSA/MRSA in the region should ideally guide the initial antibiotic choice as a part of antibiotic stewardship program. When the prevalence of MRSA is >10% in the community, it is considered as high and empiric therapy for invasive staphylococcal infection should include vancomycin till the availability of the culture report.[8]

Guiding principles for choosing antibiotics

Impetigo: Uncomplicated single skin lesion beyond neonatal period should be treated with topical mupirocin thrice a day for about 7 days. Widespread impetigo or bullous impetigo should be treated with oral cephalexin/ cefadroxil in a stable child. Though co amoxiclav is effective, it is a broad-spectrum antibiotic covering even the anaerobes and Gram-negative organisms and should be avoided. If the prevalence of CA-MRSA is high in the community, empiric therapy with a B-Lactam antibiotic is inappropriate. Clindamycin or Trimethoprim-sulfamethoxazole (TMP-SMX) is a good choice in such situation.

Abscess: Small abscess can be treated only with local cleansing / incision and drainage without systemic antibiotics. If the abscess is >5 cm in size, or is associated with rapid progression to cellulitis, with systemic signs, phlebitis, difficult to drain areas like face/hand/genitalia,

any comorbidity or immunosuppression, systemic antibiotics like cefazolin/cloxacillin/flucloxacillin can be started. If MRSA prevalence is >10% in the community, IV vancomycin can be used. Clindamycin is a fairly good choice as it covers both MSSA and MRSA but a confirmatory disc diffusion D test to rule out inducible resistance by erythromycin is required.[9] If the prevalence of clindamycin resistance in the community is >15%, empiric therapy with clindamycin should be avoided. The culture report of the drained fluid/blood, will guide further management.

For necrotizing fasciitis, apart from surgical debridement a broad spectrum antibiotic like a BL/BLI combination along with anti MRSA drug like vancomycin is used. Clindamycin is added for its effect on anaerobes and anti-toxin effect. However, it is important to remember that clindamycin is a bacteriostatic drug and doesn't not cross blood-brain barrier. So, except for a non-serious SSTI infection, it is not used alone. While dealing with serious SA infection/endocarditis/CNS infections, it should always be combined with either cloxacillin /cefazolin or vancomycin.

Non-purulent cellulitis is usually due to β-hemolytic streptococci rather than *S.aureus*. If the child is severely ill with putative *S.aureus* infection or has a HA-MRSA, serious CA-MRSA infection like SSTI infection needing hospitalization, severe sepsis, necrotizing pneumonia, toxic shock syndrome or CNS infections, vancomycin is the drug of choice.[10] Fortunately in India, the prevalence of vancomycin resistant staph infection (VRSA) and vancomycin intermediate *Staph. aureus* (VISA) infection is not of major concern as of now. The disadvantages of vancomycin are infusion related complications, poor concentrations in the alveolar space and nephrotoxicity.

If the child is receiving another nephrotoxic drug or is not able to tolerate vancomycin, linezolid/ceftaroline/ daptomycin are the other choices. However, in such situations, an infectious disease expert should be consulted due to limited data on utility of these drugs in the pediatric population.[11]

Linezolid is very well tolerated, and is as effective as vancomycin in SSTI and pneumonia caused by MRSA.[12,13] Its availability as an oral preparation with almost 100% bioavailability is an advantage. However, it is a bacteriostatic drug and should not be used in endocarditis or other intravascular infections. Idiosyncratic severe thrombocytopenia and anemia could be associated with linezolid. Those requiring longer therapy of >2 weeks or on myelosuppressive therapy should be monitored with serial CBCs. Linezolid has good CSF penetration. As linezolid is one of the drugs used in MDR TB, its use as an anti-staphylococcal antibiotic should be restricted if a safer alternative is available.

Daptomycin: It has potent bactericidal activity against MRSA.[14] It is as effective as vancomycin in the treatment of complicated SSTI. However, in community acquired pneumonia, it isnot preferred as it has a propensity to bind surfactant. It is available in intravenous form only.

Tetracycline: Oral doxycycline is found very useful in the treatment of uncomplicated CA MRSA.

Tigecycline shows good in vitro susceptibility against staphylococcal infection. However, following 2010 US FDA guidelines linking increased mortality with its use, it should be avoided in *S. aureus* infections.

Aminoglycosides: It is a potent bactericidal antibiotic. When used as monotherapy, they are poorly efficacious, while in combination with either beta lactam antibiotics or vancomycin, they are found effective in the treatment of severe staphylococcal infections like endocarditis, e.g. gentamycin.

Quinupristin: Dalfopristin: It is a combination of two streptogramin antibiotics and found effective in vitro even in MRSA infections, with synergistic bactericidal activity resulting from inhibition of protein synthesis.[15] However due to limited evaluation in children, infusion site inflammation, thrombophlebitis and arthralgia, its use is extremely limited.

Teicoplanin: A glycopeptide antibiotic which is active against a wide range of gram-positive organisms. It is mostly used in the treatment of penicillin resistant, gram-positive organisms when vancomycin is not suitable e.g., MRSA, methicillin resistant coagulase negative staphylococci and enterococcus faecium. Teicoplanin is similar to vancomycin, but has a significantly longer duration of action, allowing once daily administration.

Rifampicin: A potent bactericidal and highly active against almost all SA isolates. However, it should never be used as monotherapy due to the rapid emergence of resistance. It is used in combination with TMP-SMX/clindamycin/ doxycycline for prosthesis or device related SA infections. A unique characteristic of rifampicin that makes it useful as an anti-staphylococcal agent is its ability to penetrate leukocytes and kill intracellular organisms. It should also be combined with vancomycin in patients with CSF shunt infections caused by staphylococci, especially in cases in which shunt cannot be removed.

Trimethoprim-sulfamethoxazole: Until the recent emergence of CA-MRSA, TMP-SMX was not routinely used in the treatment of SA infection though most isolates are susceptible in vitro. The release of thymidine from the injured tissue is responsible for the discordance in clinical outcome. It is found to be useful in CA-MRSA SSTI, as the efficacy as per reports is as good as clindamycin.

Ceftaroline: This is a fifth generation cephalosporin which has excellent MRSA activity as well as gram-negative spectrum similar to ceftriaxone. Currently it is approved for use in pneumonia and SSTIs, but some clinicians use it off-label in the treatment of difficult MRSA infections including persistent bacteraemia with success.

Tedizolid: Oral and parenteral oxazolidinone group antibiotic with good MSSA and MRSA activity. Used in SSTI infection for a short course of 6 days.

When to suspect SA pneumonia and how to treat?

Child less than 1 year presenting with pneumonia, presence of a foreign body or skin infection, immunosuppression, recent viral infection like influenza and measles are some of the predisposing factors for SA infection. A rapidly progressive pneumonia with severe respiratory distress in a child with fever and associated grunting is a likely clinical clue as also X-ray findings of multiple patchy infiltrates or pleural effusion/empyema, pneumatocele or spontaneous pneumothorax.

Necrotizing pneumonia can be caused by either MSSA/MRSA strain containing Panton Valentine leukocidin (PVL) gene, even in an immunocompetent child. Severe sepsis, rapid unilateral or bilateral progression and leukopenia are typical. Timely suspicion and diagnosis, empiric therapy with vancomycin and cefazolin till the availability of culture reports from pleural fluid/blood along with drainage of the fluid by appropriate method usually results in complete recovery. Adding clindamycin/linezolid which is active against MRSA is a better option while treating pneumonia complicating influenza or necrotizing pneumonia. This approach when adopted especially in the first 24 hours of admission has been shown to reduce mortality.

Staphylococcal meningitis[16-19]

The therapy of SA meningitis is challenging because of limited therapeutic options in settings of increasing antimicrobial resistance, difficulty in achieving therapeutic drug concentrations in the CSF and lack of established management guidelines.

As empiric treatment in suspected CoNS CNS infections in immune compromised patients or nosocomial/device associated infections, meropenem 120 mg/kg/day in 3 divided doses and vancomycin 60 mg/kg/day in 4 divided doses is started.

Use of steroids in SA meningitis is controversial and is not recommended.

Shunt removal is often necessary to optimize therapy. If infections are difficult to eradicate or if shunt cannot be removed, direct instillation of anti-microbial agent (vancomycin, gentamicin) is warranted.

Staphylococcal endocarditis

Infective endocarditis (IE) is life threatening inflammation of mural endocardium. It can involve endocardial surface of heart, one or more valves, or septal defects.

Diagnosis is mainly by blood cultures, 3 or more separate blood cultures drawn at least 1 hour apart. A single blood culture positive with SA should be considered significant in case of persistent fever or bacteremia or when there is a prosthesis.

On the contrary, *S. hemolyticus*, CoNS, is a common skin colonizer and blood culture contaminant. It is considered significant only when multiple blood cultures are positive especially in presence of prosthesis.

Staphylococcal scalded skin syndrome

A skin disorder primarily affecting young children, is caused by the exfoliative toxins released by SA. Child should receive intravenous antibiotic with penicillinase resistant penicillin like cefazolin or cloxacillin. Some centers do add clindamycin in the initial regime as they reduce ribosomal production of staphylococcal toxins. Taking care of the hydration status and gentle skin care is as important as antibiotics for successful outcome. The duration of treatment is generally ten to fourteen days.

Toxic shock syndrome

It is a serious rapidly progressive disorder characterized by fever, rash, multiorgan involvement and hypotension. The patient needs ICU care and draining the relevant focus as well as removal of the foreign body is as important as IV antibiotics. A regimen incorporating clindamycin or linezolid which inhibit bacterial protein synthesis is important and ensures good response if instituted in time. If the clinical response is delayed, then intravenous immunoglobulins (IVIG) are used to combat the immunological injury.

Table II. Common drugs used in S.aureus infections

Drug	Dose
Cephalexin	25-50 mg/kg/day
Cefadroxil	30 mg/kg/day
Trimethoprim-sulfamethoxazole	8-12 mg/kg/day of trimethoprim
Cloxacillin/ flucloxacillin	100-200mg/kg/day (max 12 g/day)
Cefazolin	100 mg/kg/day (max 6 g/day)
Clindamycin	20-40 mg/kg/day
Linezolid	30 mg/kg/day
Vancomycin	60 mg/kg/day
Daptomycin	6 mg/kg/dose 12 hourly
Teicoplanin	Loading-10 mg/kg/dose (max 800 mg) 12 hourly for three doses. Maintenance: 6-10 mg/kg/dose (max 400 mg) once daily.
Ceftaroline	15 mg/kg/dose 8 hourly (max 600 mg/ dose)
Doxycycline	4.4 mg/kg/day on day1(max 200 mg) and 2.2 mg/kg/day from day 2 (max 100 mg)

Table III. Duration of antibiotic therapy

Clinical condition	Antibiotic duration
Uncomplicated SSTI	5-7 days
Pneumonia	10-14 days
Necrotising pneumonia	2-3 weeks
Bacteremia	4 weeks
Meningitis	14 days
Brain abscess	4-6 weeks
Endocarditis	2-6 weeks
Osteomyelitis	6 weeks
Septic arthritis	4 -6weeks

Food poisoning caused by SA enterotoxins needs only supportive care in terms of maintenance of hydration and antibiotics do not have any role.

Vancomycin resistant staph aureus - VISA and VRSA, are uncommon and are treated with daptomycin, linezolid, telavancin, ceftaroline or quinupristin-dalfopristin.

Table II shows the commonly used antibiotics and their doses in treatment of SA infections. Duration of therapy in various situations is summarized in Table III.

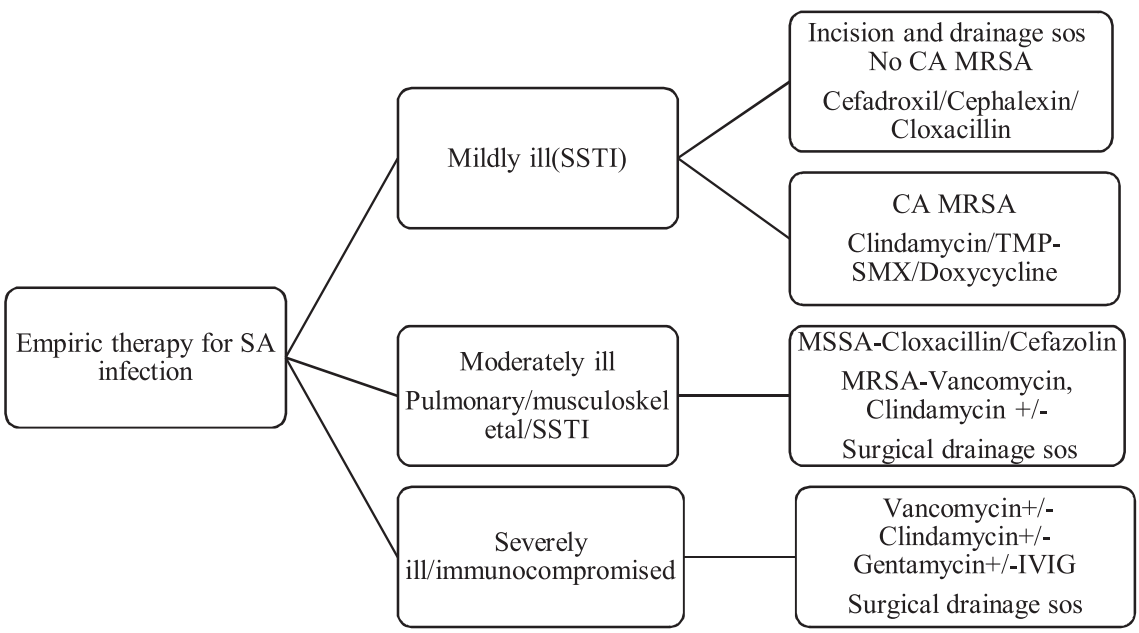

Fig.1. Empiric antibiotic therapy for *S.aureus* infection

Some newer lipoglycopeptide group of antibiotics used in SA infection are

1. Telavancin: Used mainly in complicated skin and soft tissue infection. It is administered once daily. However, it is nephrotoxic and not well studied in children.

2. Oritavancin: Active against MSSA/MRSA/VISA/VRSA strains. Because of very long half-life (393 hours), no dose adjustment is necessary in renal or hepatic insufficiency. It is not well evaluated in children.

3. Dalbavancin: Used in SSTI caused by Gram positive organisms. Works against MSSA and MRSA. It is non inferior to linezolid and vancomycin and very expensive.

Empirical antibiotics (Fig.1) should be altered as per the culture sensitivity reports.

Points to Remember

- ***Staphylococcus aureus coagulase positive is considered the most virulent amongst all gram-positive genus staphylococci.***
- ***Blood culture and sample from potential focus of infection are a must in suspected moderate/severe staphylococcal infections.***
- ***Surface cultures should be avoided as it reflects contamination rather than true infection.***
- ***MSSA is a S.aureus isolate with an oxacillin MIC ≤ 2 mcg/mL whereas MRSA is S.aureus isolate with an oxacillin MIC≥ 4 mcg/mL.***
- ***Antibiotic choice will differ while treating MSSA or MRSA infections and understanding the local prevalence of MRSA as well as inducible clindamycin resistance is essential.***

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CLIPPINGS

Repeated intravenous cardiosphere-derived cell therapy in late-stage Duchenne muscular dystrophy (HOPE-2): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial.

Cardiosphere-derived cells (CDCs) ameliorate skeletal and cardiac muscle deterioration in experimental models of Duchenne muscular dystrophy. The HOPE-2 trial examined the safety and efficacy of sequential intravenous infusions of human allogeneic CDCs in late-stage Duchenne muscular dystrophy.

In this multicentre, randomised, double-blind, placebo-controlled, phase 2 trial, patients with Duchenne muscular dystrophy, aged 10 years or older with moderate upper limb impairment, were enrolled at seven centres in the USA. Patients were randomly assigned to receive CAP-1002 (the clinical formulation of allogeneic CDCs) or placebo intravenously every 3 months for a total of four infusions. Clinicians, caregivers, patients, and clinical operations personnel were fully masked to treatment groups. The primary outcome was the change in mid-level elbow Performance of Upper Limb version 1.2 (PUL 1.2) score at 12 months, assessed in the intention-to-treat population. Safety was assessed in all individuals who received an investigational product.

Between March 1, 2018, and March 31, 2020, 26 male patients with Duchenne muscular dystrophy were enrolled, of whom eight were randomly assigned to the CAP-1002 group and 12 to the placebo group. In patients who had a post-treatment PUL 1.2 assessment (eight in the CAP-1002 group and 11 in the placebo group), the mean 12-month change from baseline in mid-level elbow PUL1.2 favoured CAP-1002 over placebo. Infusion-related hypersensitivity reactions without long-term sequelae were observed in three patients, with one patient discontinuing therapy due to a severe allergic reaction. No other major adverse reactions were noted and no deaths occurred.

CAP-1002 cell therapy appears to be safe and effective in reducing deterioration of upper limb function in patients with late-stage Duchenne muscular dystrophy. Various measures of cardiac function and structure were also improved in the CAP-1002 group compared with the placebo group. Longer-term extension studies are needed to confirm the therapeutic durability and safety of CAP-1002 beyond 12 months for the treatment of skeletal myopathy and cardiomyopathy in Duchenne muscular dystrophy.

McDonald CM, Marbán E, Hendrix S, Hogan N, Smith RR, Eagle M, et al. Repeated intravenous cardiosphere-derived cell therapy in late-stage Duchenne muscular dystrophy (HOPE-2): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2022; 399(10329): 1049-1058. doi:10.1016/S0140-6736(22)00012-5

ANTIMICROBIALS - I

ANTITUBERCULOUS THERAPY-CURRENT PRACTICE

***Gowrishankar NC**

Abstract: *Tuberculosis affects all age groups. Treatment for tuberculosis has been standardized having a 2 months intensive phase with four first line drugs followed by a 4 months continuation phase with three first line drugs given daily. Adjunctive steroids are useful in central nervous system disease and pericardial involvement. Adverse reactions to drugs, though uncommon, need to be looked for and managed appropriately. Standard regimens for treatment of resistant tuberculosis in India follow World Health Organization guideline. When there is an infectious pulmonary tuberculosis patient in the family, tuberculosis preventive treatment has to be given to all family members irrespective of age after ruling out active tuberculosis. All children after completion of treatment need to be followed up for two years.*

Keywords: *Children, Treatment, Tuberculosis, Resistant, Preventive therapy.*

Tuberculosis in children is a pauci-bacillary disease. Children of any age group can be affected. Every effort should be taken to get a microbiological diagnosis in all children suspected to have tuberculosis, though it is a difficult task. The advent and availability of cartridge based nucleic acid amplification test (CBNAAT) has made a paradigm shift, not only in making a microbiological diagnosis but also in detecting upfront, the resistance to rifampicin.

There are four different sub populations of tubercle bacilli based on the multiplication characteristics in everyone diagnosed with tuberculosis (TB). The drugs which selectively act on each sub population of organism are given in Table I.[1]

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Mechanism of action of anti-TB drugs[2]

Isonicotinic acid hydrazide (INH) acts against bacilli in active replication but not during stationary phase of growth. The enzyme catalase-peroxidase (encoded by the KatG gene) is needed to activate INH which is a pro-drug. Upon activation, it impairs the synthesis of mycolic acid. Mutations in KatG gene can lead to INH resistance.

Rifampicin inhibits gene transcription by binding with the beta subunit of RNA polymerase enzyme, thereby preventing the transcription of messenger RNA. Mutations in the rpoB gene causes modification in beta subunit of RNA leading on to rifampicin resistance.

Pyrazinamide is a prodrug. It gets converted to pyrazinoic acid (POA) in the cytoplasm of TB bacilli by enzyme pyrazinamidase / nicotinamidase which is coded by pncA gene. POA causes alteration in membrane permeability and transport, making the medium acidic, leading to cellular damage. Mutation in pncA gene causes resistance to pyrazinamide.

Ethambutol acts by inhibiting arabinosyl transferase enzyme which is involved in biosynthesis of cell wall. It is bacteriostatic against non-replicating bacilli but is bactericidal against replicating bacilli.

Bedaquiline and delamanid are the two new antituberculous drugs used in combination with other medications, in the treatment of multidrug resistant tuberculosis. Bedaquiline acts by targeting ATP synthase of TB bacilli which is essential for supply of energy to the bacilli. It is both bactericidal and sterilizing agent. As the drug is highly protein bound and extensively distributed in tissues with high volume of distribution, the drug will be present in plasma upto five and a half months after discontinuing the drug.

Delamanid is a bactericidal drug. It acts by not only blocking the synthesis of mycolic acids, but also by releasing nitric oxide when drug is metabolized, which is toxic to TB bacilli.

Combination chemotherapy[3]

The aim of combination of four drugs - INH, rifampicin, pyrazinamide and ethambutol in the treatment

Table I. Different sub-population of TB bacilli and effective drugs[1]

Sub-population	Effective drugs
Extracellular, rapidly multiplying in cavities with adequate oxygen and neutral pH	Isonicotinic acid hydrazide (INH), rifampicin, streptomycin, ethambutol
Extracellular, intermittently multiplying, growing under unfavorable conditions and low oxygen tension	Rifampicin
Extra and intracellular slowly multiplying bacilli in acidic medium especially inside macrophages	Pyrazinamide
Dormant bacilli, which are adapted to anaerobic environment and remain viable for extended period of time.	None

Table II. Anti-TB drugs

Drug and route of administration	Sub-population affected and drug charecteristics	Daily dose (range)	Max. dose (mg)	Main adverse effect
INH(H)Oral	-Extracellular rapidly multiplying bacilli -Early bactericidal activity -Prevents emergence of drug resistance to companion drugs	10 mg/kg (7-15)	300	Hepatitis, peripheral neuropathy, skin rash, sleepiness and lethargy
Rifampicin (R)Oral	-Extracellular rapidly multiplying bacilli -Extracellular semi-dormant (intermittently multiplying) bacilli -Bactericidal and sterilizing effect	15 mg/kg (10-20)	600	Hepatitis, abdominal pain, nausea, vomiting, generalised cutaneous reactions, thrombocyte- penic purpura
Pyrazinamide (Z)Oral	-Extracellular and intracellular slowly multiplying bacilli in acidic environment -Semi-dormant (intermittently multiplying) -Bactericidal and sterilizing effect	35 mg/kg (30-40)	2000	Hepatitis, arthralgia, decreased appetite, nausea, vomiting
Ethambutol (E)Oral	-Bacteriostatic -Helps to prevent emergence of drug resistance to companion drugs	20 mg/kg (15-25)	1500	Retro-bulbar neuritis
Streptomycin (S) Intramuscular	-Extracellular rapidly multiplying bacilli -Bactericidal	15 mg/kg (15-20)	1000	Allergy - severe fever,burning or tingling sensation, vertigo, blurred/double vision, hearing impairment

of TB is not only to rapidly reduce the bacillary load, but also to facilitate early bactericidal activity, sterilizing activity and prevent the emergence of drug resistant bacilli. Combination chemotherapy is effective, as different drugs act on different bacterial sub- populations. Hence, all four drugs are administered simultaneously for maximum bactericidal effect. Table II gives the first line drugs, bacillary population against which they are effective, the daily dose with range, maximum dose and adverse effects.

Drug sensitive TB – Treatment[3]

The treatment of drug sensitive TB (DS TB) has an

intensive phase (IP) of two months with four first line drugs - INH, rifampicin, pyrazinamide and ethambutol (HRZE), followed by continuation phase (CP) of four months with three first line drugs - INH, rifampicin and ethambutol (HRE). All children started on ATT must receive pyridoxine in the dose of 10 mg every day for 6 months, till ATT is completed. The aim of the intensive phase is to rapidly eliminate bacilli and reduce infectivity. The sterilizing effect of pyrazinamide helps to reduce the total duration of treatment to 6 months. During continuation phase, most of the residual bacilli are eliminated, thereby reducing treatment failure.

All new microbiologically confirmed/ clinically diagnosed pulmonary and extra-pulmonary TB and previously treated drug sensitive TB with recurrence, treatment after loss to follow up and treatment after failure are started on the standard regime of 2HRZE/4HRE.

In National TB Elimination Program (NTEP), drugs are available as fixed drug combination (FDC) in dispersible formulation. The pediatric FDC (P) has three drugs - INH, rifampicin and pyrazinamide - in the dosage of 50 mg, 75 mg and 150 mg respectively. Ethambutol (E) is available as a separate dispersible tablet in 100 mg strength. Drugs are given as per the weight of the child, classified into six weight band categories upto 39 kg. Those 40 kg and above would be managed as per the weight bands available for adults. The adult fixed dose combination [FDC (A)] has all four drugs as a single non-dispersible tablet having a composition of INH 75 mg, rifampicin 150 mg, pyrazinamide 400 mg and ethambutol 275 mg. The treatment schedule as given in NTEP is given in Table III. The total number of doses in intensive phase is 56 and during continuation phase is 112 which implies the duration of intensive phase is 56 days (8 weeks) and continuation phase is 112 (16 weeks) days respectively.

Table III. NTEP TB treatment - Weight category and FDC[3, 4]

Weight (Kg)	FDC upto 18 years
4-7	1P + 1E
8-11	2P + 2E
12-15	3P +3E
16-24	4P + 4E
25-29	3P + 3E + 1A
30-39	2P + 2E + 2 A

TB of lungs and tracheobronchial tree is classified as pulmonary, while all others are classified as extra-pulmonary TB (EPTB). If a child has both pulmonary and extra-pulmonary TB, it has to be taken as pulmonary TB only. While on ATT, clinical improvement has to be assessed at the end of intensive phase and at completion of treatment. Radiological changes sometimes may persist in spite of good clinical improvement. In extra-pulmonary TB, clinical monitoring as well as follow up imaging (USG, CT or MRI) may be needed during treatment. Gain in weight, decrease in symptoms related to the particular EPTB site and improvement in imaging findings are indicators of response to therapy. All cases have to be registered in NIKSHAY which is a web enabled application, facilitating universal access to TB patients data by all concerned and also for monitoring. It was developed jointly by the Central TB Division of the Ministry of Health and Family Welfare and National Informatics Centre and launched by the Government of India in 2012. At the end of treatment, the same has to be documented in NIKSHAY. Child needs to be followed up at 6, 12, 18 and 24 months to detect recurrence of infection after cure at the earliest.

Indications for steroids

Conditions where steroids have been found to be useful are CNS TB, tuberculous pericarditis, TB spine with cord compression, miliary TB, adrenal gland involvement due to TB, endo-bronchial or laryngeal TB with airway obstruction, pleurisy with severe distress, TB vasculitis/ aorto-arteritis, TB uveitis and immune reconstitution inflammatory syndrome (IRIS) though data to support its use are available only for CNS TB and TB pericarditis.[5] The steroid used is prednisolone in the dose of 2 mg/kg/ day in 2 divided doses for four weeks followed by tapering over 4 weeks. When child is unable to take orally, parenteral dexamethasone 0.6 mg/kg/day is given till oral intake is possible.

Management of interruptions[3]

If interruption is for less than a month, the same treatment regimen is continued to complete all the doses i.e.56 doses in intensive phase and 112 doses in continuation phase. If interruption is for more than a month, patient's sample need to be tested for drug susceptibility, to determine if the child is still drug sensitive or resistant and then treatment restarted afresh.

Management of adverse reactions

Drug induced liver injury (DILI) can occur during treatment with anti-tuberculous therapy. Isoniazid, rifampicin and pyrazinamide are the usual offending drugs.

DILI is defined by rise of serum glutamic pyruvic transaminase (SGPT) and/or serum glutamic-oxaloacetic transaminase (SGOT) five times above the upper limit of normal in the absence of symptoms or three times above upper limit of normal in presence of symptoms (nausea, vomiting, abdominal pain and jaundice) or if total serum bilirubin increases above 1.5 mg/dL. In non-severe TB, ATT needs to be stopped. Other causes for hepatitis need to be ruled out. In case of severe TB, non-hepatotoxic drugs-streptomycin and ethambutol need to be given. After liver enzymes return to baseline or within two times the upper limit of normal and symptoms resolve, ATT drugs need to be reintroduced, one drug at a time in the sequence of rifampicin, INH and then pyrazinamide taking care to monitor liver enzymes after addition of each drug once in every 3 to 7 days. Children with hypoalbuminemia and those who are on hepatotoxic co-medications have been found to be independently associated with DILI. The higher risk of hepatotoxicity with hypoalbuminemia may be due to depleted glutathione stores, which makes the child more vulnerable to oxidative injuries and disrupting hepatic drug metabolism.[6]

Itching most often occurs with INH while rash can be caused by pyrazinamide. If itching is mild, ATT may be continued with antihistamines. If rash is moderate to severe, all drugs need to be stopped. Once rash subsides, drugs are reintroduced in the following order-INH followed by rifampicin, then pyrazinamide and then ethambutol. Drugs are introduced in a small dose to reach the normal dose in three days before the next drug is added. If during ATT, pain in joints occur, it could be due to pyrazinamide. It is ideal to do uric acid levels. If uric acid levels are very high, non-steroidal anti-inflammatory drug (NSAID), colchicine can be given as allopurinol may not be effective.

Paradoxical upgrading reactions, defined as worsening of existing tuberculous lesion or development of new lesions while on appropriate anti-tuberculous medication can occur with increase in size of lymph nodes, appearance of new lesions in brain imaging, depending on the site of extra-pulmonary tuberculosis (EPTB). This has been temporally related to recovery of immune system.[7] It usually appears around 3-12 weeks after starting therapy and lasts for up to 8 weeks. It is generally self-limiting. It does not warrant discontinuation of ATT. Children can benefit from a short course of oral steroids, though guidelines for treatment with steroids are in place only for immune reconstitution inflammatory syndrome seen in immunocompromised individuals (HIV). Barr et al have found an increased risk for upgrading reaction with younger age, positive AFB in sample, lymphopenia, receipt of vitamin D supplementation at baseline and multiple sites of involvement with TB.[8]

In pregnant women, all first line drugs (HRZE) can be used except streptomycin which can cause ototoxicity to the developing fetus. In lactating women, ATT can be given, allowing the mother to breastfeed the baby, but observing cough etiquette. Baby should be given TB preventive therapy with INH for 6 months after ruling out active TB.

In those with chronic liver disease, adverse drug reaction to ATT is more common. If SGPT is more than 3 times the normal level, the regime can be either 9HRE where 2 hepatotoxic drugs are used or 2 SHE/10HE where only one hepatotoxic drug is used.[3]

In those with chronic renal insufficiency and failure, standard ATT needs to be given with modification of the frequency of certain drugs. Both INH and rifampicin are metabolized by liver, and hence no dose modification is needed. The dose and frequency of pyrazinamide and ethambutol need alteration, as both are excreted by kidneys. Pyrazinamide at a dose of 25 mg/kg and ethambutol at 15 mg/kg can be given three times a week, for those whose creatinine clearance is less than 30 ml/M^2/min and those on hemodialysis. When on hemodialysis, these drugs can be given immediately after the dialysis to avoid premature drug removal.[3]

Table IV. Types of DR TB[3]

Type	Nature
Mono-resistant TB	Resistance to any first line ATT other than R (HZE)
Poly-resistant TB	Resistance to 2 first line drugs, but not both isoniazid (H) and rifampicin (R)
Multidrug resistant TB (MDR-TB)	Resistance to at least isoniazid (H) and rifampicin(R). Rifampcin resistance-TB(RR-TB) also needs to be managed as MDR-TB
Extensively drug resistant TB (XDR-TB)	MDR-TB + Resistance to any fluoroquinolones and any second-line injectable drugs - amikacin, kanamycin and capreomycin (Am/Km/Cap)

Table V. Grouping of medicines recommended for use in longer multidrug-resistant (MDR) tuberculosis (TB) regimens[9,10]

Groups	Steps	Drugs
Group A	Include all three medicines	Levofloxacin (Lfx) OR Moxifloxacin (Mfx) Bedaquiline (Bdq), Linezolid (Lzd)
Group B	Add one or both medicines	Clofazimine (Cfz) Cycloserine (Cs) OR Terizidone (Trd)
Group C	Add to complete the regimen and when medicines from groups A and B cannot be used	Ethambutol (E) Delamanid (Dlm) Pyrazinamide, Imipenem-cilastatin (Ipm-Cln) OR Meropenem (Mpm), Amikacin (Am) OR Streptomycin (S) Ethionamide (Eto) OR Prothionamide (Pto), Para-aminosalicylic acid (PAS)

In those on antiepileptic drugs (AEDs), both INH and rifampicin can alter the metabolism of AED. The risk for seizures in those taking high dose INH can be decreased by prophylactic use of pyridoxine at a dose of 10-25 mg per day, though the optimal dose is not known.[3]

Drug resistant TB

Drug resistant tuberculosis (DR-TB) is increasing throughout the world especially in high TB burden countries like India. It can be primary or secondary DR-TB. Primary DR-TB is due to infection by DR-TB strain, while secondary DR-TB occurs during treatment of drug sensitive TB due to selection of mutant strain by suboptimal treatment. The definitions for different types of DR-TB are given in Table IV. The drugs used in DR-TB are divided into groups A, B and C (Table V) based on the efficacy, safety, experience of use and class of drug. This classification is based on the WHO consolidated guidelines for treatment of DR-TB of 2019.[9,10] Poorer outcomes when using kanamycin and capreomycin led to the non-inclusion of their use in MDR TB. While thiacetazone was not used at all, high dose INH and gatifloxacin were used in very few patients only.

MDR TB regimen - Principles[9] : While formulating treatment plan for either MDR TB/ RR TB, three drugs from group A and one drug from group B is included, so that at the time of initiation of treatment, at least four effective drugs are in place. After stopping bedaquiline, three effective drugs are given for the rest of the treatment duration. If only one or two drugs from group A can be used, both drugs from group B have to be included. Drugs from group C are added only if regimen cannot be composed with group A and B drugs.

DR-TB Treatment[3]

i) H mono/ poly DR-TB regimen(6 Lfx R E Z)

Treatment schedule for resistance to INH with or without resistance to any non-Rifampicin first line drug is six months of levofloxacin (Lfx), rifampicin(R), ethambutol(E) and pyrazinamide(Z). There is no separate intensive and continuation phase. All are given under supervision and given daily. Sunday dose alone is unsupervised. This is an all oral regimen for 6 months, which can be extended to 9-12 months in case of extensive pulmonary disease, extrapulmonary disease like bone or intracranial TB. At the time of starting treatment in this regimen, the sample is subjected to line probe assay (LPA) for second line drugs.

If resistance to levofloxacin is detected, further modification in the drugs and duration of treatment is needed. The standard duration of treatment is nine months. Once levofloxacin resistance is detected, high dose moxifloxacin (dose 400 mg max) is added in place of levofloxacin, if the LPA suggests the same. In that scenario, liquid culture drug susceptibility testing (DST) is done to detect if there is resistance to moxifloxacin and pyrazinamide too. Based on the DST, further modification can be done.

If resistance to either moxifloxacin or pyrazinamide is found, the resistant drug needs to be replaced with linezolid (Lz.). If linezolid also cannot be given, both clofazimine (Cfz) and cycloserine (Cs) needs to be given. If both moxifloxacin and pyrazinamide are found resistant, two of the three drugs - linezolid, clofazimine and cycloserine need to be given in the same order of preference.

Table VI. MDR TB- shorter regimen

Shorter MDR TB regimen	Intensive phase	Continuation phase
Pulmonary/ isolated lymph node disease/ pleural effusion (less than 6 years)	(4-6) Mfx (high dose) Km/Am Eto Cfz Z H(high dose) E	(5) Mfx(high dose) Cfz Z E

Table VII. Longer oral MDR TB regimen

All oral longer regimen	Uniphasic
Disseminated severe extra pulmonary disease	(18-20) Bdq(6) Lfx Lzd[@] Cfz Cs

[@]Linezolid dose tapered to 300 mg after the initial 6-8 months of treatment

Multidrug resistant TB- treatment[3]

There are two regimens- shorter MDR TB regimen and 'all oral' longer MDR TB regimen (Table VI and VII). All are given under supervision and given daily. The evening dose and sunday dose alone are unsupervised. The shorter regimen has an intensive phase (IP) and continuation phase (CP). The longer all oral regimen does not have a separate IP and CP. The shorter regimen duration is 9-11 months having an intensive phase of 4-6 months containing injectables followed by 5 months of continuation phase. The injectable is given six days a week. Also if the intensive phase if prolonged beyond 4 months, the injectables are given in a reduced frequency of three times a week in the extended IP. The continuation phase of shorter MDR TB is always five months only. But, while starting this regimen, test for second line injectables and fluoroquinolone resistance needs to be done and changed to individualized treatment if required.

All oral longer MDR TB regimens are used for disseminated or severe extra-pulmonary disease. There is no separate intensive phase (IP) and continuation phase (CP) (Table VII). The same regimen is also used for treatment of XDR TB patients, however for a duration of 20 months. The dose of linezolid needs to be tapered after the initial 6-8 months of treatment.

If levofloxacin cannot be used, high dose moxifloxacin can be used if the same is suggested by second line LPA. If moxifloxacin also cannot be used, then one drug from the replacement sequence of pyrazinamide, amikacin, ethionamide, para-aminosalicylic acid, ethambutol, imipenem/cilastin or meropenem need to be added. While choosing drug from the replacement sequence, drug should be chosen in the same order as given in the sequence.

If bedaquiline cannot be used, it can be replaced by delaminid. Delaminid is approved for use in children from 6 years of age. Bedaquiline or delaminid are administered for six months only. During administration of bedaquiline, systemic use of CYP3A4 inhibitors and inducers have to be avoided. These include azole antifungals if bedaquiline is used and phenytoin, carbamazepine, phenobarbital and rifamycins (rifampin, rifabutin, rifapentine) if delaminid is used.

During treatment if there is missed dose during IP, it needs to be completed before starting CP. If there are missed

Table VIII. Drugs and dosages[11, 12]

Drug	Dosage
Levofloxacin (Lf)	15-20 mg/kg/day
Rifampicin (R)	10-20 mg/kg/day
Ethambutol (E)	15-25 mg/kg/day
Pyrazinamide(Z)	30-40 mg/kg/day
INH high dose (H^h)	15-20 mg/kg/day
Delamanid (Dlm)	6-11 years: 50mg BD 12-17 years: 100mg BD
Moxifloxacin (Mfx)	10 mg/kg/day
Moxifloxacin high dose (Mfx^h)	15 mg/kg/day
Amikacin (Ak)	15–20 mg/kg once daily
Linezolid (Lzd)	<6 years : 10-12 mg/kg/day >6 years : 15 mg/kg/day
Clofazimine (Cfz)	2-5mg/kg/day
Ethionamide (Eto)	15-20 mg/kg/day
Cycloserine (Cs)	15-20 mg/kg/day

Table IX. TB preventive therapy - FDC dose

Weight in kg	Dose of HP (mg)
10-15	H 300 P 300
16-23:	H 450 P 450
24-30	H 600 P600
31-34	H 750 P 750
> 34	H 750 P 750

Table X. TB preventive therapy in contacts of DR-TB

Category	TB preventive therapy
H resistant R sensitive confirmed index pulmonary TB patients	4 months of Rifampicin: Age 10 years and older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range 10–20 mg)
Rifampicin resistant H sensitive confirmed index pulmonary TB patients	6 months of INH Age <10 years: 10 mg/kg/day (range 7-15 mg) Age 10 years and older: 5 mg/kg/day (Max dose of H -300 mg/day)
FQ sensitive confirmed index pulmonary patients	6 months of Levofloxacin (15-20 mg/kg/day)

doses during CP, this needs to be administered before ending the treatment. Table VIII gives the dosage of drugs used in DR-TB. Daily pyridoxine is given with all DR-TB regimens.

Contacts and TB preventive treatment

The risk for TB disease after infection depends on the immunological status. The risk is increased more than 25 times in contacts of bacteriologically confirmed TB patients compared to general population and 16-21 times increased risk in those with HIV co-infection. Also, if a contact of patient with active TB develops disease, 75% do so within one year of TB diagnosis of index patient and 97% within two years. In view of India's commitment to eliminate TB by 2025, new guidelines came into force in July 2021. In all household contacts of pulmonary TB patients for age less than 5 years and for those above 5 years of ag after ruling out active disease, TB preventive treatment (TPT) has to be given.

TPT recommended is six months of daily INH in the dose of 10 mg/kg/day for less than 10 years and 5mg/kg/day for those 10 years and older.[13,14] The maximum dose of INH is 300 mg/day along with 10 mg of pyridoxine. When the fixed drug combination (FDC) of INH (H) and rifapentine (P) becomes available, it is to be given weekly once for 12 weeks as an alternative to six months of INH for the age group 2 years and above. The dose of HP is based on the weight of the child (Table IX). The FDC has INH 150 mg and rifapentine 150 mg. TB preventive therapy in household contacts for INH mono-resistance, rifampicin resistance and MDR TB is given in Table X.

Conclusion

Despite the constraints, all attempts have to be made for microbiological diagnosis in every child with suspected TB. CNAAT, upfront provides information about presence or absence of rifampicin resistance which enables one to give treatment for DS-TB or do further investigations to confirm microbiologically DR-TB. While effective drugs are available for positive outcomes in all children with TB, supportive care is always needed.

Points to Remember

- ***Only one treatment schedule is recommended (2HRZE/4HRE) for all newly diagnosed TB whether microbiologically confirmed or clinically diagnosed.***
- ***Continuation phase can be extended in neurological, skeletal and disseminated TB.***
- ***Children must always be followed up for 2 years after completion of treatment for TB.***
- ***Drug resistant TB in children is to be treated with shorter or longer regimen based on extent of disease and severity.***
- ***All household contacts of adult index pulmonary TB patients have to be given TB preventive treatment after ruling out active disease, regimen being different for drug sensitive and drug resistant strains.***

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CLIPPINGS

Changes in Suicidal Ingestion Among Preadolescent Children From 2000 to 2020.

A research letter published online March 14 in *JAMA Pediatrics states that from* 2000 through 2020, there was an increase in suicidal ingestions among children, especially among preadolescent children. The researchers obtained data from the National Poison Data System for Jan. 1, 2000, through Dec. 31, 2020, to examine age specific patterns in suicidal ingestions. All cases of ingestions among patients aged 6 to 18 years were included.

The researchers found that 1,256,963 unique cases were recorded during the study period (68.0 and 32.0 percent female and male children, respectively), with a mean age of 15.3 years. Overall, there were 1,005 deaths; worse than minor clinical outcomes occurred for 28.7 percent of ingestions. During the study period, misuse or abuse ingestions remained relatively constant, although a dramatic increase was seen in suicidal ingestions. An increase in suicidal ingestions was seen for all groups older than 9 years; the change was most significant among those aged 10 to 12 years (4.5-fold increase compared with a 2.4-fold increase among adolescents).

The authors believe that this study highlights a need for better early identification of youth with mental health needs and that these findings may influence future screening guideline recommendations to extend to the preadolescent population.

Sheridan DC, Grusing S, Marshall R, Lin A, Hughes AR, Hendrickson RG, et al. Changes in Suicidal Ingestion Among Preadolescent Children From 2000 to 2020. JAMA Pediatr Published online March 14, 2022. doi:10.1001/jamapediatrics.2022.0069.

ANTIMICROBIALS - I

ANTIMALARIAL DRUG THERAPY

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Abstract: *Malaria is a major worldwide problem and a public health problem of developing countries like India. It is caused by intracellular Plasmodium protozoa transmitted to humans by the bite of female Anopheles mosquitos. Malaria is caused by four species of the genus P.vivax, P.falciparum, P.ovale, P.malariae and the fifth species P.knowlesi primarily an animal pathogen reported to cause malaria in South-East Asia especially, Borneo. The diagnosis is confirmed by identification of the organism in stained peripheral blood smear and treated by antimalarial drugs as per the situation.*

Keywords: *Plasmodium infection, Treatment, Prophylaxis, Antimalarials.*

Malaria, a vector-borne parasitic infectious disease, is a major public health burden of developing countries like India. Over the past few years, there is a declining trend in the total number of malaria cases as well as deaths due to malaria. In India, around 8.4 lakhs of confirmed cases with 194 deaths were observed in 2017.[1] Malaria is caused by four species of the genus Plasmodium namely *P.vivax, P.falciparum, P.ovale* and *P.malariae*. A fifth species *P.knowlesi*, primarily an animal pathogen, has been reported to cause malaria in human in South-East Asia, especially Borneo. In India, incidence of P. falciparum (62%) has surpassed that of *P.vivax* (37%) in the last year with a few cases of *P. ovale* reported from Orissa.[1] *P. malariae* is practically non-existent in India currently except for a few cases reported from Madhya Pradesh and Chattisgarh.[2]

The problem became far more severe when *P.falciparum* acquired resistance to first line antimalarial drug chloroquine (CQ). CQ-resistant falciparum malaria, first reported from northeastern states of India, gradually spread to other states also. Resistance to second-line antimalarial drugs sulfadoxine-pyrimethamine (SP) has also been reported from north-eastern states and some areas of West Bengal and Orissa.[3] Chloroquine is still very much efficacious against P. vivax although few cases of CQ-resistance have come into light.

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Important aspects of common antimalarials

Chloroquine

Mechanism of action: Malarial parasite utilizes host hemoglobin, which is degraded into peptides and amino acids required for its development but during this process, heme accumulates which is toxic to them. Hence they convert heme into non-toxic hemozoin crystals. Chloroquine binds to heme and prevents this process thereby killing the parasites.

Antimalarial activity: Chloroquine acts against all stages of schizonts of *P. malariae, P. ovale P. vivax,* CQ-sensitive *P. falciparum* and mature as well as immature gametocytes of *P. vivax, P. malariae, P. ovale* and immature gametocytes (Stages 1-3) of *P. falciparum*.

As hypnozoites (the dormant liver stage parasites of *P.vivax*) are not affected by chloroquine, primaquine is given in addition for radical cure.

Pharmacokinetics: CQ 250 mg tablet contains 150 mg base and 500 mg tablet contains 300 mg base. Dose is calculated based on the base. CQ has excellent oral bioavailability and reaches therapeutic concentration within 30 minutes after the first oral dosage. Due to achievement of dangerously high level after parenteral dosage in a short time causing potentially life threatening side effects, like cardiac arrhythmias, parenteral preparation are not commonly used. It is concentrated preferentially in red blood cells and more so in parasitized erythrocytes. Its elimination is slow with an elimination half-life of around 10 days (may be present upto 56 days as detected by blood level studies).

Adverse effects: Serious adverse effects are rare with usual dosage. Nausea, vomiting, transient headaches, blurred

visions etc may occur. These can be avoided by administering it after a meal. Since the drug has higher affinity for binding to melanin containing parts of skin and eyes, it can cause pruritus in dark skinned people. Antihistamines are ineffective, calamine lotion may alleviate the symptoms to some extent. Chloroquine may precipitate acute intermittent porphyria and psoriasis in susceptible patients. A rare form of retinal damage leading to irreversible visual impairment has been reported with prolonged prophylaxis.

Toxicity: Usually occurs when commercial preparation of double the prescribed dosage has been erroneously administered. Hypotension, arrhythmias, cardiovascular failure and seizures may be the presenting features. Benzodiazepines, adrenaline and mechanical ventilation may be life-saving in these cases.

Contraindications: Absolute contraindication is in persons with known hypersensitivity while epilepsy and psoriasis are relative contraindications.

Primaquine

Mechanism of action: It destroys parasite's mitochondria by competing with dihydro-orotate dehydrogenase enzyme required for pyrimidine synthesis.

Antimalarial action: It acts against all hypnozoites of *P. vivax and P. ovale* and the gametocytes of all malaria species.

Pharmacokinetics: It has good oral bioavailability and quickly reaches peak plasma concentration within 1-3 hours of administration. It is rapidly metabolized by hepatic pathway with excretion of very small amount through kidneys.

Adverse effects: Gastrointestinal adverse reactions like nausea, vomiting, abdominal cramps, anorexia etc. may occur rarely. These can be minimized by administering the drug with food. Primaquine may lead to severe hemolysis in G6PD deficient children. It can cause methemoglobinemia, leukopenia and suppression of myeloid series. Patients with borderline G6PD deficiency, 0.6-0.8 mg/Kg once weekly dose of primaquine is given for 6 weeks.

Artemisinin compounds

Mechanism of action: Artemisinin compounds contain a labile peroxide bridge in their chemical structure. Artemisinin is first activated by intra parasitic heme-iron which catalyzes the cleavage of this endoperoxide.The free radical intermediate may then kill the parasite by alkylating and poisoning one or more essential malarial protein(s). This heme mediated action explains why the drugs are selectively toxic to malaria parasites.[4]

Antimalarial activity: It is a potent and most rapidly acting schizonticidal drug acting on all stages of the parasite of all species. But it cannot destroy hypnozoites though it has considerable gametocytocidal action against all the species of *Plasmodium*. Resistance has been reported to emerge in South-East Asia and is associated with K13 mutation leading to prolonged parasitic clearance time.

Adverse effects: It is safer than other antimalarial drugs. Minor adverse effects including nausea, vomiting, abdominal pain, itching, headache, drug fever etc can occur.

Contraindication: There is no absolute contraindication for usage in children.

Quinine

Mechanism of action: Quinine prevents heme from getting converted into hemozoin and kills the parasitic cells.

Antimalarial activity: It acts against schizonts of all plasmodium species including chloroquine and anti-folate resistant strains (relatively less effective against vivax malaria) and gametocytes of all species except *P. falciparum* but does not have any hypnozoitocidal activity.

Pharmacokinetics: It has very good oral bioavailability and reaches peak plasma concentrations within 1-3 hours. It can cross blood brain and placental barrier. It is metabolized by liver followed by urinary clearance with a elimination half-life of 10-12 hours.

Adverse effects: Each 200 mg tablet is equivalent to 165 mg quinine base, each 300 mg tablet is equivalent to 248 mg quinine base. Dose is calculated based on base. Cinchonism is a symptom complex comprising of hearing difficulties, tinnitus and sometimes vertigo or dizziness which occur in a significant proportion of patients even in lower dose ranges. It is completely reversible. Serious adverse reactions are rare. Hypotension following fast intravenous infusion and slight prolongation of QT interval can occur but significant arrhythmias are extremely rare in a previously healthy heart. As hypoglycemia can occur in children, blood glucose monitoring is a must. It causes intravascular hemolysis in G6PD deficient as well as in normal patients needing switch over to artemisinin derivatives.

Toxicity: Overdosage can cause serious effects like blindness, seizures, central nervous system depression, dysrhythmias, hypotension, cardiac arrest etc.

Contraindications: It is avoided in patients with known hypersensitivity, underlying cardiac disease or ongoing use of cardiosuppressant drugs, G6PD deficiency.

Sulfadoxine-Pyrimethamine (SP)

Mechanism of action: It acts synergistically against parasitic dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) enzymes inhibiting nucleic acid synthesis.

Antimalarial activity: Though it acts on schizonts of *P. falciparum*, does not have hypnozoitocidal or gametocidal activity. Anti-folates are very weak agents against vivax malaria and hence should not to be used.

Pharmacokinetics: It is a highly protein bound drug and has a relatively long elimination half-life.

Adverse effects: It is usually well tolerated at recommended dosage. People with allergy to sulfa group of drugs may have serious hypersensitivity reactions.

Contraindications: It is contraindicated in those who have allergy to sulfa group of drugs and and in those with previous hypersensitivity to the combination.

Malaria parasite has been a notorious organism to acquire de novo mutations thus becoming resistant to antimalarial drugs. Adequate dosage and duration of antimalarial therapy is very crucial to fight malaria.[3] According to WHO, antimalarial drug combinations are now the recommended modality of treatment for *P.falciparum* infection.[5,6,7]

Artemisinin-based Combination Therapy (ACT)

Antimalarial combination therapy is simultaneous use of two or more individually effective schizonticidal drugs with separate mode of action and separate targeting of biochemical stages of the parasite. Even if the parasite acquires resistance to one drug, it gets killed by the other partner drug, thus decreasing the chances of emergence of drug resistance. WHO has recommended artemisinin and its derivatives as the cornerstone of antimalarial therapy in view of high parasiticidal action (decrease parasite load by 10,000 fold in every asexual cycle), low incidence of adverse effects, rapid elimination from blood thereby decreasing chances of developing drug-resistance by plasmodium and gametocytocidal action leading to decreased gametocyte carriage state.[3]

The following ACTs are presently used in our country:

- Artesunate (AS) + Sulfadoxine-Pyrimethamine (SP)
- Artesunate + Mefloquine (MQ)
- Artemether + Lumefantrine - This is the only form available as oral preparation and is well tolerated and effective against multidrug-resistant falciparum malaria.[8]

The slowly eliminated partner drugs (SP, MQ, lumefantrine) make the ACT regimens shorter (3 days) ensuring better adherence. In these 3 days artemisinin remain there in the system during 2 asexual parasite life cycles decreasing the parasite load by approximately a factor of one hundred million (10^8). Artemisinin derivatives have also been tried as suppositories but their effect is not predictable and thus not recommended.[9]

Treatment regimens have been decided keeping the drug resistance pattern in that particular geographic area. To combat the increasing rate of drug resistance, all falciparum cases are to be treated with ACT in government as well as in private settings. Mixed infection by *P.vivax* and *P.falciparum* infections are to be treated with ACT plus a 14-day regimen of primaquine as in vivax malaria.[3,10,11]

Recommended treatment of uncomplicated *P.vivax* malaria and *P.falciparum* malaria is given in Table I and Table II respectively.[2] Table III gives the dosage and schedule of co-formulated tablets of artemether and lumefantrine.

Table I. Treatment of uncomplicated *P.vivax* infection

		0 hour	**6** hour	**24** hour	**48** hour	Total base
CQ base PLUS	Regimen 1	10 mg/Kg	5 mg/Kg	5 mg/Kg	5 mg/Kg	25 mg/Kg
	Regimen 2	10 mg/Kg	-	10 mg/Kg	5 mg/Kg	25 mg/Kg
Primaquine	0.25 mg/Kg once daily for 14 days to prevent relapse					

Table II. Treatment of uncomplicated *Plasmodium falciparum* infection*

Regimen	Drug	Dose	Duration	
Regimen 1	Artesunate	4 mg/Kg	3 days	A single dose of primaquine (0.75 mg/Kg) for gametocytocidal action
	SP (Sulfadoxine & Pyrimethamine)	25 mg/Kg & 1.25 mg/Kg respectively	Single administration on day 1	
Regimen 2	Artesunate	4 mg/Kg	3 days	
	Mefloquine	15 mg/Kg 10 mg/kg	On day 2 On day 3	
Regimen 3	Co-formulated tablets of 20 mg Artemether plus 120 mg Lumefantrine	As per body weight	3 days	

***For North-eastern states the regimen combining artesunate with SP is not recommended. Artemether-lumefantrine is the first choice in those states with artesunate-mefloquine as an alternative regimen.*

Table III. Co-formulated tablets of artemether and lumefantrine and dose

Body weight	At diagnosis	8-12 hours	DAY 2	DAY 3
5- 14 Kg	1 tablet	1 tablet	1 tablet twice	1 tablet twice
15-24 Kg	2 tablets	2 tablets	2 tablets twice	2 tablets twice
25-34 Kg	3 tablets	3 tablets	3 tablets twice	3 tablets twice
35 Kg and above	4 tablets	4 tablets	4 tablets twice	4 tablets twice

Chloroquine is not to be given in empty stomach or at the height of temperature spikes. If patient vomits within 45 minutes of taking chloroquine, the dose is to be repeated after administering antiemetics.

Primaquine is to be given only after excluding G6PD deficiency. Patients with borderline G6PD deficiency, 0.6-0.8 mg/Kg once weekly dose of primaquine is given for 6 weeks.

Artemether-lumefantrine is not recommended for infants with weight less than 5 Kg. Lumefantrine monotherapy is never used to prevent develepment of resistance against it. Fatty foods increases oral absorption of lumefantrine.

Artesunate-mefloquine combination is not promoted by Indian health planners as not only long term safety and tolerability data regarding mefloquine at 25 mg/Kg dosage is lacking but also it has cross-resistance with another very effective and frequently administered antimalarial drug - Quinine.

Of the three regimens mentioned above, Regimen 1 is to be used in India excepting North Eastern states where Regimen 3 is indicated.. Single dose primaquine is used in the same manner in all the states.

Treatment of severe malaria[5]

Severe life threatening malaria is almost always caused by *P.falciparum.* High degree of clinical suspicion, prompt diagnosis and management are the keys to prevent fatal outcomes. It should be treated preferably in an intensive care unit, so that apart from antimalarial therapy, management of other co-existing complications and good quality of supportive and nursing care can be provided to the patient. Where delay in getting confirmatory laboratory results is anticipated, therapy should not be delayed like in cases of suspected cerebral malaria.

Table IV. Recommended treatment options for complicated and severe malaria

Quinine salt	-Loading dose: 20 mg/Kg dissolved in 10 mL normal saline/Kg by infusion over 4 hours -Maintenance dose: 10 mg/Kg every 8 hours calculated from initiation of loading dose, until patient is able to swallow oral medicine. -Subsequently quinine tablets 10 mg salt/Kg 8 hourly to complete 7 day course of therapy (parenteral plus oral). - Once patient is able to swallow, along with oral quinine one of the following drugs is to be started orally and continued for 7 days: Tetracycline (more than 8 years age) 4 mg/kg/dose 4 times daily OR Doxycycline (more than 8 years age) 3.5 mg/Kg/dose once daily OR Clindamycin 10 mg/Kg/dose twice daily
Artesunate	3 mg/Kg (for <20 Kg weight) and 2.4 mg/Kg (for ≥20 Kg) IV stat and then at 12 and 24 hours followed by once a day. Once the patient can swallow the treatment is completed by giving a course of Artemether-lumefantrine combination in North-eastern states of India as in uncomplicated falciparum malaria OR artesunate plus SP in all states other than North-eastern states of India as in uncomplicated falciparum malaria
Artemether	3.2 mg/kg (loading dose) IM, followed by 1.6 mg/Kg daily. Once patient can swallow oral medication, complete treatment by giving a course of artemether-lumefantrine combination in North-eastern states of India as in uncomplicated falciparum malaria OR artesunate plus SP combination in all states other than North-eastern states of India as in uncomplicated falciparum malaria.

Intravenous quinine or ACT is the recommended choice of therapy irrespective of chloroquine-resistance status as per the National Strategic Plan Malaria Elimination in India 2017-2022. Artemisinin derivatives due to their potential to rapidly destroy the parasite with lack of significant adverse effects (like arrhythmias seen with quinine) are gaining popularity over quinine.[12] It may be converted to oral medication when patient's clinical condition permits (Table IV). Where IV therapy is not available and delay in referral is apprehended, crushed or liquid oral preparations can be administered via nasogastric tube.

Parenteral treatment should be continued at least for 24 hours irrespective of child's ability to take oral medications.

Loading dose of quinine should not be given if patient has taken quinine, quinidine or mefloquine within last 12 hours. Alternatively, loading dose can be given as 7 mg salt/Kg IV infusion over 30 minutes, followed by 10 mg salt/Kg dissolved in 10 mL isotonic fluid/Kg by IV infusion over 24 hours. Quinine should always be given as slow infusion (infusion rate not exceeding 5 mg salt/Kg/hour). ECG and blood glucose monitoring should be done during and after quinine infusion.

Extravasated quinine (subcutaneous) can cause skin necrosis. If there is no clinical improvement after 48 hours of quinine therapy, the maintenance dose is to be reduced by one third to one half, i.e. 5-7 mg salt/Kg.

Mefloquine should be avoided in cerebral malaria due to inherent property to cause neuropsychiatric side effects.

Supportive therapy

Close monitoring of vital parameters like intake-output, heart rate, blood pressure, blood glucose, respiratory rate, oxygen saturation, level of consciousness along with good quality nursing care, proper positioning with special attention to airways, eyes, mucosa and skin is needed for unconscious child. Anticipation and correction of hypoglycemia, measures to reduce increased intracranial pressure, oxygen and respiratory supports as needed are to be given.

Salient features

- Chloroquine is not to be given in empty stomach or at the height of temperature spikes.
- If patient vomits within 45 minutes of taking chloroquine, the dose is to be repeated after administering antiemetics.

- Primaquine is to be given only after excluding G6PD deficiency.
- Artemether-lumefantrine is not recommended for infants with weight less than 5 kg.
- Lumefantrine monotherapy is never used.
- Artesunate-mefloquine combination is not recommended by Indian health planners as long term safety and tolerability data is lacking and also it has cross-resistance with quinine.
- Parenteral treatment should be continued for 24 hours irrespective of child's ability to take oral medications.
- Loading dose of quinine should not be given if patient has taken quinine, quinidine or mefloquine within last 12 hours. Alternatively, loading dose can be given as 7 mg salt/Kg IV infusion over 30 minutes, followed by 10 mg salt/Kg dissolved in 10 mL isotonic fluid/ Kg by IV infusion over 24 hours.
- Quinine should always be given as slow infusion (infusion rate not exceeding 5 mg salt/Kg/hour). ECG and blood glucose monitoring should be done during and after quinine infusion.
- Extravasated quinine (subcutaneous) can cause skin necrosis.
- If there is no clinical improvement after 48 hours of quinine therapy, the maintenance dose is to be reduced by one third to one half, i.e. 5-7 mg salt/Kg.
- Mefloquine should be avoided in cerebral malaria due to inherent property to cause neuropsychiatric side effects.

Points to Remember

- ***Treatment regimens have been decided keeping the drug resistance pattern in that particular geographic area.***
- ***For uncomplicated vivax malaria chloroquine plus primaquine is effective.***
- ***Antimalarial drug combinations are now the recommended modality of treatment for P.falciparum infection.***
- ***The following ACTs are presently use, Artesunate (AS) + Sulfadoxine-Pyrimethamine (SP), Artesunate + Mefloquine (MQ), Artemether + Lumefantrine.***
- ***Artemether + Lumefantrine is the only form available as oral preparation and is well tolerated and effective against multidrug-resistant falciparum malaria.***

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ANTIMICROBIALS - I

RATIONAL ANTIMICROBIAL THERAPY IN OFFICE PRACTICE

***Palaniraman R**

Abstract: *The most common drug prescribed by a pediatrician in office practice other than paracetamol, is an antibiotic. Ninety percent of infections seen in office practice are viral in origin. Therefore, hardly 10% of children need antibiotics. Simple, safe, first line narrow spectrum antibiotics are more than enough to treat common community acquired bacterial infections. Irrational antibiotic use may contribute to increased incidence of community acquired resistant infections, increase in complications due to partial treatment and increase in cost of treatment.*

Keywords: *Antimicrobials, Children, Outpatients, Office practice, Narrow spectrum antibiotics.*

Children with minor infections are commonly encountered in primary care settings. While many of these infections are viral, identification of the subset of patients with bacterial infections is essential for management. Such infections require judicious use of antibiotics in the outpatient setting, based on available literature evidence and review of disease-specific treatment guidelines.

Rational antibiotic therapy is not a difficult proposition. Many are apprehensive of the word rational but in simple words it is a guidance given to the care giver to give it when it is absolutely necessary, in appropriate dosage, via appropriate route and shortest duration if possible.

For a rational antibiotic prescription one has to bear in mind the following 3 issues: i) when to start ii) when not to use iii) the hazards of irrational use.

While definitive antibiotic therapy based on culture and sensitivity is ideal in a particular patient, empiric antibiotic therapy is commonly used in the outpatient setting in the following clinical situations:

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1. In clinical recognizable bacterial infections , e.g. acute suppurative otitis media, skin and soft tissue infections, acute dysentery, skin and soft tissue infections.
2. When there is a high probability of bacterial infection, waiting without antibiotics is dangerous e.g. any sick/ toxic baby, fever in immunocompromised. Appropriate investigations should be sent before starting antibiotics.
3. Suspected secondary bacterial infection in viral infection with clinical deterioration e.g. in a child with measles if fever extends beyond anticipated period of 3-5 days.

Golden rules of rational antibiotic usage

The following are useful points to remember while prescribing antibiotics. Reaching a provisional diagnosis of the clinical condition is mandatory. The most probable organism involved is suspected based on the age and site of infection.

Knowledge about the prevalent sensitivity patterns in the community is important. An appropriate antibiotic with narrow spectrum, less expensive and least side effects is chosen for therapy.

When, what, how much and how long?

All the above components should be addressed in a rational prescription. Choosing the antimicrobial regimen is based on the clinical decision, most probable bacteria involved, sensitivity pattern in the community, ease of adherence to the treatment schedule (palatability, frequency of dosing, and duration of therapy), cost, spectrum of activity of the antibiotic selected and potential side effects.

Common bacterial infections encountered and the choice of antibiotics in office practice

The common infections in office practice can be grouped into the following:

Group A

Skin and soft tissue infections, acute lymphadenitis, secondary infections following trauma, bites.

Organisms: Streptococcus, staphylococcus (anaerobes in addition for bites)

Drug of choice, mostly oral: Cefadroxil - 30 mg/kg/day, cephalexin - 50 mg/kg/day, co-amoxiclav - 40 mg/kg/day of amoxicillin component. For animal/human bites - co-amoxiclav is the drug of choice.

Duration: 5-7 days.

Group B

Common bacterial upper respiratory tract infections viz, acute otitis media (AOM), acute sinusitis and acute bacterial pharyngotonsillitis.

AOM and acute sinusitis

Common pathogens - *Streptococcus pneumoniae*, *H.influenzae* and Moraxella

Drug of choice, mostly oral route:

1st line antibiotic: Amoxycillin - 40 mg/kg/day

2nd line antibiotics:

Amoxycillin-clavulanate - 40 mg/kg/day of amoxicillin component

2nd and 3rd generation oral cephalosporins - Cefuroxime - 30 mg/kg/day, cefdinir - 15 mg/kg /day, cefpodoxime - 10 mg/kg/day

Duration: AOM <2 yrs - 10 days, >2 yrs - 5-7 days, acute sinusitis - 10-14 days or 5-7 days after symptom resolution

Acute bacterial pharyngotonsillitis

Organism - *Streptococcus pyogenes*

Drug of choice: Amoxycillin - 40 mg/kg/day for 10 days, cephalexin, cefadroxil for 10 days, macrolides in case of beta lactam allergy-azithromycin - 12 mg/kg/day for 5 days.

For outpatient management of pneumonia: According to the WHO guidelines. Dosage of amoxycillin to be doubled to 80-100 mg/kg/day. Suspected atypical pneumonias/pertussis: azithromycin10 mg/kg for 5 days.

Group C

Gut and urinary tract infections by Gram negative organisms.

Acute dysentery - Shigella, enteroinvasive *E.Coli*

UTI - *E.Coli*

Enteric fever- *Salmonella typhi* and paratyphi

Drug of choice - Cefixime - 10 mg/kg/day (dysentery and UTI), 20 mg/kg/day (typhoid)

Duration: Dysentery - 5 days, UTI and enteric fever - 14 days.

In sick children, IV Ceftriaxone is the drug of choice for all three conditions. Aminoglycosides useful only for UTI, not for the other two conditions, as shigella and salmonella are intracellular pathogens where aminoglycosides do not act.

Group D

Tropical infections which commonly includes typhoid fever, ricketsial infections, malaria and a less commonly leptospirosis.

Rickettsial infections are of two types: Indian tick typhus - spotted fever type caused by Rickettsia conori and Scrub typhus (seen in Tamil Nadu) caused by Orientia tsutsugamushi.

Drug of choice and duration

Doxycycline - 4.4 mg/kg/day in two divided doses for 5 to 7 days

Alternative: Azithromycin - 10 mg/kg/day for 5 days

Topical antibiotic therapy

Conditions and drug of choice

- **Impetigo**: Few impetiginous lesions- topical mupirocin/fucidic acid /retapamulin - 2-3 times daily for 5 days.
- **Acute bacterial conjunctivitis**: Moxifloxacin 3-5 times for 5 days. In neonatal conjunctivitis, antibiotic choice varies since organisms are different.
- **Acute otitis externa**: Ofloxacin drops - thrice daily for 5 days. In addition corticosteroid drops decreases inflammation and can help to ease the pain.

Wound care in office practice

Acute wounds usually heal without complications within 10 days and if they become infected, (approximately 5% depending on type and site) this is usually with a single microorganism which often responds to systemic antibiotic treatment. Topical antibiotic therapy is generally discouraged, to avoid contact dermatitis and development of antibiotic resistance.

Prophylactic antibiotic therapy

Antibiotics are to be given as chemoprophylaxis only in select situations in office practice as follows:

a) UTI: Cephalexin (<2months) - 10 mg/kg/day (after 2 months of age) - Co-trimoxazole (2 mg/kg/day of trimethoprim) as a single dose at night time

b) Rheumatic fever - Oral penicillin V-250 mg twice daily / long acting penicillin injection every 3 weeks.

c) Pertussis contacts - Azithromycin - 10 mg/kg/day for 5 days

d) Tuberculosis - baby of AFB positive mother: INH (10 mg/kg) for 6 months. Six months of INH chemoprophylaxis is recommended for all under-5 contacts of adult TB. The current guidelines includes >5 years as well. Dose is 10 mg/kg for < 10 years and 5 mg/kg for >10 years

e) For children with congenital heart disease before orodental procedures: Amoxycillin (50 mg/kg/day) 1 hour before the procedure.

Antibiotic resistance in office practice

ESBL producing *E.Coli* causing resistant UTI is on the rise, comprising roughly 30% of all UTIs. Hence urine for culture has to be sent before antibiotic therapy Children who are not responding to therapy in 48 hours one should consider ESBL organisms. If patient is not ill and hydration is good, once a day IV amikacin as an infusion over 60 min is a fairly good choice. Otherwise, patient needs to be hospitalized.

In case of community acquired methicillin resistant staphylococci (CA-MRSA) infections of soft tissues, clindamycin and co trimoxazole are the drugs of choice.

Prevalence of drug resistant *S. pneumoniae* is still very less in the community with respect to non-meningeal infections. One can easily treat with low dose amoxicillin 40 mg/kg/d, unlike in the west, where 90 mg/kg/day is recommended.

Hazards of irrational use of antibiotics

About 90% of fevers, colds, coughs and diarrheas seen in office practice are viral in origin, where use of antibiotics would be irrational. So also, in fever without focus. Possible reasons for misuse are: ignorance of the above given scientific facts, fear of secondary infection, false sense of security, parental anxiety and fear of losing the patient.

Such irrational use would cause: i) an increase the circulation of resistant organisms in the community ii) increase in complications due to inadequate treatment and an iii) increase in cost of treatment.

Educating the parents about these facts is important, so that they are not driven to misuse previous antibiotic prescriptions, seek pharmacists' suggestions about antibiotics for various conditions or give their children inappropriate antibiotics or incomplete dosages.

Conclusion

Antibiotic therapy in office practice has to be rational. Evidence based science complemented by self discipline among the physicians is essential to achieve this.

Points to Remember

- ***Majority of infections seen in office practice are viral. Only 10% or less are of bacterial etiology like acute otitis media, dysentery, skin and soft tissue infection etc.***
- ***In short, amoxycillin is the drug of choice for respiratory infections, cefixime for gastrointestinal and genitourinary infections, cephalosporins (1st generation) for skin and soft tissue infections and doxycyline for scrub typhus.***
- ***Antibiotic resistance in community acquired UTI and skin infections are on the rise.***
- ***Rational antibiotic therapy should be based on the available scientific evidence.***

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ANTIMICROBIALS - I

PROPHYLACTIC ANTIMICROBIALS

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Abstract: *Prophylactic use of antimicrobials is the use of an antimicrobial agent to prevent infection. The focus of this review is on everyday situations in which a general pediatrician may have to use prophylactic antimicrobials such as preventing recurrent urinary tract infections, recurrent otitis media, surgical site infections, infective endocarditis, rheumatic fever, malaria in travellers and for contacts of highly contagious diseases. Special situations like immunodeficiency disorders, post-transplant state, pediatric hemato-oncology and intensive care settings are distinct entities and have not been addressed in this article in detail.*

Keywords: *Infection, Children, Chemoprophylaxis, Antimicrobial, Prophylaxis.*

Prophylactic use of antimicrobials, also called "chemoprophylaxis", is the use of an antimicrobial agent - antibiotic, antiviral or antifungal, to prevent infection. For chemoprophylaxis, the host should have a well-defined increased risk of a disease and its use should fulfill certain criteria for antimicrobial use (Box 1).

Before initiation of prophylaxis, active infection should be ruled out. Attention should be paid to screening for mycobacterial infection before azithromycin use, due to the high risk of development of resistance. Baseline screening may be needed depending on the adverse reaction profile of the considered antibiotic, e.g. consider asking for electrocardiogram (ECG) while using agents which can cause QTc prolongation and audiological testing for ototoxic drugs.

Box 1. Chemoprophylaxis - Antimicrobial

- Must have activity against likely infectious agent
- Have acceptable risk-to-benefit ratio
- Should have adequate tissue concentrations at the time of exposure

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For several years, inappropriate use of antibiotics for infection prevention has been happening due to lack of awareness and poor understanding as in the case of infective endocarditis prevention and perioperative situations. This is a waste of resources and it contributes to antimicrobial resistance as well as adverse effects of the antimicrobial used. This article aims to review the current guidelines for the use of prophylactic antibiotics in general pediatric practice like prevention of recurrent urinary tract infections (UTI), recurrent otitis media, surgical site infections, infective endocarditis, rheumatic fever, malaria in travelers from non endemic regions and in contacts of highly contagious diseases. Special situations like post transplant state, pediatric hemato-oncology and intensive care settings have not been addressed here. The importance of non-pharmacological measures, vaccination and infection control measures should always be borne in mind as they are superior, safer and more effective in prevention of infections. The guidelines given below should be periodically reviewed in the background of emerging evidence and regional antimicrobial resistance patterns.

Recurrent urinary tract infection (UTI)

Recurrent UTI may be due to bowel bladder dysfunction, urinary tract anomalies or vesicoureteric reflux (VUR). In UTI with VUR, renal parenchymal scarring may occur and over time, cause renal dysfunction and hypertension. Continuous antibiotic use results in sterile urine so that reflux does not cause renal damage. Reflux spontaneously resolves in most cases over time.

The accepted indications for chemoprophylaxis to prevent recurrent UTI are as follows:

i) UTI below one year of age while waiting for imaging studies,

ii) All patients with high-grade reflux - Grade 3 to 5 till 5 years of age,

Box 2. Drugs used for prophylaxis in UTI

- Trimethoprim - sulfamethoxazole (TMP-SMX) 2 mg TMP/kg as a single daily dose*
- Nitrofurantoin - 1-2 mg/kg, single daily dose*
- Cephalexin - 10 mg/kg for infants < 2 months

*Not for < 2 months of age

iii) In patients with VUR < Grade 3, for those not yet toilet-trained (< 2 years) and those with bladder and bowel dysfunction (BBD) till 2 years of age,

iv) Recurrent febrile UTI (more than 2 episodes in a year) if associated with bladder and bowel dysfunction (BBD) - prophylaxis given for 6 months.[1]

The recommended antibiotics are given in Box 2.

Since antibiotics can do more harm than good, promoting resistance to available oral antibiotics, for recurrent UTI without reflux/BBD, the focus has shifted from chemoprophylaxis to early diagnosis.[2] Clinicians need to educate parents on symptoms of recurrence and urge them to seek prompt diagnosis and therapy when suspicions arise. There is no evidence that prophylaxis prevents renal scarring. Also, there is increasing evidence that recurrent UTIs do not contribute to chronic renal failure in children with no structural anomaly.[3] Antibiotics are not indicated for children with urinary tract obstruction and neurogenic bladder on clean intermittent self-catheterization.

Recurrent otitis media (OM)

Recurrent OM should be managed initially with immunization with annual influenza vaccine and pneumococcal conjugate vaccines, preventing recurrent viral respiratory infections, parent education about not feeding the child in lying down positions and avoidance of environmental risk factors (ie, smoke exposure, large group day-care). Antibiotic prophylaxis may be warranted for children with recurrent distinct and well-documented AOM (≥3 episodes in six months or ≥4 episodes in 12 months) despite these measures. Early initiation of antibiotic prophylaxis may be warranted for children who have one of the following indications (Box 3).

Antibiotic prophylaxis should be provided during the fall, winter and early spring months when respiratory infections are most prevalent, but for no longer than six months. The potential benefits (20 to 50 percent fewer episodes) must be balanced with the risk of adverse events associated with long-term antibiotic exposure and that of development of nasopharyngeal colonization with

Box 3. Indication for prophylaxis – Recurrent AOM

- Age < than 2 years
- Risk factors for recurrent AOM (e.g. first episode at age <6 months, day-care attendance, family history of recurrent AOM, a large number of siblings)
- Underlying conditions that predispose to AOM (e.g. cleft palate, immotile cilia syndrome, IgG or subclass deficiency, Down syndrome, persistent eustachian tube dysfunction)
- Developmental or language delays
- Recurrent spontaneous perforation of the tympanic membrane, which may be associated with chronic suppurative otitis media
- Severe episodes (e.g. severe ear pain, pain for ≥48 hours, temperature ≥39°C [102.2°F]

antibiotic-resistant organisms. Antibiotic prophylaxis to prevent recurrent otitis media targets the common causative organisms-*Streptococcus pneumoniae, Moraxella catarrhalis* and non-typable *H. influenza*. It should be made on a case-by-case basis.[4]

Antibiotic choice and regimen-Amoxicillin 20-40mg/kg orally once daily. The higher dose should be reserved for communities where the prevalence of penicillin-non-susceptible *S. pneumoniae* is high. Sulfisoxazole 50 mg/kg orally once per day is an alternative.

Surgical site infection

Surgical site infection is a common hospital-acquired infection usually due to *S. aureus* or coagulase negative Staphylococcus (CoNS). For prevention, injection cefazolin (30 mg/kg, maximum dose - 2 grams) is the first choice while vancomycin (15 mg/kg) and clindamycin (10 mg/kg) are acceptable alternatives. The antibiotic should be administered - within one hour before the surgical incision (within 2 hours for vancomycin / fluoroquinolones) and the entire dose should be infused before tourniquet inflation. For clean and clean-contaminated procedures, re-administration is not warranted, even when there is a drain. The infusion is repeated intraoperatively for procedures lasting >4 hours and when substantial blood loss (> 1.5 L) occurs. For surgeries in the head and neck, colon/rectum and gynecological procedures, addition of metronidazole is recommended in the dose of 15 mg/kg as a single dose.[5]

Box 4. Highest risk for IE

- Valve repair with a prosthetic valve/material
- Previous IE
- Unrepaired cyanotic CHD
- Repaired CHD with prosthetic material /device within six months
- Repaired CHD with residual defects
- Cardiac transplants

Infective endocarditis (IE)

Prevention of infective endocarditis in children with heart diseases is essential but the focus has shifted from antibiotic prophylaxis during procedures to oral hygiene and prevention of oral disease. National Institute for Health and Care Excellence (NICE) guidelines have eliminated prophylactic antibiotic drugs altogether for all patients under any circumstances.[6] The 2017 AHA guidelines recommend IE prophylaxis before high-risk procedures only, for those at the highest risk.[7] Patients considered to be at the highest risk are given in Box 4.

Dental procedures that involve manipulation of gingival tissue, periapical region of teeth or breach of the oral mucosa and invasive respiratory tract procedures that breach the respiratory mucosa (e.g. tonsillectomy, adenoidectomy) need an antibiotic active against *Streptococcus viridans.* The recommended antibiotic is amoxicillin 50 mg/kg orally 60 minutes before the procedure (single dose) max 2 g/dose. Alternative drugs include - cephalexin/cephazolin (50 mg/kg). In patients with a history of immediate-type hypersensitivity penicillin allergy, azithromycin or clarithromycin - 15 mg/kg PO (not to exceed 500 mg/dose) can be given. If the child is unable to take oral medication any of the following can be given: ampicillin 50 mg/kg IV/IM; max 2 g/dose or cefazolin or ceftriaxone 50 mg/kg IV/IM (not to exceed 1 g/dose) 30 min before procedure.

Patients who undergo a surgical procedure that involves infected respiratory, skin, soft tissue or musculoskeletal tissue should receive an agent active against both staphylococci and beta-hemolytic streptococci (e.g. anti staphylococcal penicillin, cephalosporin).

In procedures for infection with known or suspected *Staphylococcus aureus*, anti-staphylococcal penicillin or vancomycin is recommended.

Antibiotics are no longer recommended for endocarditis prophylaxis for genitourinary or gastrointestinal tract procedures.

Rheumatic fever

Chemoprophylaxis is indicated in children with a well-documented history of acute rheumatic fever (Modified Jones criteria) to prevent recurrent attacks.[8] The antibiotic of choice for prevention is benzathine penicillin in a dose of 1.2 million units IM for children weighing > 27 kg and 600,000 units for those weighing < 27 kg. Since adequate serum antibiotic levels may not persist beyond three weeks, three weekly injections are preferred in high-exposure situations rather than every four weeks. The duration of prophylaxis is individualized as follows

i) minimum 5 years or till until 21 years, whichever is later for those without carditis,

ii) minimum ten years for those with carditis without residual heart disease and

iii) lifelong (or > 40 years) for those with carditis and residual heart disease. Prophylaxis for children with rheumatic chorea is similar.

Routine prophylaxis is not recommended for other poststreptococcal sequelae like pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). The goal of treatment of scarlet fever is not only to shorten the course of the illness but also prevent acute rheumatic fever. It is important that children with scarlet fever are promptly identified and given a full course of antibiotic to prevent the development of rheumatic fever and other sequelae including PANDAS.

Malaria prevention in travelers

The Center for Disease Control, Atlanta and UK considers India a high risk zone for chloroquine resistance and recommend chemoprophylaxis with atovaquone-proguanil, mefloquine, or doxycycline.[9] All have comparable efficacy. No antimalarial drug is 100% protective and chemoprophylaxis must be combined with personal protective measures. Some drugs that need to be started 1-2 weeks before travel are not a good choice for last-minute travelers and trips of short duration, some people would rather not take medication for four weeks after travel.

Mefloquine is available as an oral tablet (250 mg) and the dose is based on the body weight as follows:

- ≤9 kg: 4.6 mg/kg base (5 mg/kg salt), weekly
- 10-19 kg: ¼ tablet weekly
- 20-30 kg: ½ tablet weekly
- 31-45 kg: ¾ tablet weekly

- > 45 kg: 1 tablet weekly
- Adults: 228 mg base (250 mg salt), weekly

Regimen to be started 1-2 weeks before travel, taken weekly during stay at endemic zone and for four weeks after leaving the country.

Atovaquone-proguanil: One adult tablet has 250 mg atovaquone/100 mg proguanil and pediatric tablet has 62.5 mg atovaquone / 25 mg proguanil. The dose is based on body weight as follows:

- 5-8 kg: ½ pediatric tablet daily
- 8-10 kg: ½ pediatric tablet daily
- 10-20 kg: 1 pediatric tablet daily
- 20-30 kg: 2 pediatric tablets daily
- 30-40 kg 3 pediatric tablets daily
- 40 kg and over: 1 adult tablet daily

It should be started two days before travel, taken daily during stay and travel and for 7 days after leaving.

Doxycycline is available as 50 and 100 mg tablets and the dose is 2.2 mg/kg/day in children more than 8 years of age. (max is adult dose). Adult dose is 100 mg daily. It should be begun 1-2 days before travel, taken daily during travel and continued for four weeks after leaving.

Chloroquine can be used for travel to areas without high chloroquine resistance. Each tablet has 300 mg base; 500 mg salt. The dose is 5 mg/kg base (8.3 mg/kg salt) once/week. Max adult dose 300 mg base (500 mg salt). It should be started 1-2 weeks before travel, taken once/week during travel and for continued for 4 weeks after leaving.

Chemoprophylaxis for tuberculosis contacts

Pulmonary tuberculosis (TB): After ruling out drug-resistant TB in the index case and active disease in the contact by a thorough history, clinical examination and appropriate investigations, chemoprophylaxis with INH 10 mg/kg/day for six months is indicated in the following situations:

- Household contacts < 5 years years of age regardless of BCG/ TST status
- All household contacts above 5 years after ruling out active TB.
- All Mantoux positive children with HIV or on immunosuppressives
- For all HIV infected children aged 1 to 5 years

If the index case has drug resistant TB, chemoprophylaxis is recommended as mentioned in the following table.[10]

Influenza: Immunization is the best way to prevent influenza and antiviral drugs should not be used as a substitute. Post-exposure chemoprophylaxis is indicated within 48 hours of exposure only for those at high risk of developing complications as listed below:

- Children <5 years, especially <2 years
- Neurologic and neurodevelopmental conditions
- Chronic lung disease (cystic fibrosis, persistent asthma)
- Blood disorders (e.g. sickle cell disease), metabolic disorders
- Congenital heart disease / kidney / liver disorders
- Immunodeficiency - HIV, AIDS, cancer, chemotherapy, steroids

Table I. Drug resistant TB - TB preventive therapy

Category	TB preventive therapy
H resistant R sensitive confirmed pulmonary index patients	4 months of rifampicin Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10-20 mg)
RR resistant H sensitive confirmed pulmonary index patients	6 months of INH Age <10 years: 10 mg/kg/day (range, 7-15 mg) Age 10 years & older: 5 mg/kg/day (Max dose of H - 300 mg/day)
FQ sensitive confirmed pulmonary index patients	6 months of levofloxacin (15-20 mg/kg/day)

- Children <19 years on long-term aspirin therapy
- Class III obesity

Oseltamivir is active against both influenza A and B. The dose is given once daily as follows:

3 mon. to 1 year - 3 mg/kg

>1 year 15 kg - 30 mg

15-23 kg - 45 mg

23-35 g- 60 mg

>35 kg - 75 mg

For unvaccinated persons - The influenza vaccine should be administered promptly and antiviral prophylaxis should be continued for two weeks following influenza vaccination. For vaccinated persons, post-exposure prophylaxis should be given for one week after the last known exposure.[11]

Meningococcal meningitis: The attack rate among close contacts is 400-fold greater than in the general population. Chemoprophylaxis should be offered to close contacts to eradicate nasopharyngeal carriage and prevent secondary cases. It is indicated for the following categories of contacts:[12]

- Those who have been living with a patient within 7 days before the disease onset, regardless of vaccination status (household members, hostel students, army)
- Those in direct contact with patient's respiratory secretions during medical procedures (mouth-to-mouth resuscitation, suctioning, and intubation) < 24 hours after antimicrobial therapy was initiated
- Those traveling in same plane, ship, bus, car for > 8 hours

One of the following regimes may be used:

- Rifampicin: 5 mg/kg (<1 month), 10 mg/kg, max 600 mg (≥1 month) PO BD for 2 days
- Ciprofloxacin: 30 mg/kg PO as a single dose; maximum dose 125 mg for <5 years, 250 mg for 5-12 years and 500 mg for ≥12 years
- Ceftriaxone - 250 mg (≥ 12 years) 125 mg (<12 years) IM as a single dose

Haemophilus influenza meningitis: The primary strategy for preventing Hib disease is immunization. However, chemoprophylaxis with rifampicin is effective in high risk exposures and is recommended in the following situations.[13]

1. Children <4 years of age who are household contacts of a case of invasive Hib disease (including children who have not received an age-appropriate number of doses of Hib conjugate vaccine OR child <12 months of age who has not completed the primary Hib series). In addition to chemoprophylaxis, the susceptible child should receive a dose of Hib conjugate vaccine and be scheduled for completion of Hib immunization
2. Household contact <18 years who is immunocompromised, regardless of that child's Hib immunization status
3. In day-care set ups where systemic Hib disease has occurred, and one or more children under 2 years old have been exposed, rifampin prophylaxis is recommended for all children and staff

Dose - 20 mg/kg per dose once daily (maximal daily dose 600 mg) for 4 days and neonates - 10 mg/kg once daily for 4 days

Diphtheria - The goal of instituting post exposure chemoprophylaxis in diphtheria is to prevent disease and reduce transmission. Close contacts (household contacts, medical personnel) should be identified and screened. After cultures have been obtained, contacts should be treated with a single dose of Penicillin G benzathine (600,000 units intramuscularly [IM] for individuals <6 years of age and 1.2 million units IM for individuals ≥6 years of age OR oral erythromycin (500 mg four times daily for 7 to 10 days.[14]

If immunizations are not up to date, diphtheria toxoid immunization should be administered.

Cholera

Antibiotic prophylaxis has been provided in the past to the contacts of people with cholera during outbreaks. However, WHO and CDC currently do not recommend chemo prophylaxis as it can have adverse effects by increasing antimicrobial resistance and provides a false sense of security.[15] The emphasis is on the prevention of transmission by ensuring access to clean water and sanitation. Oral cholera vaccines may be considered.

Sickle cell disease (SCD)

These children are at increased risk of overwhelming bacterial infections, particularly before five years of age due to poor antibody production, dysfunctional opsonophagocytosis and functional asplenia. Oral antibiotic prophylaxis should be given to all individuals with severe combined immunodeficiency

(SCID) until the age of five.[16] Penicillin V is used at a dose of 125 mg orally twice daily for children 3 months to 3 years of age and 250 mg twice daily for children >3 years until the age of five. Alternatives include amoxicillin 10 mg/kg twice daily (maximum 250 mg per dose), cephalexin 25 mg/kg twice daily (maximum 250 mg per dose) and azithromycin 5 mg/kg once daily (maximum 250 mg per dose).

The decision of whether to continue antibiotic prophylaxis after the age of five must be made on a case-by-case basis.[17] Some clinicians elect to stop prophylaxis, if the child has not had a prior severe pneumococcal infection or splenectomy and has taken the pneumococcal conjugate and polysaccharide vaccine (PPSV23). However, others will continue penicillin prophylaxis through adulthood, because of the lifelong risk including infection with serotypes not included in the vaccine. Fever is a medical emergency for a patient with SCD, regardless of whether they are taking penicillin.

Primary immunodeficiency disorders (PIDD)

There are over 400 PIDDs with a spectrum of severity and most patients with PIDD present with recurrent or chronic infections.

Specific PIDDs increase the risk of a specific type of in predictable locations.

Bacterial infections are common in cellular, complement, or antibody defects. Eg. *Neisseria*/ infections in complement deficiency and *Staphylococcus aureus*/ *Serratia marcescens*/*Burkholderia cepacia* and *Nocardia*/ infection chronic granulomatous disease (CGD) Specific risk may be elevated during particular times of year (e.g. during the winter).

Fungal infections are more common in children with CGD (*Aspergillus*) and X-linked hyper immunoglobulin M syndrome (*Pneumocystis jirovecii*/*Cryptococcus).*

Mycobacterial disease is common in children with Mendelian susceptibility to Mycobacterium, such as defects of the interferon gamma-interleukin-12 axis and nuclear factor-kappa-B essential modifier (NEMO) deficiency.

Chronic gastrointestinal infections (*Enterovirus, Giardia*/*C. jejuni* or *Salmonella*) occur in patients with common variable immunodeficiency (CVID), antibody deficiency disorders and T cell deficiencies. Prolonged infections with gastrointestinal pathogens such as *Norovirus* or *Cryptosporidium* can also cause chronic diarrhea and wasting.

Severe and recurrent viral infections (*Cytomegalovirus, Epstein-Barr, Varicella-zoster*) are found in children with defects in T cells, natural killer cells, or innate pathogen signaling. Adenovirus infection, recurrent mucosal or skin disease due to herpes simplex virus 1 and 2 and *human papillomavirus* virus (HPV) can also occur.

Management: Immunologic reconstitution may be possible in several types of PIDD in the form of hematopoietic cell transplantation (HCT), enzyme replacement, thymic transplantation, or gene therapies. Preventing initial infections is critical in severe forms of PIDD. There is no standardized approach or consensus guidelines on the use of prophylactic antimicrobials in patients with immunodeficiency and the use needs to be decided on a case by case basis.[18]

The antimicrobials commonly used for chemoprophylaxis are listed below

Antibacterial prophylaxis- TMP-SMX - 5 mg/kg/day of TMP (maximum of 320 mg) orally in two divided daily doses) lifelong. Several centers use once-daily dosing to enhance treatment adherence. Alternatives for patients allergic to sulfonamide drugs include trimethoprim without sulfamethoxazole, beta-lactamase-stable penicillins (e.g., Cloxacillin), cephalosporins, or fluoroquinolones.

Antifungal prophylaxis- Itraconazole 5 mg/kg oral once daily, maximum dose 200 mg. Itraconazole-resistant fungal infections do occur, but most have been responsive to/ voriconazole/or/posaconazole.

SCID: Prior to definitive therapy (hematopoietic stem cell transplant or gene therapy) patients with SCID should receive antibacterial, antiviral/and/or/antifungal prophylaxis.

Chronic granulomatous disease (CGD):The cornerstones of CGD management are lifelong antibacterial and antifungal prophylaxis and early diagnosis and aggressive management of infectious complications.

Immunomodulatory therapy with interferon gamma (IFN-gamma)- (50 mcg/m^2/subcutaneously three times per week) as part of the prophylactic therapy for CGD, especially for those who have had more severe recurrent infections. For children less than 0.5 m^2, 1.5 mcg/kg subcutaneously three times weekly is the suggested dose. Fever and myalgias are the most common adverse events associated with IFN-gamma, minimized by concomitant administration of acetaminophen and dosing of IFN-gamma before bedtime.

Children with severe antibody deficiency receiving/ immunoglobulin/may have an increased rate of bacterial infections chronically or at certain times of the year (e.g., during the winter). Azithromycin/prophylaxis significantly reduces the rate of pulmonary exacerbations with no drug-related adverse events or increase in macrolide-resistance. Chemoprophylaxis for influenza should be avoided and immunization of children, their household contacts, and their out-of-home caregivers is preferred. Early treatment of exposed individuals is an alternative to chemoprophylaxis as it reduces the use and/ or duration of antiviral agents, lessening the risk of emergent resistance.

Other PIDDs: Antiviral prophylaxis is indicated in some patients with recurrent mucosal or skin herpes simplex outbreaks. Patients with combined immunodeficiencies and a history of chickenpox or CMV infection may also require prolonged antiviral prophylaxis.

Antifungal prophylaxis targeting *Candida* species may be required in disorders with high susceptibility to recurrent fungal infection, such as defects in the interleukin pathway, or in the presence of anti-cytokine autoantibodies. Chronic suppressive therapy with fluconazole is preferred, though drug resistance may occur. The dose can be escalated if increasing resistance is an issue, but ultimately another azole agent will need to be used. Itraconazole, voriconazole, or posaconazole can be tried, in that order. Liver function should be carefully monitored while patients are on systemic therapy with these drugs.

Prophylaxis against mycobacterial infections is indicated in patients with Mendelian susceptibility to mycobacterial disease. Aggressive treatment with antimycobacterial antibiotics is important, and the duration of treatment is based upon clinical response, radiologic improvement, and microbiologic cure. Patients should be maintained on secondary antibiotic prophylaxis once the infection is successfully cleared, typically with daily/ azithromycin. Cytokine replacement therapy with interferon (IFN) gamma is an additional treatment option but it should be used with expert consultation.

Post exposure management of HBV/HCV

Antimicrobials are not indicated for post exposure prophylaxis of HBV/HCV but immunoglobulins are given.

Post exposure prophylaxis (PEP) and prevention of vertical transmission for HIV

Following exposure to HIV, PEP needs to be started as soon as possible (within 1- 2 hours) after the exposure and within 72 hours.[19,20] A baseline rapid HIV testing should be done before starting PEP. Initiation of PEP should not be delayed while waiting for the results of HIV testing of the source of exposure. Informed consent should be obtained before testing of the source as per national HIV testing guidelines.

NACO guidelines recommend a 2-drug regimen (basic PEP regimen) which includes:

Zidovudine (AZT) 300 mg twice daily + Lamivudine (3TC) 150 mg twice daily OR

Stavudine (d4T) 30 mg twice daily + Lamivudine (3TC)

This is used when the source is HIV positive and asymptomatic / has mild disease or when the HIV status of the source if unknown.

3-drug regimen (expanded PEP regimen) - Lopinavir / ritonavir, indinavir or nelfinavir may be added to the 2 drug regimen if the source is HIV positive with moderate to severe disease.

The duration of prophylaxis is 28 days.

Prevention of parent to child transmission of HIV:[20] Antiretroviral prophylaxis is required for all infants born to HIV infected women receiving ART to further reduce pre-partum and postpartum HIV transmission, in addition to the protection received from the mother's ART regimen.

Infants of mothers who are receiving ART and are exclusively breastfeeding or doing exclusive replacement feeding should receive at least 6 weeks of infant prophylaxis with daily Syp. Nevirapine (2 mg/kg once daily). Infant prophylaxis should begin at birth or when HIV exposure is known. Treatment may be extended to 12 weeks if the mother started ART late in pregnancy, had suboptimal adherence to ART or had not achieved full HIV viral suppression. Early infant diagnosis (EID) should be done at 6 weeks by dry blood spot test for HIV DNA PCR. Concomitant prophylaxis with cotrimoxazole should also be started at 6 weeks for all HIV exposed infants and continued upto 18 months of age regardless of EID results and thereafter only if child is positive.

Points to Remember

- ***Antimicrobials should be used for prophylaxis only when there is a clear indication and the benefits outweigh the risk.***
- ***Active infection should be ruled out before initiating prophylaxis.***

- ***The importance of non- pharmacological measures, vaccination and infection control should always be borne in mind as they are superior, safer and more effective in prevention of infections.***
- ***Attention must be paid for side effects while using certain drugs for prophylaxis such as azithromycin.***
- ***The guidelines should be periodically reviewed in the background of emerging evidence and regional antimicrobial resistance patterns.***
- ***Monitoring for adverse effects of the drugs used long term is essential.***

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CLIPPINGS

Rapid Point-of-Care Genotyping to Avoid Aminoglycoside-Induced Ototoxicity in Neonatal Intensive Care.

Aminoglycosides are commonly prescribed antibiotics used for the treatment of neonatal sepsis. The *MT RNR1* m.1555A>G variant predisposes to profound aminoglycoside-induced ototoxicity (AIO). Current genotyping approaches take several days, which is unfeasible in acute settings.

This study aimed to develop a rapid point-of-care test (POCT) for the m.1555A>G variant before implementation of this technology in the acute neonatal setting to guide antibiotic prescribing and avoid AIO. The researchers recruited neonates admitted to 2 large neonatal intensive care units between January 6, 2020, and November 30, 2020, in the UK. Neonates were tested for the m.1555A>G variant via the rapid POCT on admission to the neonatal intensive care unit.

The primary outcome assessed the proportion of neonates successfully tested for the variant of all infants prescribed antibiotics. Secondary outcomes measured whether implementation was negatively associated with routine clinical practice and the performance of the system. The study was statistically powered to detect a significant difference between time to antibiotic administration before and after implementation of the *MT-RNR1* POCT.

A total of 751 neonates were recruited and had a median (range) age of 2.5 (0-198) days. The *MT-RNR1* POCT was able to genotype the m.1555A>G variant in 26 minutes. Preclinical validation demonstrated a 100% sensitivity and specificity. Three participants with the m.1555A>G variant were identified, all of whom avoided aminoglycoside antibiotics. Overall, 424 infants (80.6%) receiving antibiotics were successfully tested for the variant, and the mean time to antibiotics was equivalent to previous practice.

McDermott JH, Mahaveer A, James RA, Booth N, Turner M, Harvey KE, et al for the PALOH Study Team. Rapid Point-of-Care Genotyping to Avoid Aminoglycoside-Induced Ototoxicity in Neonatal Intensive Care. JAMA Pediatr. Published online March 21, 2022. doi:10.1001jamapediatrics.2022.0187

NEWS AND NOTES

MADURAI PEDICON 2022

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ANTIMICROBIALS - I

NEWER ANTIBIOTICS

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****Lakshan Raj S**

Abstract: *Antibiotics have revolutionised medical practice and their over zealous use has resulted in increased incidences of emerging resistant organisms. As newer molecules were identified especially for Gram negative organisms, many clinical trials were conducted. However, only few trials included children between 0 and 18 of age. Newer beta lactamase inhibitors were also recognized and they are first generation beta lactamase inhibitors with beta lactum rings, the second generation beta lactamase inhibitors with diaxabicyclooctane molecules and third generation beta lactamase are boronic acid compounds. Liberal and indiscriminate use of antibiotics have resulted in emergence of antibiotic resistance in the bacteriae with newer mechanisms, which in turn led on to higher medical costs and the increased mortality. Hence, there is a need for newer antibiotics and this article deals with antibiotics found in the last two decades and their uses.*

Keywords: *Antibiotics, Beta lactamase inhibitors, Synthetic aminoglycoside, Tetracyclines, Siderophore, Plazomycin, Ervacycline, Cefiderocol, Glycopeptides, Oxazolidinones.*

Antimicrobial resistance poses the greatest threat to human lives. Though the discovery of antibiotics have revolutionised medical practice, misuse of these wonder drugs has resulted in the emergence of resistant strains. Beta-lactam antibiotics are one of the most commonly used antibiotics in clinical practice and as a consequence of their extensive use, extended spectrum beta-lactamase (ESBL) and carbapenamase producing organisms are increasing, leading on to development of resistnace and limited treatment options. The problem of antimicrobial resistance is further compounded by the fact that no new class of antibiotic has been introduced in the last 20 years. Most of the drugs which have been recently approved are modifications of existing drug molecules.

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Box 1. Antimicrobial susceptibility pattern among the Indian isolates[1]

- ESBL production seen in 70% of E.coli and Klebsiella species
- Carbapenem resistance (CR) seen in 10% of E, Coli, 40%, of klebsiella, 25% of pseudomonas and 70% of Acinetobacter species.

Need for novel anti-Gram-negative antibiotics

The current antimicrobial susceptibility pattern that is seen in the Indian isolates are given in Box 1.

Though colistin remains the backbone in the treatment of CR isolates, the recent Infectious Disease Society of America (IDSA) guidelines recommend against the use of colistin in CRE (Carbapenem Resistant Enterobacteriaceae) considering the nephrotoxicity, clinical effectiveness and the accuracy of in vitro sensitivity testing.[2] Also, colistin resistance is increasing and worrisome. Colistin resistance was seen in 40% of CR *K.pneumoniae*, 10% of CR *E.coli* and <5% in *Pseudomonas* and *Acinetobacter*.[1]

Moreover, AMR (Antimicrobial Resistance) determinants responsible for drug resistance are different for different geographical locations. Each of the newer antibiotics inhibit only certain classes of beta-lactamases and therefore, understanding the local epidemiology will help choose the right empiric antibiotic.

Recently, newer antibiotics with predominant activity against Gram-negative bacteria were approved by the U.S. Food and Drug Administration (FDA) and the European Medical Agency (EMA), which include plazomicin, eravacycline, cefiderocol and newer beta-lactamase inhibitors. Even though many clinical trials were conducted in adults, only few trials recruited children between 0 and 18 years of age which are described below in each individual drug description.

Box 2. Beta lactam inhibitors

- First generation: (have beta lactam ring): clavulanate, sulbactam and tazobactam
- Second generation: (no beta lactam ring): avibactam, relebactam, zidebactam and nacubactam
- Third generation : (From boronic acid compound) : vaborbactam and taniborbactam

1) Newer beta-lactam/beta-lactamase inhibitors

Enzymatic degradation of beta-lactam antibiotics by beta-lactamases has emerged as an important cause of antimicrobial resistance. Therefore, to overcome the emergence of resistance, newer beta-lactamase inhibitors (BLIs) with broad spectrum of activity are being developed. The first generation BLI have beta-lactam ring in their structure which includes clavulanate, sulbactam and tazobactam. However, their inhibitory profiles are largely limited to class A serine penicillinases (e.g. TEM-1, SHV-1) and extended-spectrum beta-lactamases [ESBLs] (e.g. CTX-M-15) as well as some class C and D β-lactamases (e.g. AmpC and OXA-1). Second generation BLIs are non-beta-lactam based (no beta-lactam ring in their structure) and are derived from DBO (diazabicyclooctane), which includes avibactam, relebactam, zidebactam and nacubactam. Third generation BLIs are derivatives of boronic acid compounds, which includes vaborbactam and taniborbactam (Box 2).

Among these newer BL-BLIs, Ceftazidime-avibactam, Ceftolozane-tazobactam, Meropenem-vaborbactam, Imipenam-cilastatin-relebactam are FDA approved combination drugs. Since they are beta-lactam antibiotics, the percentage of the free drug concentration that remains above the MIC (%fT>MIC) determines the efficacy (Anti-bacterial activity of meropenem is related to the fraction of time (fT) between doses during which the plasma concentration (Cp) is maintained above the minimum inhibitory concentration (MIC) for the infecting organism. e.g. In vitro and in vivo animal models suggest that for the optimal bactericidal activity for carbapenems, the Cp must remain above the MIC for the pathogen for at least 40% of dosing interval (fT>MIC>40). These drugs are not metabolised to any great extent and are primarily eliminated unchanged in the urine and hence need dosage adjustment in renal impairment. However, they do not undergo significant hepatic metabolism, so no dosage adjustment is recommended for hepatic impairment.

Dosage, indications and spectrum of activity of newer beta-lactam/beta-lactamase inhibitors are summarised in Table I.

i) Ceftazidime-avibactam (CAZ-AVI)

It is an intravenously administered combination of the third-generation cephalosporin ceftazidime and the novel, non-β-lactam β-lactamase inhibitor avibactam in a fixed ratio of 4:1. Avibactam has no antibacterial activity by itself

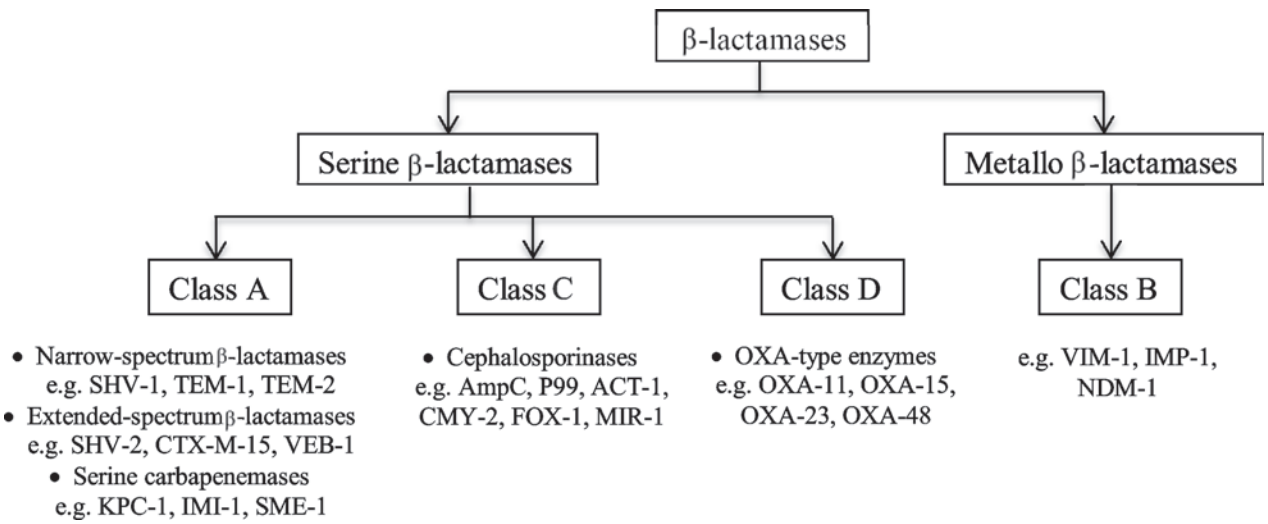

Fig.1. Ambler functional classification of Beta lactamases

(*Ambler made the first molecular classification of β-lactamases in Gram-negative bacteria that divided into four classes, A, B, C, and D. For classes A, C, and D, the active enzyme site contains serine and class B includes Zn-dependent metallo-enzymes)*

Source: Vrancianu CO, Gheorghe I, Dobre E-G, Barbu IC, Cristian RE, Popa M et al. Emerging Strategies to Combat β-Lactamase Producing ESKAPE Pathogens. Int J Mol Sci 2020; 21(22): 8527. doi: 10.3390/ijms21228527.

Table I. Dosage, indications and spectrum of activity of newer antibiotics

Drugs	Approved indications	Coverage	Dosage
1. Beta-lactam-beta-lactamase inhibitors			
Ceftazidime/ avibactam Ceftazidime-avibactam	*c-IAI, c-UTI, HAP/VAP.	Active against class A, C and D beta-lactamases. It is not active against Class B beta-lactamases. Limited activity against *Acinetobacter spp*. and anaerobes. Inactive against Gram-positive cocci.	**3 months to 6 months** Ceftazidime (40mg/kg/dose) + Avibactum(10 mg/kg/dose) IV TDS **6 months to < 18 years** Ceftazidime (50 mg/kg/dose) + Avibactum (12.5 mg/kg/dose) IV TDS **Maximum dose** 2.5 grams IV TDS Ceftazidime (2gram/dose) + Avibactum (500 mg/dose) IV TDS Needs dose adjustment infestimated creatinine clearance (CLcr) ≤ 50 mL/min
Ceftolozane/ tazobactam	c-IAI (combined with metronidazole), c-UTI, HAP/VAP.	Active against ESBL and Amp-C betalactamase producing *enterobacteriaceae* especially, MDR, XDR *P. aeruginosa*. Limited activity against *Acinetobacter spp*. anaerobes and carbapenemase producing *enterobacteriaceae* (serine and MBL)	Safety and efficacy not established in pediatric age group Adult dose - IV TDS (1 gm ceftalozone. 0.5 gm of tazobactam) Dose adjustment in renal impairment.
Meropenem/ vaborbactam	c-IAI, c-UTI, HAP, VAP	Effective against class A carbapenamases. No activity against class B and Class D carbapenamses.	Pediatric dosage not available. Adult dose - 4 gm (Meropenem 2 gm and vaborbactam 2 gm) IV TDS
Imipenem-cilastin/ relebactam	c-UTI and c-IAI, HAP,VAP	Inhibits Class A & C beta-lactamases. No activity against MBL and CR- *Acinetobacter*	Not approved yet in children. Adult dose-1.25 gm (Imipenem 500 mg, cilastin 500 mg, and relebactam 250 mg) IV, QID.
2. Synthetic aminoglycoside			
Plazomicin	c-UTI	Active against ESBL isolates, KPC gene-harbouring isolates, Less activity against OXA-48 and limited activity against MBL-harbouring isolates	Not approved yet in children. Adults > 18 years-15 mg/kg IV, QID.
3. Tetracyclines			
Eravacycline	c-IAI	Active against ESBL, CRE and Colistin resistant *Enterobacteriaceae, Acinetobacter spp*. Has limited activity against *P. aeruginosa.*	Not approved yet in children. Adult dose -1 mg/kg IV, BD
4. Siderophore			
Cefiderocol	c-UTI, HAP/VAP	Active against > 90% of *Enterobacterales, Acinetobacter* spp. and *P. aeruginosa* isolates, which are ESBL, Amp-C and carbapenem-resistant.	Not yet approved in children Adult dose - 2 gm IV, TDS

** c-IAI- complicated intra-abdominal infections, c-UTI-complicated urinary tract infections, HAP- Hospital acquired pneumonia/VAP-ventilator associated pneumonia, KPC-Klebsiella pneumonia carbapenemase, OXA -48- oxacillinase, MBL- metallo beta lactamases*

but it restores the activity of ceftazidime against the majority of β-lactamases (ESBLs and carbapenemases, including KPCs- Ambler Class A, Amp C -Class C and oxacillinase OXA-48 Class D), resulting in extended spectrum of CAZ-AVI. But, it cannot inhibit strains producing metallo-β-lactamases (MBL-Class B), as well as many of the Class D enzymes.[3,4]

The International Network for Optimal Resistance Monitoring (INFORM) global surveillance program demonstrated 99.4% susceptibility for all Enterobacteriaceae isolates and 98.5% for meropenem-non susceptible metallo-beta-lactamase (MBL)-negative isolates, respectively.[5] For MBL producing isolates, which frequently harbour additional determinants that produce other serine beta-lactamases, combination of CAZ-AVI with aztreonam (ATM) is synergistic. Here, avibactam protects aztreonam from hydrolysis by other ESBLs and AmpC and bacterial killing is likely achieved by the action of aztreonam.[6] It has excellent activity against most of the *Enterobacteriaceae* including *E.coli, Klebsiella pneumoniae, Enterobacter spp* and *Proteus mirabilis*. It also exhibits excellent in vitro activity against *P. aeruginosa.*

Acinetobacter spp. and *Stenotrophomonas maltophilia* are generally not susceptible to ceftazidime-avibactam.[7] It has little or no in vitro activity against the majority of Gram-positive bacteria and anaerobes.

It is currently approved for complicated urinary tract infection (cU TI), complicated intra-abdominal infections (cIAI), in combination with metronidazole for children >3 months of age and hospital acquired pneumonia/ ventilator associated pneumonia(HAP/VAP) in adults.

ii) Ceftolozane-tazobactam

It is a fifth generation cephalosporin/beta-lactamase inhibitor and is effective against several multi-drugresistant (MDR) Gram-negative bacilli, particularly MDR or XDR (extremely drug resistant) *P. aeruginosa*. Its novel anti-pseudomonal agent property is due to the stability of ceftolozane against AmpC enzymes, active efflux process, porin-channel changes and modification of penicillin binding proteins. It is also active against AmpC and ESBL-producing enterobacteriaceae but with limited activity against ESBL- producing *Klebsiella pneumonia*.[8] It is also active against Streptococcus spp. (excluding Enterococcus spp.) and some anaerobes.[9]

It is not active against serine carbapenamases and MBL produced by gram negative bacteria. There is limited or no activity against *Acinetobacter spp., Clostridium difficile,* anaerobes and carbapenamase producing gram negative organisms.[10]

It is approved in the US and Europe for cIAIs (with metronidazole) and cUTIs in adults.[11] The recent infectitious disease society of America (IDSA) guidance also recommends it as a preferred antibiotic for difficult-to-treat *P.aeruginosa* in uncomplicated cystitis, cUTI and also for infections outside the urinary tract.[2] Even though, it is recommended for MDR *Pseudomonas aeruginosa* infection, there is an emergence of resistance mostly by the hyper production and modification of the AmpC enzymes.

iii) Meropenem-vaborbactam

Vaborbactam, is a boronic acid, non-β-lactam β-lactamase inhibitor. Meropenem vaborbactam has a broad spectrum of enzyme inhibition covering also several CRE strains with an excellent activity against KPC carbapenemase-producing Klebsiella pneumonia. It inhibits various class A carbapenemases (KPC) but does not inhibit Amber class B or D carbapenemases. It does improve the activity of meropenem against MDR non fermenting Gram-negative bacilli, notably *Acinetobacter spp*. and *Pseudomonas aeruginosa*.[12] Anaerobic activity of meropenem is also not enhanced by vaborbactam. It also inhibits class A ESBLs and class C cephalosporinases and a weaker activity against some class D carbapenemases.

European medicine agency (EMA) approved its use in adult patients with cIAI, cUTI, HAP, VAP and infections due to aerobic Gram-negative organisms where treatment options are limited.

iv) Imipenem-cilastatin - relebactam

Imipenem/cilastatin/relebactam is a combination of the carbapenem imipenem, the renal dehydropeptidase-I inhibitor cilastatin and the novel β-lactamase inhibitor relebactam.

Relebactam inhibits a broad spectrum of β-lactamases such as class A and class C β-lactamases, including carbapenemases.[13] Thus relebactam restores imipenem activity against several imipenem-resistant bacteria, including CR *Enterobacteriaceae* and MDR *Pseudomonas aeruginosa*. It has no activity against class B beta-lactamases MBL and CR *Acinetobacter baumannii*.[14]

It is approved in USA and EU for the treatment of adults with HAP, VAP and other Gram-negative infections including cUTIs and cIAIs

When co-administered with valproic acid, as like other carbapenems, imipenem will decrease the levels of valproic acid, thereby decreasing the seizure threshold. Few CNS adverse events like seizures, mental confusion have been reported in patients with preexisting CNS disorders and those with renal impairment.[15] Other commonly reported side effects included anemia, elevated liver enzymes, electrolyte imbalances, phlebitis and/or infusion-site reactions etc.

BL-BLIs in development process

1. Aztreonam-avibactam

The combination of the monobactam aztreonam together with avibactam has been shown as having in vitro activity against *Enterobacteriaceae* with class B, A, C and some D beta-lactamases. Aztreonam is not hydrolysed by MBL and it has the potential to inhibit serine beta-lactamases also, which is co-produced with MBLs. Since it is not yet available,concurrent administration of aztreonam and ceftazidime-avibactam has been found to be effective if MBL is identified.[2]

2.Plazomicin

Plazomicin is a next-generation semisynthetic aminoglycoside. It is active against MDR Enterobacteriaceae, including the ESBL and carbapenemase producing organisms due to its stability against strains that express aminoglycoside modifying enzymes.[16] However, there are resistance noted among *Enterobacteriaceae* due to alteration in ribosomal binding site due to expression of ribosomal ribonucleic acid (rRNA) methyltransferase enzymes. It does not have additional improved activity over traditional aminoglycosides against *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[17]

It retains the activity against the vast majority of MBL-producing Enterobacteriaceae in the absence of 16S ribosomal RNA methytransferase (16S-RMTase) co-expression.[18] It was granted FDA approval for adults with cUTI. Side effects includes nephrotoxicity, ototoxicity, neuromuscular blockade and harm to growing fetus in pregnant women. Dose reduction and therapeutic drug monitoring is needed in patients with moderate and severe renal impairment.[19]

Approved indication, spectrum of activity of newer antibiotics against Gram negative bacilli (GNB) are mentioned in Table II.

3. Eravacycline

Eravacycline is a fully synthetic fluorocycline, with similarities to tigecycline in mechanism of action, structure and antibacterial spectrum. Intravenous eravacycline was approved for cIAIs by both FDA and EMA.

Table II. Possible applications of newer antibiotics against GNB

	ESBL/ Amp-C	KPC	OXA-48	MBL	Carbapenem Non-susceptible A.baumanii	Carbapenem non-susceptible P.aeruginosa
Ceftazidime - Avibactum	++	++	++	+/-	-	+/-
Ceftalozone - tazobactum	++	-	-	-	-	+/-
Meropenam - Vaborbactum	++	++	-	-	-	-
Imipenam - relebactum	++	++	-	-	-	+/-
Plazomicin	++	++	++	+/-	- No additional advantage over traditional aminoglycosides	- No additional advantage over traditional aminoglycosides
Eravacycline	++	++	++	+	++	-
Cefiderocol	++	++	++	++	++	++

It exhibits potent activity against a broad spectrum of Gram-positive and -negative aerobic and anaerobic bacteria with the exception of *Pseudomonas aeruginosa* and Burkholderia spp.[20] In vitro, it is active against bacteria expressing tetracycline, carbapenem, extended-spectrum cephalosporin, methicillin and vancomycin- specific acquired resistance mechanisms and ESBL producing Enterobacteriaceae.[21] Eravacycline typically exhibits bacteriostatic activity; however, it also exhibits bactericidal activity against certain strains of *Acinetobacter baumannii, E. coli* and *K. pneumoniae* in vitro.[20] Even among colistin resistant mcr-1 positive isolates, it exhibits very good in vitro activity against *E. coli* and *K.pneumoniae*.[22]

When compared to tigecycline, it achieves higher concentration in serum and tissues (especially lung), has excellent oral bioavailability, improved tolerability, lower potential for drug interaction and has superior activity in biofilms.

Side effects similar to the tetracycline class of antibiotics include hypersensitivity reactions, photosensitivity, pseudotumor cerebri and anti-anabolic actions. Use of eravacycline during tooth development (last half of pregnancy, infancy and childhood up to the age of 8) may cause permanent discolouration of teeth and enamel hypoplasia and it may cause reversible inhibition of bone growth.

Approved indications, spectrum of activity are mentioned in Table II.

4. Cefiderocol

Cefiderocol is an injectable siderophore cephalosporin that combines a catechol-type siderophore and cephalosporin core with side chains similar to cefepime and ceftazidime. Because of its structure and unique mechanism of action it is stable against many β-lactamases including carbapenemases such as Klebsiella pneumonia carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM), Verona Integron - encoded metallo beta lactamases (VIM), active on Imepenem (IMP), oxacillinase (OXA)-23, OXA-48-like, OXA-51-like and OXA-58. Thus it is active against >90% of *Enterobacteriaceae* isolates, with ESBL and AmpC production.[23] It is also active against >90% of *Acinetobacter spp*. and *P. aeruginosa* isolates, including those which are carbapenem-resistant.[24]

It is approved by the FDA for the treatment of cUTI and now extended to HAP/VAP, where there are limited treatment options. It has an FDA label warning for higher all-cause mortality versus other antibiotics in critically ill patients with MDR GNB infections. Even though it has an excellent activity against MDR Gram negative infections, in CREDIBLE-CR study, they reported higher mortality rate especially among patients with pneumonia due to CR-*Acinetobacter* infections.[25] However, there are now case reports of effective use of this drug due to *A. baumannii* infections.[26] Cefiderocol had a good tolerability and safety profile in clinical trials.

Based on the available evidence, the recent IDSA guidelines recommend cefiderocol as an alternative treatment option for CRE, regardless of the mechanism of resistance though there was a slight increase in mortality among patients with pneumonia and bacteremia.[2] Hence, it should be used for CRE infections when the preferred agents cannot be used because of resistance or intolerance.

Approved indications, spectrum of activity are mentioned in Table II.

Resurgence of old and established antibiotics

1. Colistin

Colistin, systemically administered in the form of the prodrug colistin methane sulfonate (CMS), was considered as the last resort due to the steep increase of resistance rates and the lack of new effective antimicrobial agents.[27] The antimicrobial spectrum of colistin includes MDR and XDR Gram-negatives regardless of mechanism of resistance, mainly *K. pneumoniae*, *A. baumannii and P. aeruginosa*, whereas Proteae (*Proteus*, *Morganella* and *Providencia*) are inherently resistant.[27] The Proteeae are normal fecal flora that often cause infection in patients when normal flora is disturbed by antibiotic therapy, which constitutes at least 3 genera of Gram-negative organisms: *P. mirabilis*, *P. vulgaris* and *P. myxofaciens*. Regarding the management of CRE infections, the combination of colistin with another active in vitro antibiotic has been reported to be beneficial.[28]

But considering the nephrotoxicity, clinical efficacy and the accuracy of in vivo testing, colistin is not preferred in the management of CRE infections except as a last resort agent against CRE cystitis.[2]

2. Fosfomycin

It was reintroduced into clinical practice, for XDR and PDR (pan drug resistant) GNB in critically ill patients.[29] It inhibits the first step of peptidogly can synthesis, making cross-resistance with other agents unlikely.[30] High concentrations are achieved in serum and urine, well above minimum inhibitory concentrations

(MICs) of susceptible organisms, while penetration to other compartments (lung, cerebrospinal fluid, abscess fluid) is satisfactory.[31,32] Therefore, it can be used in the management of UTI and also it has a comparable efficacy in the management of VAP and BSIs.[29]

It was active against more than 80% of *Staphylococcus aureus*, *Enterococcus faecium*, ESBL-producing *Escherichia coli* and *K. pneumonia* and slightly less against CR *K. pneumonia*.[33] It can be sometimes effective even in the presence of colistin resistance and against MBL producers. It has no activity against *A. baumannii* strains.[34] It has few toxicity concerns like hypokalemia and sodium overload.

3. Tigecycline

The glycylcycline, tigecycline has been used as a salvage treatment for infections caused by CRE and Carbapenem-resistant *Acinetobacter baumannii* (CRAB).[35] Treatment outcomes have been hampered by the low serum concentrations of the drug in the approved dosing regimen and the low penetration in the epithelial lining fluid of mechanically ventilated patients.[36] Therefore, a higher dose of tigecycline has been suggested, particularly for VAP/HAP, *A. baumannii* infections and bacteremic infections, although all the above represent off label use of the drug.[37] Combination treatments of tigecycline seem mandatory, given the above-mentioned characteristics of the drug, particularly in critically ill patients.[38]

Novel anti-Gram-positive antibiotics

Increasing multidrug-resistance to Gram-positive pathogens, particularly those caused by Methicillin Resistant *Staphylococcus aureus* (MRSA), Vancomycin Resistant *Enterococci* (VRE) and *Streptococcus. pneumoniae*, has become a major problem especially in hospital environments, resulting in significant morbidity and mortality.

A. β-lactams

1.Ceftaroline

It is a novel 5th generation cephalosporin that was approved by the FDA and EMA for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired bacterial pneumonia (CABP).[39]

Its mechanism of action involves cell wall synthesis inhibition by inactivating penicillin-binding proteins (PBP) and it binds to PBP-1a, -2a, -2b and -2x proteins with a greater affinity, giving it enhanced activity towards MRSA and penicillin-resistant *S. pneumonia*.[40] It has bactericidal activity against MSSA, MRSA, vancomycin-resistant *S. aureus*, daptomycin non-susceptible *S. aureus*, linezolid-resistant *S. aureus, Streptococcus pyogenes, Streptococcus agalactiae*, resistant *S. pneumoniae*, while the activity against *Enterococcus faecalis* (including vancomycin-resistant enterococci [VRE] strains) is modest. It is not active against *E. faecium*. Dosage adjustment is required in patients with renal impairment.

2. Ceftobiprole

It exerts activity by binding to PBPs, including the PBP-2a of MRSA and blocking bacterial cell wall synthesis.[41] It has a broad spectrum of activity against MRSA, ampicillin-susceptible enterococci, penicillin-resistant pneumococci and Gram-negatives; its Gram-negative spectrum is similar to that of 3rd and 4th generation cephalosporins, i.e., not active against Gram-negative strains producing ESBL.[41] It is used in the management of *S. aureus* bacteremia (SAB), ABSSSI and CABP.

B. Glycopeptides

Dalbavancin

It is a semisynthetic lipoglycopeptide. Its mechanism of action is similar to vancomycin, which consists of binding to D-alanyl-D-alanine terminus of the stem pentapeptide in peptidoglycan, thereby preventing cross-linking of cell wall synthesis.[42] However, dalbavancin has an additional lipophilic side chain that anchors it to the cellular membrane, allowing it to have enhanced activity.[43] The major advantage of dalbavancin is its long half-life i.e. approximately 8.5 days, allowing it to be administered once-weekly.[44] Dalbavancin was approved for treating acute bacterial skin and skin structure infections (ABSSSIs) in adults by both the FDA and the EMA. Pediatric clinical trials are on the run.

C. Oxazolidinones

Tedizolid

Tedizolid phosphate, exerts bacteriostatic activity by binding to the 23S ribosomal RNA (rRNA) of the 50S subunit of the bacterial ribosome and thus inhibiting protein synthesis. The unique D-ring and a hydroxymethyl group has important contribution to tedizolid's activity against linezolid-resistant strains.[45] No dose adjustment is required for renal failure or liver failure, even though approximately 35% is excreted by the kidneys.[46] Tedizolid phosphate was approved by the FDA for the treatment of adult patients with ABSSSI. Adverse reactions such as lactic acidosis, anemia, neutropenia, thrombocytopenia and neuropathy (optic and peripheral) have been reported.

D. Quinolones

Delafloxacin

It is a novel fluoroquinolone which inhibits DNA gyrase and topoisomerase IV. It's distinct chemical structure confers a weakly acidic character that results in increased cellular penetration as well as increased bactericidal activity in the acidic environment of the infection site.[47] It covers a broad-spectrum of Gram-positive pathogens, including *S. aureus* (MRSA and MSSA), *S. pneumoniae* except enterococci. It is also very active against gram-negative respiratory pathogens including *Haemophilus influenzae* and *Moraxella catarrhalis*. It is eliminated via the kidneys, therefore adjustment for intravenous dosing is required in patients with renal impairment but not hepatic impairment. Delafloxacin was approved by the FDA for the treatment of ABSSSIs in adults and is being evaluated for the treatment of CAP.

E. Tetracyclines

Omadacycline

Omadacycline binds to the 30S ribosomal subunit and inhibits protein synthesis.[48] In vitro, omadacycline is active against bacteria associated with ABSSSIs and CABP including MRSA, penicillin-resistant and multidrug-resistant *S. pneumoniae* and vancomycin-resistant *Enterococcus spp*.[49] It also has a broad range of activity against Gram-negative bacteria, except *P. aeruginosa*. It is eliminated via the kidneys but does not require dose adjustment in either kidney or liver impairments. FDA has approved omadacycline for CABP and ABSSSIs as both IV and tablet formulations.

Points to Remember

- ***Microbiological identification of infections should be the norm and newer drugs should not be used empirically.***
- ***Excellent new drugs are available for ESBL producers.***
- ***In India, carbapenamase producers are predominantly NDM and OXA-48 and to target this mechanism of resistance, more effective drugs are needed.***
- ***Majority of the trials were conducted only in adults hence more data on the pharmacokinetics / pharmacodynamics of drugs are needed in children including newborns.***
- ***Newer antibiotics should be reserved only for infections where there are limited therapeutic options.***

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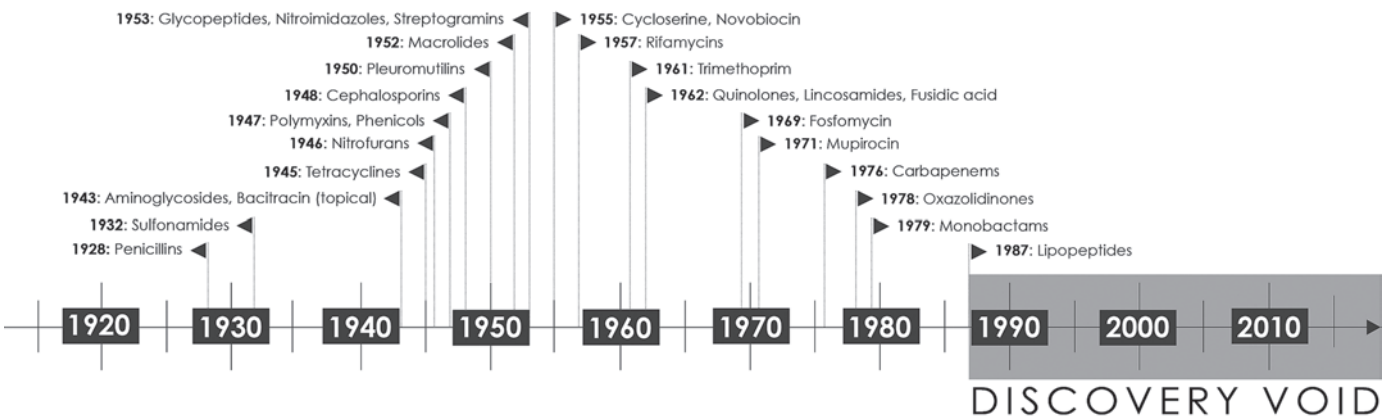
CLIPPINGS

Discovery of antibiotics – Timeline



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GENERAL ARTICLE

CAREER GUIDANCE FOR PEDIATRICIANS

***Julius Xavier Scott**
****Nisha Kalaiarasan**

Abstract: *Pediatrics is one of the most sought after branches amongst medical undergraduates. That said, the struggles and difficulties of establishing oneself as a successful pediatrician, after postgraduation, is not child's play. Pediatricians, at various points in life, are left at crossroads, as they even try to shift focus away from Pediatrics, as their career, owing to various compelling circumstances. This article focuses on ways and means to better oneself as a pediatrician and also the spread of other career options available to them.*

Keywords: *Pediatrics practice, Subspecialities, Foreign assignments, Work-life balance.*

"Opportunity to serve the society is a blessing "as quoted by a great Tamil poet Mahakavi Bharathiyar. In accordance with the quote, "health care" is still a "great opportunity to serve the society", despite the gradual transition from "noble profession" to "health industry". Being a pediatrician in the health care system is a delight ! Our day at work gets complete, when we see the happy faces of children, receive their cheers and endearments, in return. We treat children right from birth (sometimes even before birth) until adolescence and sometimes, even their future generations..

Pediatrics is one of the most preferred branches for undergraduates. In a survey done by Latha, et al, it was found that 50% of undergraduates wished to pursue pediatrics as their career.[1] Anand, et al also found "pediatrics" as one of the most preferred career among the MBBS undergraduates.[2] Even after the covid outbreak, career choices to select "pediatrics" did not drop significantly. In fact, there has been a positive impact of the COVID-19 outbreak on strengthening 66.7% of students' beliefs and choices to become good pediatricians as reported by a study in Fudan university by Hu, et al.[3]

Nevertheless, it is not always cheerful and optimistic. Pediatricians face trials and hardships even for simple issues, leave alone a complicated bone marrow transplantation/PICU related event. As general pediatricians, inferring on some finding as 'normal', requiring no intervention, and disclosing the same to the caretaker, is a more difficult task. We are constantly facing anxious and apprehensive parents, at times frustrated ones, and have to deal with unrealistic expectations and instantaneous solutions for stopping an " incessant cry", with few medicinal drops as advertised, which might have been due to a self-limiting infantile colic. Work hours can be erratic, as children with even minor ailments can be brought to the emergency department at odd hours. It is challenging to diagnose, when a newborn presents only with lethargy and we are left clueless, vis-a-vis the assessment and intervention. .

Struggles of being a woman/mother and a pediatrician is documented by Aroskar. A study conducted recruiting 141 women who finished their pediatric residency between 1960 and 1987, concerning their decisions regarding marriage, pregnancy, child care and career, showed that 26% among those 141 believed that they were penalized for their maternity leaves and 24% believed that their pregnancies were actively discouraged. Most found that their life-styles were challenging but rewarding, and with the benefit of hindsight, they suggested that they would make the same choices again.[5]

There are innumerable branches to pediatrics as a career and it can be a tough decision to choose the best, as every decision is fraught with its consequences.

The common posers encountered by pediatricians include -

It is impossible to answer all these questions initially, and most people find the right choice by trial and error

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Box 1. Career options

Career options in front of every young pediatric specialist after completing the postgraduation.

1. Should we study further and take up DM courses or fellowships or be contented as a general pediatrician?

2. Should we opt to work in an a teaching institution or corporate sector; start our own setup of private practice or be part of an established hospital ?

3. Should we go abroad or serve in our own country?

4. Should we accept and undergo the compulsory government posting?

What is my priority for the next three years in life as a woman? - to complete my social responsibilities or personal mile stones such as pregnancy and child birth or study further? As a male, should I look for a source of stable income alone or take calculated risks and buy a vehicle or house ?

only. However, we can reduce the number of wrong turns by understanding each of these questions and analyzing the pros and cons. As the distant grass might appear green, any decision has to be based on a complete assessment of the choices made. Executing a decision with utmost passion allows one to be stress free, even if it ends in failure.

Community pediatric practice

(Starting an OPD practice independently or as a part of a smaller hospital)

General pediatricians are the cornerstone to building robust health for the kids, promoting breastfeeding and nutrition, ensuring adequate growth and development, various immunization practices, and treating common childhood ailments etc. In addition, they carry out an appropriate assessment and prompt referral of cases, requiring further expert care to specialists. General pediatricians manage cases across multiple specialties, avoiding monotony, Ranging from a child with fever and slapped cheek appearance with a possibility of parvovirus infection to a child with dramatic onset of breathlessness suggestive of a foreign body in the airway.

In general practice, some of you might prefer to start your own clinic or nursing homes. It gives us a feeling of independence and flexibility. It is possible to establish one with acceptable expenses, especially in the suburbs or in our native places away from cities. Practicing by oneself can be exhausting, busy and demanding. We can coordinate with other doctors to have group practice to counter that and cover up for another person's absentia. The disadvantage is the difficulty in finding compatible colleagues sharing finances and administrative needs. Starting private practice in one's own native place, preferably in semi urban or rural areas is a suitable option for those who want to practice pediatrics and stay in one's native place/house, connected with the immediate and extended families. One such will be identified as a close associate of neighborhood and friends and be flooded with invites of all kinds. As a prominent member of the community, a community pediatrician will be given an important role in every social function in the town, whether it is a school independence day function or a marriage function or a cultural meet. But at the same time you will have to face the landslide part is that, one might also land up facing the menace of criticisms and conflicts from the same population whenever something goes wrong, such as sudden deterioration or death or untoward incidents in the clinic, and also unnecessary interference in the management of the children. In such situations, the parents and caretakers might take undue privilege and misuse their association with pediatrician. Most of the times, opting for, office practice and providing inpatient care in an established hospital as a consultant, is very much a better option without much of investment and later, construct one's own hospital after few years of practice. Emmett, et al has reported significant negative impact on pediatricians' spouses and families due to their after hour's work.[6]

Majority work as general pediatricians in private hospitals - from small ones to large corporate hospitals and mostly in cities. There is a wide variation in the personal experiences of those working in private hospitals. Facilities, work conditions and remuneration are generally good. However, there can be a perceived loss of independence, disconnect with academic activities and reduced job security and with the unexpected changes in hospital administration, may influence our practice positively or negatively which is not in our control.

Medical science is advancing rapidly, and even as a general pediatrician, one needs to keep our knowledge updated, as all the patients and their relatives are updated with medical knowledge obtained from social media sources like Whatspp and Google. Participating in Indian academy of pediatrics, conducting CMEs and attending CMEs both are very useful for updating knowledge, scientific and political.

Getting a job in medical college as teaching faculty

One can be a faculty of teaching institutions/ medical colleges, if interested in academics/teaching, research activities and continued learning. Authoring papers and publications are relatively more straightforward, when in a medical college hospital. The work hours are usually fixed with colleagues to share work. The elements of job security and employee benefits are important factors to be considered. The negative aspect of this is lesser remuneration, in comparison with the corporate sector. But, finding a place in a good medical college hospital is challenging and many medical colleges have very less patients to cater to. The uncertainity of promotion to higher cadres and transfers to distant places is a real challenge in government medical colleges.The biggest advantages of working in a medical college, however, are the chances of working in any private/ affiliated institute, post retirement, earn a substantial amount and stop being dependent on one's children/ grandchildren to manage their living.

Pediatric superspeciality (subspeciality) courses

There are lots of options, if one want to specialize after pediatrics. Pediatric sub specialties that can be pursued include cardiology, nephrology, gastroenterology, neurology, rheumatology, hemato-oncology, endocrinology, pulmonology, intensive care, neonatology, emergency medicine, developmental pediatrics, palliative care, infectious diseases and many more. Though there is a recent trend of rise in more pediatric sub specialty DM courses in the last decade, many are restricted predominantly to central institutes like AIIMS and PGI and also not all specialties have pediatric DM course. There are only small number of seats in DM pediatric sub-specialties throughout India, more in neonatology. DM in medical genetics is a recently started course that can be of interest to pediatricians. DM pediatric oncology is available in regional cancer centers, but without a component of hematology. DM pediatric hematology and oncology is available only in PGI Chandigarh. Entry into any of these courses is through the NEET-SS or Institute of National Importance Combined Entrance Test (INI-CET). So it is highly competitive to enter into a sub-specialty course and there is no guarantee, even if one dotes on preparation for these exams, without working, studying 18 hours/day, sacrificing personal milestones like marriage etc. The national board has FNB (Fellow of National Board) courses for - pediatric hemato-oncology, pediatric nephrology and pediatric gastroenterology, etc, which is considered equivalent to DM degrees. DM after pediatrics is a necessity to develop DM courses under the headman ship of one, in medical colleges[7,8]

IAP fellowship courses for post MD pediatrics cover a vast range of subjects too. Various institutes run these courses across India and recruitment is done through local interviews. Unfortunately, there is no centralized data on all the available fellowships and individual inquiries must be made to specific sub-chapters. Pediatric hemato-oncology and pediatric intensive care chapter run fellowship courses across the countries in various institutes. Other fellowships include - pediatric gastroenterology, pediatric cardiology, neonatology, pediatric nephrology, pediatric neurology, pediatric endocrinology, allergy and asthma, neurodevelopmental and behavioural pediatrics.[9,10]

Apart from this, fellowships run by individual hospitals or institutes which are not recognized or accredited by NMC, can serve to increase one's exposure to a particular area of expertise and help to pursue DM or FNB later in the same specialty.[11]

Every subspecialty has some pros and cons. Neonatology was the most chosen speciality followed by critical care and cardiology as reported by Latha , et al in a study from South India conducted among the pediatric residents, the reasons stated being 'financial' and 'scope for opportunities'.[12] The stress of dealing with family expectations of patient survival even in dire circumstances is unique to the pediatric environment as reported by Dennis, et al, among the pediatric intensivists.[13]

There are not much of studies with regard to preferences of pediatric subspecialty. However, some specialists reported good satisfaction and some have reported it to be on the stressful side.[14] There are some pediatric subspecialties like genetics or palliative care, which might be opted by pediatric residents in future, as in developed countries.[15]

Every pediatrician should remember the fact that speciality doesn't provide you a higher status to draw more patients or higher speciality status, as after pediatric nephrology, specialist has to work harder for another five years to become a pediatric nephrologist. One more additional problem is the availability of nephrology or subspeciality centre to work. Only in three specialities i.e. pediatric emergency medicine, neonatology and pediatric intensive care, one can start functioning as subspeciality experts, as they are specialities truly developed within the span of pediatrics. Every time one decides on pursuing higher studies of third tier (i.e after MBBS, MD and a DM course) one should consider the pros and cons of compromising on marriage, child birth, financial stability as against one's career choices.

Assignment in foreign countries

There will be a significant number of pediatricians considering the option of going abroad. This can either be for training purposes or as a career move itself. The preferred destinations include English speaking countries like the United States of America (USA), United Kingdom (UK), Australia and Canada. The desire to move permanently can be attributed to the perceived higher quality of life, better salary, undisturbed period in post duty times better work life balance, security and better quality of life for their children. They might see less number of patients, but come off better, professionally. However, treating a poor child with a simple vitamin A deficiency due to poverty and saving the child's vision in your own land makes your profession more meaningful. In the long haul, the children of couples who relocated abroad, have faced hardships. With the Covid-19 pandemic taking hold, we have witnessed many such families move further away. Many children have missed the last rituals of their parents and haven't been available to provide emotional support, while ill. Though these changes are commonly encountered, this depends on the mental attitude of the persons facing the challenge.

However, in this competitive health care system, though our country empowers doctors with remarkable training, getting exposed to training abroad is very important in terms of training with great professionalism. It also emphasizes the need for multidisciplinary meetings with professional boundaries, family meetings and social support given even for a terminally dying child at home with pain management to reduce avoidable suffering, support for disabled children and many more, thereby reinforcing a significant change in attitude and perspective towards the whole of human medicine. A degree/training abroad in foreign countries, although, won't make a difference in terms of promotion in medical colleges, it is well preferred and given importance in corporate set up. However, relocation after middle age, have made settling down, socially and professionally difficult in the competitive rat race.

Among the countries preferred for training abroad, USA is still the most in-demand destination and most students start their residency in USA after their MBBS. It means nothing for those who have completed their MD pediatrics in India and you are essentially starting from post MBBS. One has to complete all three steps of USMLE and apply for a "match" in the National Residency Matching Program and go through pediatric residency all over again. Even if one wants to get trained in a particular specialized field for a limited period, the resident has to clear USMLE to work with patients.

The relatively more straightforward option is to do fellowships in the United Kingdom. Sub-specialty fellowships are available in the UK, which one can directly apply for, after MD in India, without the need to pass PLAB or have an MRCPCH degree. One can either become a part of the Medical Training Initiative-Pediatrics-MTI (p), and start in a short term post and if necessary, later apply for a consultant post. One can also directly apply with the NHS jobs website to work as a locally employed doctor (LED), Doctor or Consultant. The NHS Jobs website is the largest repository of available posts in the NHS across the UK. International doctors can use it to seek both training and non-training posts. Those who have completed their MRCPCH, can apply with GMC for full registration with a license to practice.

Australia is another popular option among Indian graduates. While pediatric training is not directly recognized as valid, there are two pathways for international medical graduates. The "standard pathway" is preferred for MBBS students who appear for an exam conducted by the Australian Medical Council and if successful, enter into trainee positions. The "Specialist Pathway" is more suited for MD graduates, wherein one can directly approach colleges and are assessed in the respective field of study, and would be allotted to work in the particular specialization, if deemed "comparable". Those looking for temporary experience can apply for Short Term Training Program (STTP) in a Medical Specialty Pathway.[16,17,18]

One can also apply for jobs in countries like Canada, Singapore and Ireland, especially if one possesses an MRCPCH degree. MSF (Médecins Sans Frontières) is an out of the box option for those select few, interested in providing service to the population in distress in areas of natural or man-made disasters.[19,20]

Getting a job in middle east countries like Kingdom of Saudi Arabia, Kuwait, UAE is an another option for earning money as well as work in well equipped hospitals for a short period which enriches the financial status and provide an opportunity to undergo courses in western countries like MRCPCH. Work here in these countries may prove as a turning point in the career for many professionals.

Service in rural areas

Concept of working in rural areas as a compulsory option for post MBBS degree graduates, might be an influencing factor for pediatricians, in choosing their

career. Some opt to do that, even voluntarily and not out of compulsion alone. Working in rural and outreach areas gives utmost job satisfaction, if done willingly. It also provides them the need for clinical skills and the need for a doctor to serve to families in the remote rural areas. Some state government encourages the compulsory government posting and compensate by providing reservation in getting postgraduate seats.

Pursuing a different career like civil services or silver screen

After pediatrics training, doing an MBA or IAS, changing the career to hospital administration, starting an NGO, entering politics or even cinema industry could be opted too, as these may prove to be greener pastures.

Consecrated qualities of a doctor

Irrespective of the place of work, a doctor has professional qualities, which should cover four aspects in their professional career- clinical work, teaching, research and social and family responsibilities/activities. As pediatricians, we can easily achieve all these, if we choose our path wisely. We should never decide/choose a career path out of necessity or as the last resort. Just gaining more degrees for more money should not be the motive. There is no endpoint and in the future, we shouldn't be surprised if we come across a pediatric Fanconi anemia specialist or a pediatric inguinal lymph node specialist.

One should never forget the family members, old parents, partner and children. Patients will get another doctor easily, but our family might end up losing a dear member. You can see a patient smile, but don't miss your child's first social smile. So decide your profession, based on your goals as a clinician while considering the ways and means to support your family and it's needs, while leading a satisfactory and healthy life. Don't ever get trapped into unethical incentive systems, from any hospital or for investigations. Don't view a patient as a property of your hospital and fight for the hospital, but serve as an advocate for the child. As, we are bound by ethics to do the best for the child and not otherwise. Set "it" free, it will come back if you are ethical/dedicated with good knowledge. Children and their parents will recognize that. Beware of what you speak and what you write, since the so called 'common man' has all facilities to record or take copies or direct relay the prescriptions or consultations instantaneously, to people with vested interests, or in the pretext of seeking a second opinion.

Children are God's apostles, sent to preach love, hope and peace.

Proud to be a pediatrician!

Points to Remember

- ***Pediatrics, as such is a blessed work irrespective of the place or position.***
- ***Immediately after the MD or DNB pediatric i.e a second tier course pursuing a superspecialitiy course always compromise the life mile stones, which are more precious than the career.***
- ***Accepting any compulsory postings, though appear to be stressful, it has its own advantages.***
- ***Taking up a foreign assignment as job or postgraduate career depends on the country and one should weigh the pros and cons and also decide whether it is a short term or long term career.***
- ***Community practice is not a bad option provide one choose a right place where local support is available.***
- ***Whatever the career one choose, basic sacred qualities of a pediatrician can be always performed in all the situations.***
- ***Many of the pediatricians balance life mile stones and career options, giving priority to the first one.***

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CLIPPINGS

Laparoscopic versus open reduction of idiopathic intussusception in children: an updated institutional experience

A retrospective review was performed to evaluate outcomes for patients with idiopathic intussusception who were treated laparoscopically (LAP group) from January 2015 to December 2019 and to compare the outcomes with laparotomy (OPEN group) during the same period.

During the period studied, there were 162 patients treated surgically for intussusception, 62 LAP and 100 OPEN.

No statistical differences were found in demographic data, clinical symptoms and signs, duration of symptoms, location and types of intussusception between the two groups. Conversion to open procedure was required for 11 patients in the LAP group. The operation time, time to oral intake were length of stay significantly shorter (< 0.05) in the LAP group. Intraoperative and postoperative complication rates between the two groups were comparable ($P = 1.0$).

Laparoscopy was safe and effective in the treatment of pediatric idiopathic intussusceptions.

Zhao J, Sun J, Li D, Xu WJ. Laparoscopic versus open reduction of idiopathic intussusception in children: an updated institutional experience. BMC Pediatr 2022; 22(1):44. doi: 10.1186/s12887-022-03112-9. PMID: 35038989; PMCID: PMC8762853.

DRUG PROFILE

THERAPY OF ACNE VULGARIS

***Jeeson C.Unni**

Abstract: *Acne vulgaris is common in adolescents though children may also be affected. Topical and systemic drugs are prescribed depending on the severity and stage of the disease in a given child. Pediatricians need to be aware of the various modalities of treatment and must be actively involved in the long drawn therapy. This article reviews the various options and recommendations.*

Keywords: *Acne vulgaris, Benzoylperoxide, Azelaic acid, Retinoids, Topical antibiotics.*

Acne vulgaris commonly affects 90% of children around puberty and persists into adulthood in approximately 12%-14% of cases with psychological and social implications.[1] Acne can occasionally affect infants.[2] Treatment of acne should be commenced early to prevent scarring.[3] It is important to counsel adolescents and the family that, on commencing treatment, the lesions may worsen before improving. The choice of treatment depends on age, severity and whether the acne is predominantly inflammatory or comedonal.

Treatment principles

Mild to moderate acne is generally treated with topical preparations, such as benzoyl peroxide, azelaic acid and retinoids (Box 1).

For moderate to severe inflammatory acne or where topical preparations are not tolerated or are ineffective or where application to the site is difficult, systemic treatment with oral antibacterials may be effective.[4] Co-cyprindiol (cyproterone acetate with ethinylestradiol) has antiandrogenic properties and may be useful in young women with acne refractory to other treatments.[5]

Severe acne, acne unresponsive to prolonged courses of oral antibacterials, acne with scarring, or acne associated with psychological problems may be treated with oral isotretinoin under supervision of pediatric dermatologist. However, a Cochrane review has not shown any clear evidence from RCTs that isotretinoin improves acne severity compared with standard oral antibiotic and topical treatment.[6]

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Acne in neonates and infants

Inflammatory papules, pustules and occasionally comedones may develop at birth or within the first month; most neonates with acne do not require treatment. Acne developing at 3-6 months of age may be more severe and persistent; lesions are usually confined to the face. Topical preparations containing benzoyl peroxide (at the lowest strength possible to avoid irritation), adapalene, or tretinoin may be used if treatment for infantile acne is necessary.

In infants with inflammatory acne, oral erythromycin is used because topical preparations for acne are not well tolerated.[2] In cases of erythromycin-resistant acne, oral isotretinoin can be given on the advice of a pediatric dermatologist.

1. Topical preparations (Box 1)

a) Benzoyl peroxide

Topical benzoyl peroxide (BPO) is a widely used acne treatment as both comedones and inflamed lesions respond well in mild to moderate acne. Current evidence suggests that BPO as monotherapy or add-on treatment may be more effective than placebo or no treatment for improving acne and there may be little to no difference between BPO and either adapalene or clindamycin.[7]

Dose: Acne vulgaris and infantile acne: Apply to area after washing with soap water and drying[8] - Child 1 month-17 years: 1-2 times a day, preferably starting with a lower strength preparation and increasing the concentration of benzoyl peroxide gradually - the lower concentrations seem to be as effective as higher concentrations in reducing inflammation. It is usual to start with a lower strength and to increase the concentration of benzoyl peroxide gradually. In India only the 2.5% preparation is available. If excessive peeling or redness occurs - decrease to alternate day. If the

Box 1. Topical agents used for acne

1. Retinoids: They are comedolytic and anti-inflammatory. The most common preparations are adapalene, tazarotene and tretinoin. These cause thinning of the stratum corneum, associated with sun sensitivity.

2. Azelaic acid: A naturally occurring dicarboxylic acid that has antimicrobial activity and decreases hyperketatosis, has also been used for the treatment of acne.

3. Antibiotics: They are not comedolytic,but have anti-inflammatory property and bacterial resistance may develop to any of these agents. Commonly prescribed topical antibiotics include clindamycin, erythromycin, and, more recently, dapsone and minocycline. Antibiotic resistance in *C acnes* is common and is a significant threat to acne treatment. They should be used with benzoyl peroxide to reduce the likelihood of resistance.

4. Benzoyl peroxide: This products work as an antiseptic to reduce the number of bacteria on the surface of the skin are also effective against *C acnes* and bacterial resistance to benzoyl peroxide has not been reported.

5. Androgen receptor antagonists: Clascoterone 1% topical cream is an androgen receptor inhibitor approved by the FDA for acne vulgaris in patients aged beyond 12 years. Believed to compete with androgens, specifically dihydrotestosterone, for binding to the androgen receptors within the sebaceous gland and hair follicles.

acne does not respond after 2 months, then use of a topical antibacterial should be considered.

The choice of product and formulation (gel, solution, lotion, or cream) is largely determined by skin type, patient preference and previous usage of acne products. In general in wet or oozy skin conditions creams, lotions and drying pastes are most suitable. Ointments and oils are appropriate for dry scaly skin, wet compresses and soaks followed by creams or ointments are used for inflammed skin. Cream or a lotion is used in areas with skin folds.

Avoid in patients with known hypersensitivity to benzoyl peroxide. Avoid contact with eyes, mouth and other mucous membranes. Apply with care to neck and other sensitive areas. Benzoyl peroxide may bleach dyed fabrics.

Adverse effects include local skin irritation, particularly when therapy is initiated, but the scaling and redness often subside with a reduction in benzoyl peroxide concentration, frequency and area of application. It is important to avoid contact with broken skin, eyes, mouth, mucous membranes and excessive exposure to sunlight.

b) Azelaic acid

Azelaic acid (AZA), due to its anti-inflammatory, anti-oxidant, anti-keratinizing, antimicrobial and anticomedonal properties,[9] may be used as an alternative to benzoyl peroxide or a topical retinoid for treating mild to moderate comedonal acne, particularly of the face. It causes lesser local irritation than benzoyl peroxide. Azelaic acid can be used to manage dyspigmentation that occurs with inflammatory acne.[10]

The affected area is washed with water alone, dried and cream applied sparingly, rubbed well, initially once a day for a week to check for skin sensitivity and later twice daily.[8] The amount of cream applied is reduced if marked irritation of skin occurs. Distinct improvement is apparent after 4 weeks and it should not be applied for more than 6 months as continuous use causes local itching, burning, stinging and redness; necessitating need for novel preparations (liposomes, niosomes, micro sponges, lipid nanocarriers, etc.), which could enhance the overall pharmaceutical and pharmacological profile of the drug.[11]

c) Topical antibacterials

Topical preparations of erythromycin or clindamycin may be no more effective than topical benzoyl peroxide or tretinoin in management of mild to moderate inflammatory acne but may be tried when topical benzoyl peroxide or tretinoin is ineffective or poorly tolerated or as a first line therapy, as single or in combination.[10] They may be used in children who cannot tolerate oral antibacterials. Topical antibacterials can produce mild irritation of the skin and on rare occasions cause sensitisation; gastrointestinal disturbances have been reported with topical clindamycin.

Antibacterial resistance of *Propionibacterium acnes* is increasing; there is cross-resistance between erythromycin and clindamycin.

To avoid development of resistance,[12]

- avoid monotherapy with topical antibacterials
- when possible use non-antibiotic antimicrobials (such as benzoyl peroxide or azelaic acid)
- avoid concomitant treatment with different oral and topical antibacterials

- if a particular antibacterial is effective, use it for repeat courses if needed (short intervening courses of benzoyl peroxide or azelaic acid may eliminate any resistant *propionibacteria)*;
- do not continue oral antibacterials for longer than necessary (but treatment with a topical preparation should be continued for at least 6 months).

Topical clindamycin 1% w/w, available as a foam, a gel, a solution (liquid), a lotion, and a pledget (swab) may be applied as thin film twice daily with lotion and once with gel.[8] Topical erythromycin 3% w/v - applied twice daily directly to the affected area after washing .

d) Retinoids and related preparations

Topical tretinoin (all-trans-retinoic acid), isotretinoin (13-cis retinoic acid) as well as the synthetic third-generation polyaromatic retinoid adapalene and tazarotene, are useful for treating comedones and inflammatory lesions in mild to moderate acne.[13] Patients should be warned that some redness and skin peeling can occur initially but settles with time. If undue irritation occurs, the frequency of application should be reduced or treatment suspended until the reaction subsides; if irritation persists, discontinue treatment. Several months of treatment may be needed to achieve an optimal response and the treatment should be continued until no new lesions develop. Topical retinoids can be used under specialist supervision. The preparations are given in (Box 2).

The safety profile of topical retinoids differs from their systemic counterparts and is related mainly to local adverse effects, such as erythema, dryness, itching and stinging. The currently available evidence justifies the use of topical retinoids in most types of acne and during maintenance treatment.

Box 2. Topical retinoids

Tretinoin 0.025%, 0.05% and 0.1% gel and cream

Isotretinoin 0.05% gel

Tazarotene 0.1% (approved for use in USA), is more effective than tretinoin 0.025% or 0.1% microsphere gel or adapalene 0.1% gel or cream

Adapalene 0.1% is equally effective to tretinoin 0.025% or tretinoin microsphere 0.1% gel or tretinoin 0.05% cream or isotretinoin 0.05% gel

Adapalene 0.1% gel is significantly better tolerated than tazarotene 0.1% gel, tretinoin 0.025% and tretinoin 0.05% gel, tretinoin 0.05% cream, tretinoin microsphere 0.1% gel or isotretinoin 0.05% gel

Tretinoin 0.025%, 0.05% and 0.1% gel and cream are available:[8] The skin should be thoroughly washed first and the drug applied 1 to 2 times as a thin application. Cream is recommended for dry or fair skin, gel for oily or dark skin. Tretinoin is also available in combination with either erythromycin or clindamycin. Avoid contact with eye, nostrils, mouth and mucous membranes. Do not use simultaneously with peeling agent such as salicylic acid. Avoid ultraviolet lamps and minimize exposure to sunlight.

Isotretinoin 0.05% gel: Applied 1-2 times a day, thinly for mild to moderate acne. Contraindication for topical use include perioral dermatitis and rosacea.

It is preferable to allow peeling (resulting from other irritant treatments) to subside before using a topical retinoid. Alternating a preparation that causes peeling with a topical retinoid may give rise to contact dermatitis (reduce frequency of retinoid application), avoid accumulation in angles of the nose. Contact with eyes, nostrils, mouth and mucous membranes, eczematous, broken or sunburned skin, exposure to UV light (including sunlight, solariums) avoided. Also avoided in severe acne involving large areas and on sensitive areas such as the neck, with abrasive cleaners, comedogenic or astringent cosmetics and if there is a personal or family history of skin cancer.

2. Oral preparations

a) Antibacterials

Oral antibacterials may be used in moderate to severe inflammatory acne when topical treatment is not effective or is inappropriate.[12] Concomitant anticomedonal treatment with topical benzoyl peroxide or azelaic acid may also be required.

Either oxytetracycline or tetracycline are the first-choice antibiotic to be tried in children older than 12 years (Box 3). Watch for response for 3 months - maximum response occurs by 4 to 6 months and in some adolescents, therapy needs to be continued for 2 years or longer. If there is no improvement after 3 months of adequate therapy, other antibiotics like doxycycline or lymecycline may be tried.

Minocycline is effective but lupus erythematosus-like syndrome and irreversible pigmentation limit its use. Erythromycin is an alternative but emergence of *propionibacteria* strains resistant to erythromycin results in poor response.[14]

Rising concerns of antibiotic resistance and the perception of “antibiotic phobia” create potential limitations on integration of oral antibiotics in an acne treatment regimen.[15] Monotherapy with oral antibiotic is to be strictly avoided.

Box 3. Oral antibacterial and dosage

Tetracycline/oxytetracycline: 12 -17 years: 500 mg twice daily

Doxycycline: 12-17 years: 100 mg once daily

Minocycline: 12-17 years: 100 mg once daily, alternatively 50 mg twice daily

Lymecycline: 12-17 years: 408 mg daily for at least 8 weeks

Erythromycin: 1-23 months: 250 mg once daily, alternatively 125 mg twice daily; 12-17 years: 500 mg twice daily

b) Hormone therapy

Co-cyprindiol below (cyproterone acetate with ethinylestradiol) contains an anti-androgen. It is no more effective than an oral broad-spectrum antibacterial but is useful in females of childbearing age who also wish to receive oral contraception.[5]

Improvement of acne with co-cyprindiol probably occurs because of decreased sebum secretion which is under androgen control. Some females with moderately severe hirsutism may also benefit because hair growth is also androgen-dependent.

Dosage: Orally 1 tablet (Ethinylestradiol 35 microgram plus Cyproterone acetate 2 mg) for moderate to severe acne in females of child-bearing age refractory to topical therapy or oral antibacterials daily for 21 days, to be started on day 1 of menstrual cycle; subsequent courses repeated after a 7-day interval (during which withdrawal bleeding occurs), time to symptom remission, at least 3 months; review need for treatment regularly.

Need to consult specialists for use of this medication as the prescriber needs to be fully aware of a number of its contraindications, warnings and side effects.[12] One needs to be aware that the drug is to be avoided in pregnancy, due to risk of feminisation of male fetus and in lactating mothers, due to possibility of anti-androgen effects in the neonate.

c) Retinoids

The oral retinoid isotretinoin that reduces sebum secretion must only be prescribed under guidance and follow up of a pediatric dermatologist. Isotretinoin is used for the treatment of severe infantile acne resistant to erythromycin. It is given for at least 16 weeks; repeat courses are not normally required.

Isotretinoin is a toxic drug, is teratogenic and must not be given, to females of child-bearing age unless they practise effective contraception (oral progestogen-only contraceptives not considered effective). Adolescents with psychiatric illnesses may not be given this drug as suicidal ideation has been reported as a side effect, though not proved conclusively; the drug is to be discontinued if psychiatric manifestations are suspected while on treatment. Rarely, erectile dysfunction and decreased libido have been reported.

Dosage:[12] For severe acne and acne which is associated with psychological problems acne which has not responded to an adequate course of a systemic antibacterial, acne with scarring and systemic treatment of nodulo-cystic and conglobate acne-12-17 years: Initially 500 micrograms/kg daily oral in 1-2 divided doses, increased if necessary to 1 mg/kg daily for 16-24 weeks, repeat treatment course after a period of at least 8 weeks if relapse after first course; maximum 150 mg/kg per course.

Severe infantile acne - 1month-1 year: Initially 200 micrograms/kg daily oral in 1-2 divided doses, increased if necessary to 1 mg/kg daily for 16-24 weeks; maximum 150 mg/kg per course.

Points to Remember

- ***Therapy of acne targets the four factors responsible for lesion formation: increased sebum production, hyperkeratinization, colonization by Propionibacterium acnes and the resultant inflammatory reaction.***
- ***Treatment goals include scar prevention, reduction of psychological morbidity and resolution of lesions.***
- ***Mild to moderate acne is treated with topical preparations, such as benzoyl peroxide, azelaic acid, retinoids and topical antibiotics.***
- ***Benzoyl peroxide is an over-the-counter bactericidal agent that does not lead to bacterial resistance.***
- ***Topical retinoids are effective in treating inflammatory and noninflammatory lesions by preventing comedones, reducing existing comedones and targeting inflammation.***
- ***Topical and oral antibiotics are effective, more so when combined with topical benzoyl peroxide and/or retinoids which reduces the risk of bacterial resistance.***
- ***Moderate to severe inflammatory acne is treated with oral antibacterials, oral isotretinoin or Co-cyprindiol (cyproterone acetate with ethinylestradiol) an antiandrogenic drug.***

- ***Oral isotretinoin is approved for the treatment of severe recalcitrant acne - requires specialist intervention.***

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RADIOLOGY

INTRODUCTION TO CHEST X-RAY

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Chest X-rays are the first line investigation in a child with respiratory illness. Chest X-rays are commonly taken in frontal projections (antero-posterior/postero-anterior view) in adults and older children (Fig.1a and 1b). CXR for pediatric patients are taken in supine antero-posterior view most often. In antero-posterior view, the X-ray beam passes from the source and crosses the patient antero-posteriorly to hit the cassette and filmed. X-ray is basically a two dimensional image of the superimposed shadows of three dimensional thorax.

Chest X-ray is usually taken during inspiration and in older children to hold the breath is easier, otherwise the technician's expertise helps. The normal chest X-ray in inspiration shows well aerated lungs upto the dome of the diaphragm where the anterior ends of the 6th, 7th or 8th ribs meet the diaphragm.

Reading an X-ray should be methodical and stepwise

A. Patient information such as name, age, gender, date of birth in newborns and any other relevant data should be verified first. Following this, one would set out to read an X-ray chest in a step wise fashion, usually starting with a) orientation-erect, supine or lateral, b) position - AP or PA and c) side marking - right or left (Fig.2).

B. Amongst these, most important point to be noted is the marking of the sides of the film (right or left). For uniformity usually the marker is placed on the right side. It must not be assumed that the heart is on the left side of the chest at any time - dextrocardia or more ominous diaphragmatic hernia on the left in neonates may spell disaster if not noticed.

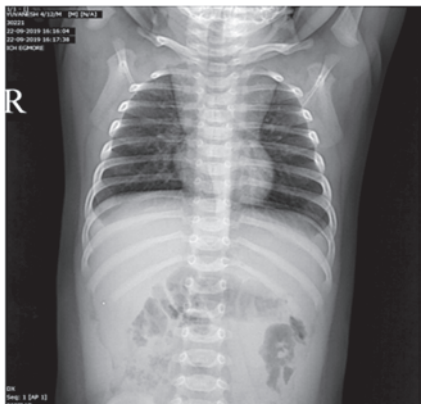

Fig.1a. Chest X-Ray

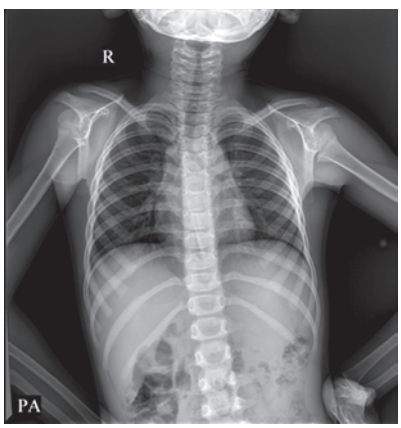

Fig.1b. Chest X-Ray PA view

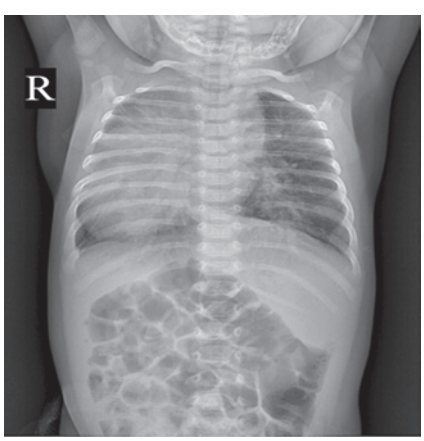

Fig.2. Situs inversus totalis

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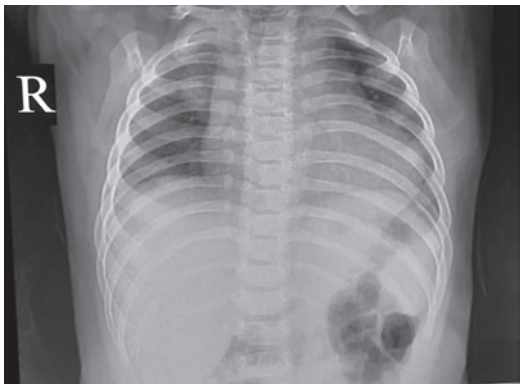

Fig.3. Chest X-Ray: Expiratory film

C. As pointed earlier, in infants and children the film is an antero-posterior projection and taken supine. Images will be more magnified and less sharp on an AP film compared to a PA, causing the size of the heart to look larger (Fig.3).

D. Whenever one looks at any chest film the point to be noted is to see whether it has readable quality or not.

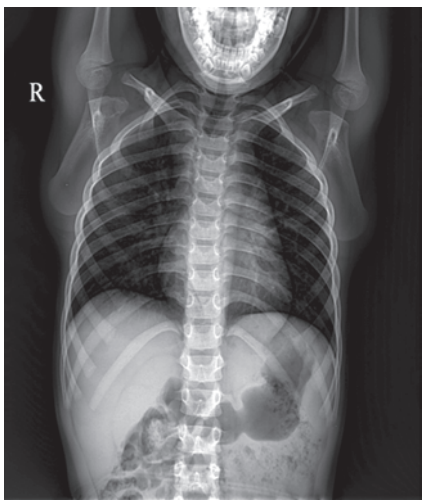

Fig.4a. Over exposed

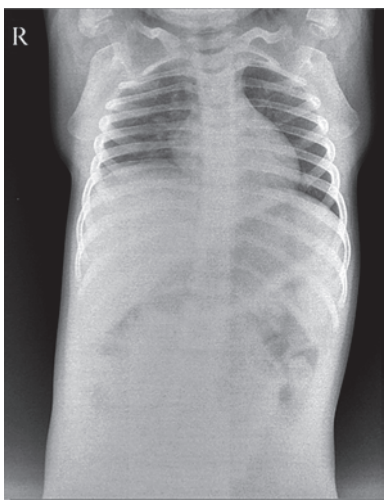

Fig.4b. Under exposed

The readable quality is dependent on both penetration and exposure. It should not be too black or too white (Fig.4a and 4b). If the penetration is perfect one should barely see the thoracic vertebrae behind the heart and in proper exposure the costophrenic angle on both the sides are to be seen well.

E. The position of the patient in the film has to be checked by noting the following points. The medial ends of the clavicles should be symmetrical and equidistant from the spines / sternal border. There should neither be over crowding nor widening of the rib spaces. In a properly centered film, the trachea is just off midline to the right because of the left aortic arch. Nearly one-third of the heart is seen to the right and two-thirds on the left of vertebral column. More often right border of the heart merges with

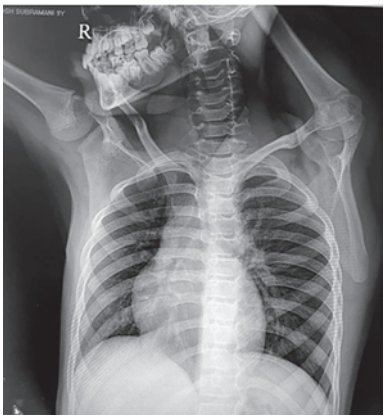

Fig.5. Chest X-Ray: Rotated to right side

the right sternal border. If an image is rotated to the right, the right clavicle would be farther away from the spinous process of the vertebrae / sternal border and with the left shoulder being lifted up towards the X-ray beam, the heart will appear larger as more of the left ventricle will be seen and a normal thymus may look like left upper lobe infiltrate (Fig.5).

F. The thymus is seen in the anterior mediastinum. The thymic shadow will not cause mass effect on the trachea or vascular structures and can be prominently seen

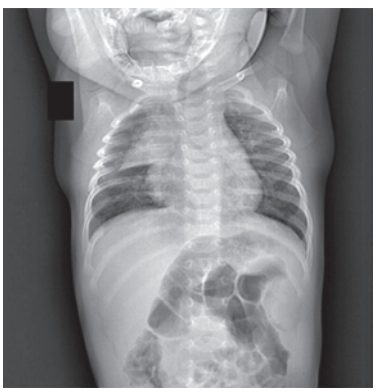

Fig.6a. Thymic sail sign

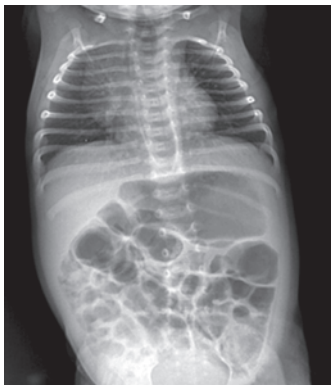

Fig.6b. Wavy border

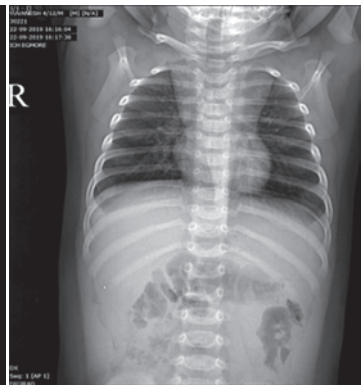

Fig.6c. Quadrilateral shape

up to 2 years of age. Thymic shadow gets reduced in size as the child gets older and may not be visualised after 8 years of age. Thymic shadow may be of any shape or size and may project laterally on both the sides. The lateral border of the thymus may be indented by the anterior ribs resulting in a wavy border (Fig.6a and 6b). In neonates, it usually projects to right side with a sharp inferior border resulting in thymic sail sign (Fig.6c), otherwise the cardio-thymic silhouette appears as a continuous shadow.

In pnuemomediastinum, both lobes of thymus are separated from cardiac shadow forming 'Spinnaker sail sign' (Fig.7).

After taking meticulous care to check the above points X-ray chest review can be under taken looking for signs specific to the clinical scenario. It can be read in more than one way. The order in which chest X-ray is read is usually from the periphery to the centre. However, there is no perfect way to read an X-ray and the guidelines are to adopt one or the other approach and to use the chosen approach consistently. X-ray chest review is the key competency for medical students and residents. ABCDE approach is a helpful systematic method (Box 1).

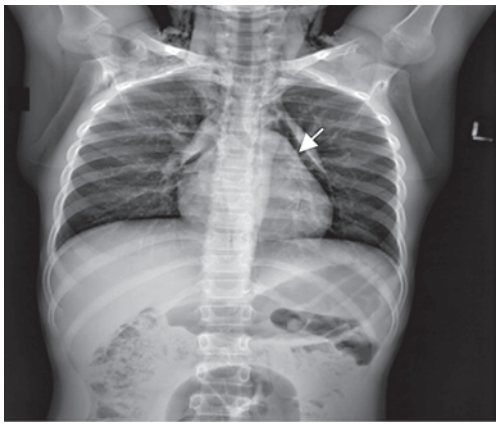

Fig.7. X-ray chest: Spinnaker sail sign

Box 1. Stepwise approach to reading X-ray chest

A: Airways and lungs, air spaces, lung fields

B: Bones and soft tissue of chest wall

C: Cardiac shadow and blood vessels

D: Diaphragm, costophrenic and cardiophrenic angles

E: Everything else below the diaphragm, liver density, gastric bubble, any air under diaphragm, bowel shadows

Airways and lungs, air spaces, lung fields

One should trace down the trachea from the neck to the carina to check whether it is straight and slightly to the right. Trachea gets pushed away, in pleural effusion or tension pneumothorax and gets pulled towards the same side in atelectasis and fibrosis. Trachea is normally the narrowest at the vocal cords level and hence seen starting as the narrowest top most structure. The carinal angle should be between 60-100 degrees. Carinal angle when more than 100 degrees is abnormal and is seen in left atrial enlargement, lymph node enlargement (mediastinal / carinal) and in left upper lobe atelectasis. Then one must see and follow the main stem bronchi on the both sides.

Meticulously checking for tubes, nasogastric, chest tubes, pacemaker, wires, central lines and foreign bodies are to be the norm. Any foreign body in the neck should not be missed. External objects are never to be in the line of X-ray beam at any time. Migratory foreign bodies inside the heart are to be carefully looked for, if clinical scenario warrants.

If an endotracheal tube is in place, one must check the position; the distal tip of the tube should be 3-4cm above the carina.

Both lungs should be well expanded and similar in volume (one lung must not be larger than the other) and in translucency. One should be able to count 10 posterior ribs bilaterally and six to eight anterior ribs bilaterally.

It is mandatory comparing the apical, upper, middle and lower zones in turn, for any areas of increased density or increased lucency. Both the lung fields are assessed systematically and looked for asymmetric densities.

Tracing the lung vascular markings to see whether they branch out progressively and uniformly is useful. Also one should look for retro cardiac and any other abnormal retro diaphragmatic vessels.

In expiratory film, the diaphragm is seen up and lungs appear less dark with ribs crowded and heart appear bigger. Meticulously one should examine the plural space area for any altered density or lucency.

Bones and soft tissue of chest wall

One must check for any bony pathology (fracture or lytic lesions) in the ribs, shoulders and upper humerus and trace along the posterior (horizontal) rib on both the side of the chest. Costochondral beading or fraying anterior ends of ribs must be looked for. It is wise to look for features of rickets and lead lines with increase density in the upper ends of humerus, anterior ends of ribs and inferior angle of scapula in lead poisoning. Subcutaneous emphysema can be seen in the soft tissue in the neck and chest wall in trauma and air leak syndrome.

The vertebral bodies should be checked for their shape (rectangular), height and disc spaces.

Both the paravertebral lines are also to be assessed for any widening.

Cardiac shadow and blood vessels

One must examine the cardiac position and shape looking for any known typical shapes like coer en sabot, etc. The cardiac size is estimated by cardiothoracic ratio (normal 55% / 60%). Check the position and size of the aortic arch and pulmonary trunk, width of the upper mediastinum for any widening and hilar vessels of both sides and note whether they are at the same level.

Pulmonary vessels are seen branching and tapering towards the periphery and their end on views are seen as white specks or dots accompanying bronchial branches. The right side of the superior mediastinum from above downwards shows the superior venacava which is seen as a straight line extending down to the level of right bronchus which marks the cavo-atrial junction. When a central venous line is in the internal jugular vein, the tip of the central venous catheter should not extend below the right bronchus level. The right cardiac border is formed by the right atrium. The lowermost border merges with the diaphragm as the IVC enters the right atrium. As the right atrium enlarges, this point moves further to the right, whereas when the right cardiac border is formed by the enlarged left atrium, the border curves medially towards the midline towards the atrioventricular groove.

The left border of mediastinum shows the aortic knuckle, pulmonary artery (above the level of left main bronchus), left atrial appendage and left ventricle above downwards.

Diaphragm

The left diaphragm appears a little lower than the right by two intercostal spaces. Costophrenic and cardiophrenic angles are to be checked whether they are free or obliterated.

Everything else

Before venturing into scrutinizing areas below the diaphragm one must look for any unusual densities such as lymph nodes, coin / ring shadows or lucent lesions such as localized emphysema or congenital cysts / pneumatoceles in the lung fields.

- One must look for free gas under the diaphragms, subcutaneous emphysema, gastric bubble in the correct place, hiatus hernia and any surgical clips
- Lateral view may be complementary to the frontal view in localising the site of lesion in thoracic pathology. In the lateral view, the lower dorsal vertebrae are seen clearly than the upper ones because of decrease in the quantum of soft tissue and more lucent lungs. The lucency is reduced in lesions of the lower lobe.

Request for a chest X-ray in a child would be commonly to identify the cause of respiratory distress or focus of infection.

Consolidation is seen with air-bronchogram without volume loss. 'Silhouetting'of right cardiac border is seen in right middle lobe consolidation, similar shadowing of the diaphragms in the lower lobe consolidation and left cardiac border in lingual lobe consolidation (Fig.8).

When there is collapse there will be signs of volume loss like crowding of ribs, elevation of diaphragm and mediastinal shift to same side (Fig.9).

Inhalation of vegetable foreign bodies are radiolucent

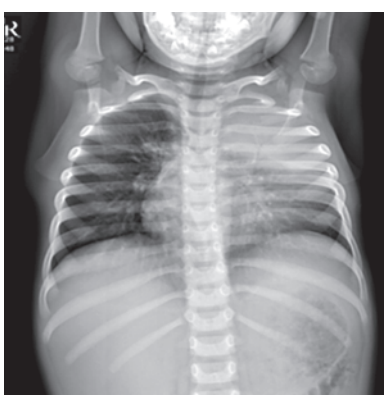

Fig.8. X-ray chest: Left upper lobe consolidation. Lingular involvement silhouettes the left cardiac border

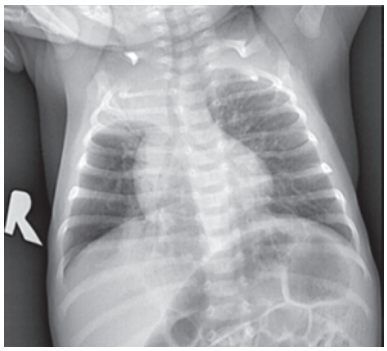

Fig.9. X-ray chest: Right upper lobe collapse - Minor fissure pulled up, right diaphragm elevated and trachea shifted to right

and can cause obstructive emphysema resulting in hyperlucent, overinflated ipsilateral chest (Fig.10). In the presence of obstructive emphysema bronchovascular markings are less distinctive and there will not be a collapsed lung border. But in pneumothorax brochovascular marking will be completely absent and collapsed lung border can be identified. Radio opaque foreign bodies should be looked for and traced in the air ways and in the lung fields.

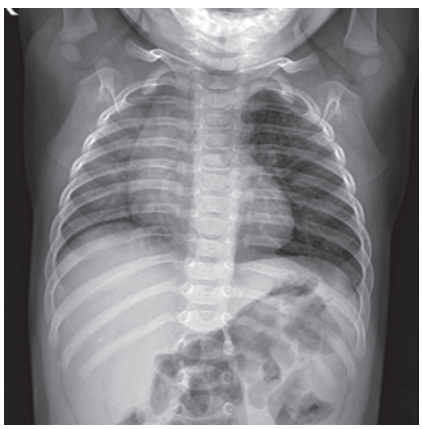

Fig.10. X-ray chest: Left obstructive emphysema due to radiolucent foreign body

When there is small amount of fluid or air, they can be identified in a lateral decubitus view taking advantage of gravity. In this view, the patient is made to lie in lateral position and the X-ray beam passes antero-posteriorly. Since air rises to the top, the side suspected to have pnuemothorax should be up, (in right pnuemothorax the right side of the chest should be up) wherein the air can be

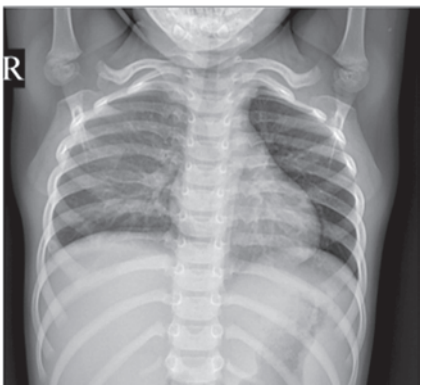

Fig.11. X-ray chest: Right pleural fluid. Increased opacity of right hemithorax

Pleural fluid is seen as an increase in opacity of that hemithorax as the fluid layers behind the lungs (Fig.11).

Pnuemothorax is identified by the sharp white line (visceral pleura) beyond which no vascular markings are seen (Fig.12). Skin folds are differentiated by their extension beyond the lung fields and presence of vascular markings lateral to the fold.

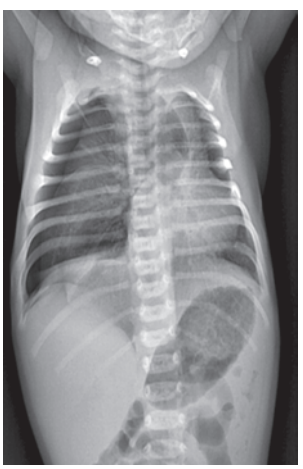

Fig.12. X-Ray chest: Right pneumothorax

distinctly seen on top. Whereas in the case of fluid in the right side the lateral decubitus film should be taken with the right side of the chest kept below.

The eyes see only what the mind knows. Radiological help is always taken as a third eye when one has a sound knowledge of the clinical scenario.

CASE REPORT

MALIGNANT INFANTILE OSTEOPETROSIS

***Preethi N**
****Latha Kanchi Parthasarathy**
*****Ramya Uppuluri**
******Devimeenakshi K**

Abstract: *Malignant infantile osteopetrosis is a rare congenital disorder characterized by increased bone density due to defective resorption of bone by osteoclasts. Infantile malignant osteopetrosis usually presents in infancy with bone marrow failure leading to hematological abnormalities like pancytopenia and hepatosplenomegaly due to extramedullary hematopoiesis. Though it commonly presents in early infancy, it should be suspected even in neonates presenting with characteristic features.*

Keywords: *Osteopetrosis, Bone marrow, Osteoclast.*

Osteopetrosis comprises a group of clinically and genetically heterogeneous conditions with increased bone density.[1] The increased bone density is a result of defective formation of ruffled borders of osteoclast required for bone resorption.[2] Autosomal recessive malignant infantile osteopetrosis is a rare congenital disorder presenting within the first year of life, mostly within the first 3 months of life with an average incidence of 1 in 250000 births.[1,3] We present here, a case of infantile malignant osteopetrosis diagnosed in the neonatal period.

A 21 hour old female baby born of second-degree consanguineous marriage was referred to our hospital in view of previous two sibling deaths in infancy. Antenatal period was uneventful and baby was delivered at 39 weeks of gestation by caesarean section. On admission, the baby was euthermic and euglycemic with stable vitals and normal anthropometry. The baby had facial dysmorphism with frontal bossing, hypertelorism, depressed nasal bridge, low set ears, anti mongoloid slant of palpebral fissure, high arched palate and retrognathia. Per abdominal examination revealed soft hepatosplenomegaly and other systems were clinically normal.

In view of consanguinity and death of siblings in infancy we proceeded to investigate for inborn errors of metabolism. The initial complete blood count, renal and liver function tests were normal. Urine for reducing substances, tandem mass spectrometry and urine metabolic screening turned out to be negative.

Hepatosplenomegaly progressively increased in the following days and was firm in consistency. Baby developed respiratory distress and CXR revealed increased bone density giving a clue to osteopetrosis (Fig.1). A skeletal survey was performed which showed dense, homogenously sclerotic bones with no corticomedullary differentiation (Fig.2). On further evaluation serum phosphorous was found decreased (2.1 mg/dL), alkaline phosphatase normal (58), LDH elevated (1854 U/L), serum calcium low 5.9 mg/dL. With these findings diagnosis of osteopetrosis was made. By day 13, peripheral smear showed bicytopenia (platelet 16000, Hb 6.3 g/dL) requiring platelet and PRBC transfusion. As per the parents' wish the neonate was discharged and got admitted in another hospital for further treatment.

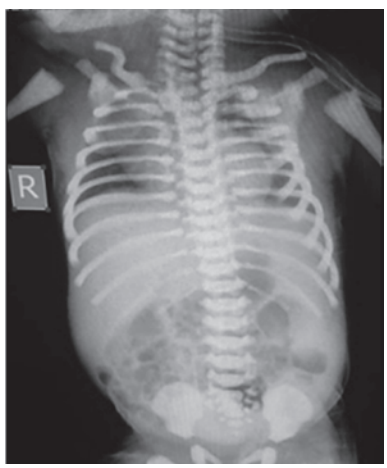

Fig.1. Chest X-ray showing increased bone density

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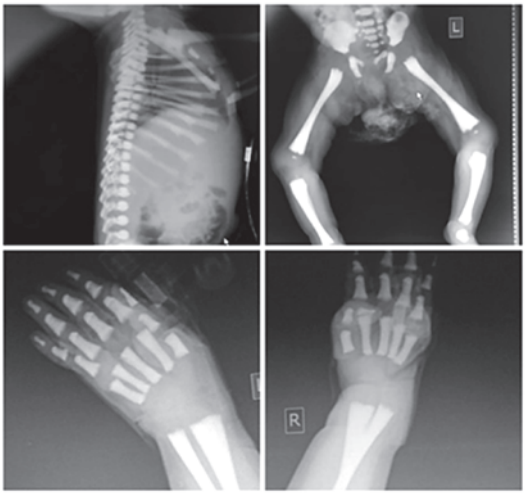

Fig.2. Skeletal survey showing loss of corticomedullary differentiation

In the second hospital the child continued to deteriorate and was given supportive management with further transfusions. Genetic testing was done which confirmed autosomal recessive osteopetrosis due to CLCN7 mutation. When the prognosis and line of management was explained to parents, they requested discharge against medical advice. Baby succumbed at home on 54th day of life.

Discussion

Malignant osteopetrosis is commonly diagnosed within the first year of life with bone marrow failure and pancytopenia. Extramedullary hematopoiesis results in hepatosplenomegaly, macrocephaly and frontal bossing which mimics facial dysmorphism. Narrowing of cranial nerve foramina and foramen magnum can affect optic, oculomotor, auditory, facial nerve and cause hydrocephalus respectively.[1,4] Visual impairment tends to be irreversible even after bone marrow transplantation.[1] Malignant infantile osteopetrosis can present with hypocalcemia.[5] LDH and alkaline phosphatase are elevated, but normal range of alkaline phosphatase was seen in 4 out of 20 patients in a study, as in our case.[6] X-ray shows "bone in bone" appearance due to bone sclerosis.

Older infants present with failure to thrive, either due to anemia, renal tubular acidosis or recurrent infections. These infections can be due to an unexplained defect in the production of neutrophil superoxide function.[7] Majority of patients are anemic and become transfusion dependent. Transfusion dependency before 3 months of age is a sign of severe disease and poor prognosis.[1]

A previous study done in 20 patients with infantile malignant osteopetrosis showed mutations in TCIRG1, OSTM1, CLCN7 and TNFRSF11A mutation in 14 patients.[6] All these genes are involved in establishing an acidic environment for osteoclastic resorption.[8] TCIRG1 gene encoding for alpha 3 subunit of vacuolar ATPase is an important gene for autosomal recessive osteopetrosis followed by CLCN7 gene encoding for chloride channel or chloride/proton exchanger.[8] Calcitriol, interferon gamma and prednisolone therapy have been tried with inconsistent outcomes.[7,9] Bone marrow transplantation done early remains the definitive treatment. This case is discussed because of the early presentation in neonatal period and for the positive genetic mutation.

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CASE REPORT

SPORADIC HEMIPLEGIC MIGRAINE IN A CHILD

***Arulmozhi T**
****Suba Rajinikanth**

Abstract: *Hemiplegic migraine is a rare form of migraine with aura presenting with reversible weakness. In an emergency room setting with a child having headache and focal deficits it is a diagnostic challenge with an immediate need to rule out underlying life-threatening conditions. Identifying this easily treatable condition will avoid undue anxiety and unnecessary investigations.*

Keywords: *Hemiplegic migraine, Childhood headaches, Focal weakness.*

Hemiplegic migraine is defined as a type of migraine with aura characterized by headache and motor weakness with an associated deficit which may include either visual, sensory, speech or language dysfunction. Based on family history and inheritance pattern they are classified as familial and sporadic types.[1] Studies on the disease burden of childhood migraine in Indian school children have reported a high prevalence in both community[2] and hospital[3] settings. However, data on childhood migraine with motor weakness are sparse. Hence hemiplegic migraine may be considered as an uncommon presentation of a common disorder. A high index of clinical suspicion and proper approach will help us in early identification of this easily treatable condition.

Miss G, an eight-year-old girl presented to the emergency room with dizziness, unsteadiness and inability to use the right upper and lower limb for 3 hours. The child had headache after waking up in the morning but she was able to carry out her routines and was sent to school as the headache was considered as "usual". However, the intensity worsened through the day and resulted in vomiting and subsequent dizziness and a feeling of light headedness towards the evening. The child developed unsteadiness while returning from school and then difficulty in using the right upper limb. She also noticed tingling and pain in the right upper and lower limb. There was a past history of recurrent headaches for 2 years with about 2-3 episodes in a month each lasting for 6 to 12 hours and requiring analgesics. These episodes were getting more frequent prior to this event. There was a recent history of trivial head trauma resulting in only scalp injury. Her mother had migraine headaches throughout childhood.

Clinical examination revealed an alert, afebrile and cooperative child. Gaze evoked nystagmus was present with normal pupils and ocular fundi. Visual fields were normal by confrontation. Right upper motor neuron facial weakness was present with weakness of right upper and lower limbs of grade 3. There was tingling and pain without any sensory deficit. Left upper and lower limbs were normal. Meningeal signs were absent. After admission and during the period of supportive care and evaluation the weakness recovered and power returned to grade 5 in 60 minutes. The gaze evoked nystagmus however persisted for 24 hrs and child was able to walk unsupported the next day and headache subsided.

Basic blood chemistries including glucose, electrolytes, renal, thyroid and liver function tests were normal. Neuro imaging with MRI including angiogram was normal. Blood lactate and pyruvate levels were normal. Tandem mass spectroscopy for metabolic disorders was normal. Procoagulant workup with homocysteine levels protein C, protein S and antithrombin 3 came negative. As the child recovered, EEG and CSF analysis were not done.

A differential diagnosis of focal neurological deficits on a background of headaches was considered. This includes stroke, demyelination, focal seizures and space occupying lesions which were ruled out with the above investigations. A final diagnosis of sporadic hemiplegic migraine (SHM) was made and child started on tablet flunarizine 5 mg HS and propranolol 1mg / kg in 2 divided doses as prophylactic agents. As the child had rapidly recovered, there was no need for acute or abortive therapy for migraine. A transient hyperammonemia was

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noted which subsided on the 4th day of admission. Genetic test by next generation whole exom e sequencing was sent which detected a heterogenous mutation in the SPTBN2 gene on chromosome 11. This had no clear correlation with the phenotype and parents were not willing for a parental Sanger testing due to affordability issues. Child has been followed up for 1 year with no relapse of headache or neurological symptoms.

Discussion

Sporadic hemiplegic migraine (SHM) of childhood is classified under migraine with aura which includes fully reversible motor weakness and /or visual, sensory, speech, language symptoms by the international headache society (IHS).[1] These symptoms of aura are usually accompanied or followed by headache. The rapid recovery of the focal symptoms restricts the differential to paroxysmal episodic disorders that are common in the particular age group. The index child had unsteadiness and gaze evoked nystagmus in addition to the transient motor weakness suggestive of basilar type symptoms. Interestingly in previous published studies 72% of the patients with SHM fulfilled the IHS criteria for basilar migraine during SHM attacks.[6] The real challenge however is to exclude serious underlying conditions with potential life-threatening causes from the primary headaches. Previous studies have shown that bilateral pain and non-pulsatile quality are clinical clues for presence of these secondary headaches.[4] Focal seizures with Todd's palsy, vascular insults like childhood stroke presenting with TIA, arteriovenous malformation, cerebral venous sinus thrombosis, episodic ataxias, demyelinating diseases, inherited mitochondrial diseases such as MELAS presenting with stroke like episodes and metabolic diseases must be excluded.[7] As migraine with aura is disease of exclusion, secondary causes must be ruled out with certainty and it is prudent to follow up these children before a final diagnosis is reached.

The index case had past recurrent migrainous headaches with family history of headaches. However, there was no diagnosis of hemiplegic migraine in family members. Interestingly she also had transient cerebellar signs in the form of unsteadiness and gaze evoked nystagmus suggestive of brainstem involvement. Genetic evaluation has picked up SPTBN2 mutation in spectrin binding protein which normally maintains the stability of membrane channels and when defective cause cerebellar dysfunction.[5] However, its role in causing headache and periodic syndromes are not known and further studies are required. No pathogenic variants of FHM types 1-3 (CACNA1A, ATP1A2 and SCN1A) were detected.

A child presenting with headaches and focal neurological deficits to the ER is a challenge because of possibility of underlying life-threatening causes. A stepwise approach, close observation and follow up will be required for correct diagnosis. Attention to the past history of recurrent headaches with complete recovery, trigger factors which sometimes may be an insignificant trauma and family history of episodic headaches will help us diagnose this condition.

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CASE VIGNETTE

AN UNUSUAL CASE OF FOREIGN BODY ASPIRATION IN AN INFANT

***Anil Kumar P**
****Vishnu Priya R**

A 7-month-old female child, born out of non-consanguineous marriage, presented with complains of sudden onset of cough and breathing difficulty for 1 day with no obvious history of choking. Hoarseness of voice, tachypnoea and suprasternal retractions were noted. The patient was initially treated as 'croup'. Serial chest X-rays failed to give any clue. Subsequently the child developed wheeze which partially responded to bronchodilators and steroids. Foreign body aspiration was suspected as the symptoms persisted and bronchoscopy was planned. But on the same day, the child had bouts of cough and a foreign body was expelled-size of 0.7mm x 0.6mm (Fig.1). Probably it must have been lodged in the upper airway in larynx. Immediately following expulsion, the child's symptoms improved and she was discharged successfully after 2 days.

Most common age group in which foreign body aspiration is encountered is 1-3 years of age with choking as the most common symptom. The most common foreign bodies encountered are organic seeds related to edible materials.[1] The foreign body aspirated in this case was the seed of Indian sandbur (Cenchrus biflorus Roxb) or bhurut. (Fig.2). It is a common weed growing in dry areas, sand dunes or bare sandy ground, desert fringes, disturbed land, areas of abandoned cultivation and fallow land. Seeds dispersal is through the attachment of burs to passing cars, animals and human clothes. It is common in Africa, south of the Sahara. In India, it is particularly found in Rajasthan and Punjab. Due to its sharp spines, it gets stuck in the upper aerodigestive tract and seldom reaches the esophagus or airway.. Bhurut was usually found to be attached to the pharynx and larynx.[2] Retrospectively the father recounted that when he was working on the farm holding the child, symptoms started acutely. Probably the seed was on his dress and the child might have sucked and swallowed the foreign body.

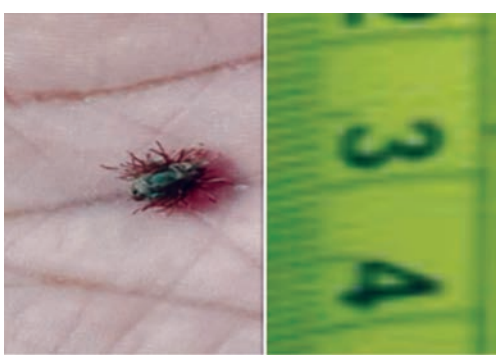

Fig.1. Expelled foreign body

Fig.2. Indian sandbur

The highlights of this case include - a negative choking history, absent radiological findings, intermittent response to steroids and bronchodilators with an unusual foreign body (spinous seed) being expelled spontaneously. As this type of foreign body got stuck in the upper aerodigestive tract, there was no radiological changes observed. However, a study showed that chest X-ray had only 67% diagnostic accuracy.[3] The lesson learnt from this case is that in any child presenting with with sudden onset of respiratory symptoms irrespective of age and negative history, foreign body aspiration must be suspected.

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CLIPPINGS

The potential hepatoprotective effect of metformin in hepatitis C virus-infected adolescent patients with beta thalassemia major: Randomised clinical trial.

This was a 6 month prospective, randomised, parallel, controlled, open-label study. A total of 225 patients aged 11 to 18 years with β-TM on regular blood transfusion and iron chelation therapy were screened for HCV antibodies. 91 patients were found to be HCV positive. (40.44%). 60 HCV positive children, weighing 35 kg or more, and receiving no antiviral therapy were selected. Those with renal impairment, heart failure, sepsis or severe infection, diabetes mellitus, regular consumption of medication with potential hepatotoxicity, gastrointestinal conditions preventing absorption of oral medications were excluded. They were randomly assigned to treatment or control group in 1:1 allocation. Both groups were receiving standard-of-care regimen. Metformin (500 mg, twice daily) was added to the treatment group's regimen only(29 patients). Patients were prospectively followed up for 6 months. Liver biochemical profile, oxidative stress markers(total antioxidant capacity and malondialdehyde serum levels), fasting blood glucose and creatinine were done at baseline, 3 and 6 months. Fibroscan and serum ferritin were done at baseline and at 6 months. Clinical symptom improvement and metformin's adverse effects were also noted.

Result: Aspartate aminotransferase serum level decreased significantly over time in the treatment group only ($P = .013$). However, improvement was not clinically significant and did not attain normality. Change in total antioxidant capacity and malondialdehyde serum levels indicated significantly improved oxidative stress status in the treatment group versus significant deterioration in the control group ($P < .001$). Fibrosis grade improvement was observed in 14 patients in the treatment group versus one improved case in the control group. Only 10.34% of patients reported some GIT upset that resolved before the end of their first week of treatment. The study concluded that metformin may be used as a supportive adjuvant treatment till the patients are eligible for HCV antiviral treatment

Talebi A, Kargar M. Hepatoprotective effects of metformin in hepatitis C virus-infected adolescents with beta thalassemia major. Int J Clin Pract 2021; 75(12):e14951. doi.org/10.1111/ijcp.14951

NEWS AND NOTES

NCPID 2022

24th National Conference of Pediatric Infectious Diseases

IAP-ID Chapter

From Concepts to Consensus

Date: 19th & 20th November, 2022

Venue: VIT Auditorium Vellore

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CASE VIGNETTE

ORCHITIS AS AN UNUSUAL MANIFESTATION IN MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

***Kalpana S**
****Shobha SR**

An 8 year old male child presented with complaints of fever for 5 days, loose stools, abdominal pain and erythema of the palms and soles for 3 days. There was history of short duration fever in all his family members one month back, but none of them were tested for COVID-19 infection. On admission, he was febrile and had erythematous extremities. There was no organomegaly. He presented with hypotensive shock which was managed with fluid boluses and inotrope support. Fever workup including cultures were negative. His covid antibody was positive (16.17 index units). Inflammatory markers were elevated: ESR - 50 mm in 1 hour; C reactive protein - 51 mg/dL; ferritin - >1000 ng/mL; D dimer - 8260 ng/mL. Echocardiogram was normal. As he met the criteria for multisystem inflammatory syndrome in children (MISC), he was managed with intravenous immunoglobulin, methylprednisolone and other supportive measures.

His fever subsided within 48 hours and his inflammatory markers showed a declining trend. On third day of becoming afebrile, the child complained of swelling, pain and redness of right scrotum. There was no recurrence of fever. There was no parotid swelling associated with the orchitis. On examination, the right testis was enlarged, tender, located in the normal anatomic position with an intact ipsilateral cremasteric reflex. Testicular torsion was ruled out by ultrasound doppler. The unilateral orchitis was managed with supportive measures and subsided by 48 hours.

Literature search was done to find a possible association between MISC and unilateral orchitis. Epididymoorchitis has been infrequently reported in case series of MISC.[1,2] Acute epididymitis is known to occur in systemic diseases such as Kawasaki disease, and Henoch–Schoenlein purpura. But underlying pathophysiological mechanism in MISC is not known. Awareness about the association will be helpful in avoiding unnecessary investigations in these children.

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NEWS AND NOTES

23rd National Conference of IAP Intensive Care Chapter
PEDICRITICON 2021
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Conference Secretariat
Mobile : +91-9829300541; E-mail: pedicriticon2021jaipur@gmail.com
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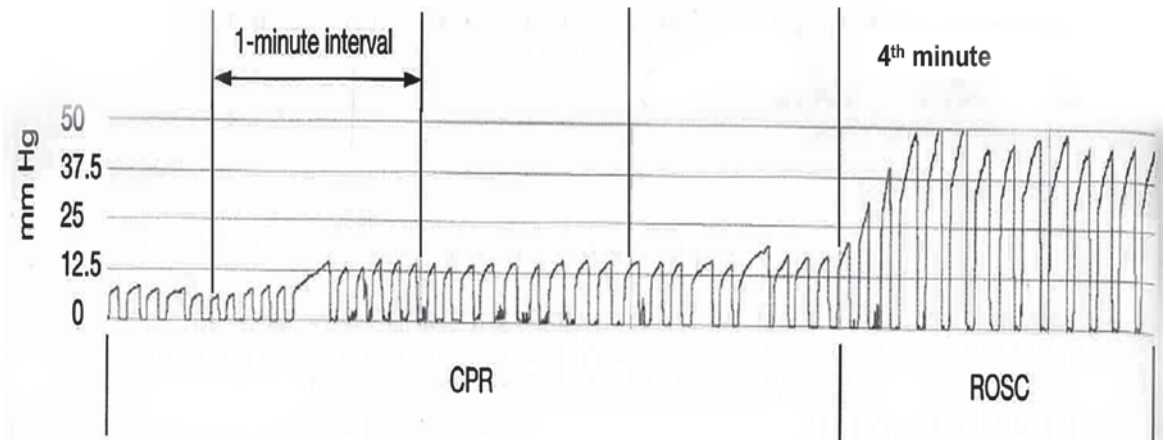
LEARNING TOGETHER

OSCE

OSCE 1



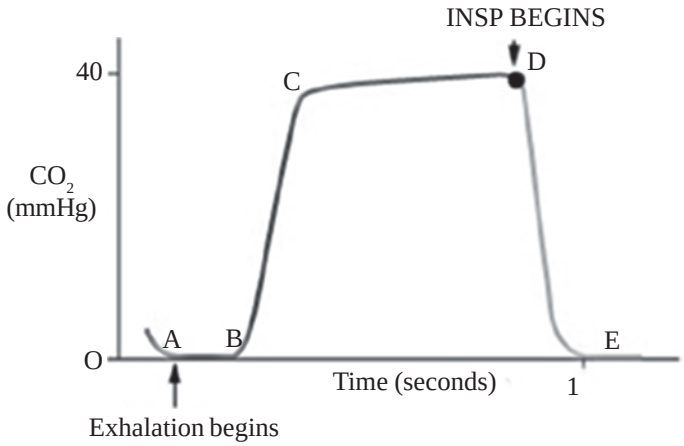
1) What is the tracing?

2) What is ROSC?

3) What has happened at the 4th minute?

4) What are the physiological functions reflected in this tracing?

OSCE 2

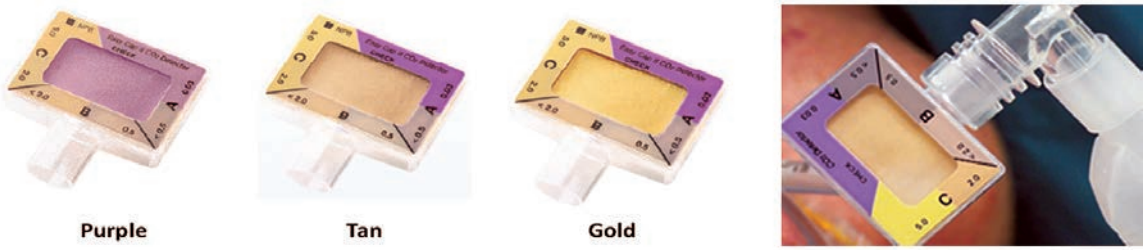


1) What is this tracing?

2) Identify A-B, B-C, C-D, D-E?

3) What are the ways in which this data is expressed?

OSCE 3

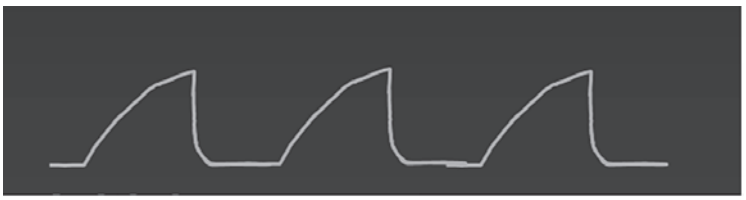


1) Identify the device?

2) Interpret the different colour changes observed in this device?

OSCE 4

Interpret the following tracing. a, b, c, d, e, f, g and h



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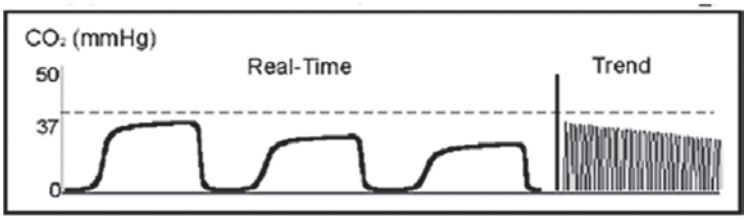

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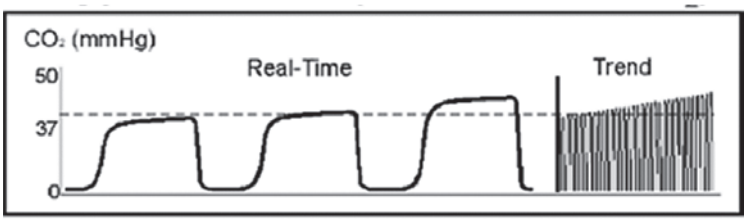

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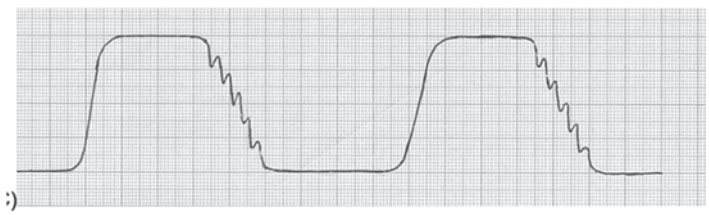

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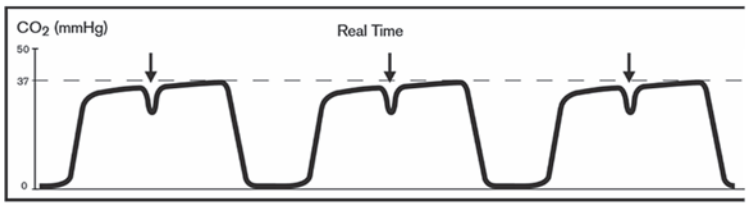

e

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g

h

OSCE 5

Mention the best study design for the following research questions.

Study Question	**Study Design**
1. Prevalence of vitamin A deficiency	1.
2. Clinical course of Zika virus infection	2.
3. Efficacy of ranitidine against omeprazole in acid peptic disease	3.
4. Usefulness of procalcitonin in the diagnosis of neonatal sepsis	4.
5. Spectrum of clinical features of a rare genetic disorder	5.

OSCE 6

Match the following

1. Variable	a. Over which the researcher has no control; which is presumed to be influenced by the other variable
2. Independent variable	b. A specific value on a variable
3. Attribute	c. Over which the researcher has control; and is manipulated (or nature) in some way
4. Dependent variable	d. Those that may effect a dependent variable but are not independent variables
5. Extraneous variables	e. Any observation that can take different values

OSCE 7. Janani Shishu Suraksha Karyakaram (JSSK)

1) Who has to implement the scheme?

2) What are the objectives of the program?

3) Who are the beneficiaries?

4) Name any four of the entitlements.

OSCE 8

1) What is RBSK?

2) What are the targeted age groups?

3) Where is it done?

4) What are the selected conditions?

5) Name any four in each category?

OSCE 9

1) What is NMCP and NMEP?

2) What are the phases of NMEP program?

3) When did the modified plan of operation come into force and what is it?

4) What is the definition of endemicity under the modified plan of operation?

5) What are the parameters used for surveillance?

OSCE 10

1) Where is the National Institute of Nutrition (NIN) is located?

2) What is the age group for giving iron and folic acid in the prevention of nutritional anemia?

3) What is the aim of special nutrition program?

4) What is the nutritional value of food supplement provided in balwadi nutrition program started in 1970 and for whom was it started?

5) a) What is ICDS scheme? b) who are the beneficiaries?

6) Who delivers the care at the village level?

OSCE - Answers

OSCE 1

1) Capnography (trend) tracing during CPR

2) Return Of Spontaneous Circulation

3) Abrupt increase in partial pressure of end tidal or exhaled carbon dioxide ($PETCO_2$) from 25 to 40 mm

4) It reflects three important physiological functions. 1. Ventilation 2. Perfusion 3. Cellular metabolism

OSCE 2

1) Capnographic wave form.

2) A-B: Base line / Dead space ventilation; B-C: Ascending expiratory phase/expiratory upstroke; C-D: Alveolar (Expiratory) Plateau; D-E: Descending inspiratory phase.

3) Digital display, capnographic wave form, trend for one hour, histogram for 8 hours, colorimetric CO2 detectors.

OSCE 3

1) Colorimetric CO2 detectors or colorimetric capnometry is a technique of detecting CO2 in exhaled gas using a color changing pH paper. They are commonly used for resuscitation in out of the hospital settings in an emergency to confirm ET placement.

2) Purple - [means (P) problem] ET is in the esophagus

Golden Yellow - [means (Y) yes] ET is in position

Tan - [means (T) think] Indecisive

OSCE 4

a. Bronchospasm. Here expiratory upstroke is gradual and plateau is lost. Uneven emptying of alveolar gas alters emptying on exhalation producing a "shark fin" appearance.

b. Hyperventilation leading to gradual decrease in ETCO2. Possible causes are increase in respiratory rate or tidal volume, decrease in metabolic rate

c. Hypoventilation leading to gradual increase in ETCO2. Possible causes are decrease in respiratory rate or tidal volume, increase in metabolic rate or rapid rise in body temperature as in malignant hypothermia

d. Cardiac oscillation. It has no clinical significance and it is caused by tiny exhalations as a result of the heart beating against the lungs.

e. Curare cleft - a negative wave seen in the plateau portion of the capnographic wave form. It happens due to waning of the muscle relaxant drugs and appearance of spontaneous ventilation efforts.

f. Verification of ETT placement - Esophageal intubation

Exhaled air present in the stomach during bag mask ventilation produces the initial wave form and finally wave form is lost as the endotracheal tube is in esophagus

g. Sudden loss of wave form due to ventilator circuit disconnection or sudden accidental extubation

h. Normal capnographic wave form for comparison.

OSCE 5

1. Cross sectional survey, 2. Cohort study, 3. Double blinded radomized controlled trial, 4. Descriptive study, 5. Case series

OSCE 6

1-e, 2-c, 3-b, 4-a, 5-d

OSCE 7

1) All the States and Union territories (UTs) have initiated implementation of the scheme

2) Achieve 100% institutional delivery and elimination of out of pocket expenditure for both pregnant women and sick neonates.

3) Pregnant mothers, new borns up to 30 days and sick new borns.

4) The following are the free entitlements for pregnant women: cashless delivery, C-Section, drugs and consumables, diagnostics, diet during stay in the health institutions, provision of blood, transport from home to health institutions and return after 48 hours stay, transport between facilities in case of referral.

The following are the free entitlements for sick newborns till 30 days after birth. This has now been expanded to cover sick infants: free treatment, drugs and consumables diagnostics, provision of blood, transport from home to health institutions and return, transport between facilities in case of referral.

OSCE 8

1) Rashtriya Bal Swasthya Karyakram (RBSK) envisages Child Health Screening and Early Intervention Services, a systemic approach of early identification of medical conditions and link to care, support and treatment.

2) Babies born at public health facilities and home - Birth to 6 weeks, preschool children in rural areas and urban slum-6weeks to 6 years, School children enrolled in classes 1st to 12th in government and government aided schools - 6yrs to 18 yrs.

3) 0 - 6 years age group is specifically managed at District Early Intervention Center (DEIC) level while for 6 -18 years age group, management of conditions is done through existing public health facilities.

4) Selected Health Conditions for Child Health Screening & Early Intervention Services

5) a) Defects at birth: Neural tube defect, Down's syndrome, cleft lip & palate / cleft palate alone, talipes (club foot), developmental dysplasia of the hip, congenital cataract, congenital deafness, congenital heart diseases, retinopathy of prematurity.

b) Deficiencies: Anemia especially severe anemia, vitamin A deficiency (Bitot spot), vitamin D deficiency, (rickets), severe acute malnutrition, goiter.

c) Diseases of Childhood: Skin conditions (scabies, fungal infection and eczema), otitis media, rheumatic heart disease, reactive airway disease, dental conditions, convulsive disorders,

d) Developmental delays and Disabilities: Vision impairment, hearing impairment, neuro-motor impairment, motor delay, cognitive delay, language delay, behavior disorder (autism), learning disorder, attention deficit hyperactivity disorder, congenital hypothyroidism, sickle cell anemia, beta thalassemia (optional).

OSCE 9

1) National Malaria Control Program, National Malaria Eradication Program.

2) Phases - Preparatory, Attack, Consolidation, Maintenance.

3) Modified in 1977 within the modified plan of operation an additional component known as P Falciparum containment program was introduced.

4) Endemicity is defined as annual parasite index more than 2.

5) Annual parasite index, % Plasmodium falciparum (Pf), annual blood examination rate, annual falciparum incidence, slide positivity rate, slide falciparum rate

OSCE 10

1) Hyderabad

2) Age 1 to 12 years

3) For benefit of children below 6 years of age, pregnant and nursing women

4) 300 K.cal and 10 grams of protein for children 3 to 6 years of age

5) a) Integrated Child Development Services Scheme. b) Children below 6 years, pregnant and lactating women, women in the age group of 15-44 years, adolescent girls in selected blocks.

6) Anganwadi workers

CLIPPINGS

Does treatment with hydroxychloroquine or chloroquine lead to QTc prolongation in children?

Hydroxychloroquine and chloroquine are drugs with a long history of therapeutic use in the prevention of both rheumatologic and infectious diseases. However, the cardiotoxic potential of therapy with these medications, particularly in children, remains a noted concern. This review aims to identify whether treatment with hydroxychloroquine or chloroquine results in clinically meaningful QTc prolongation and increased risk of arrhythmia in comparison to baseline risk in the pediatric population.

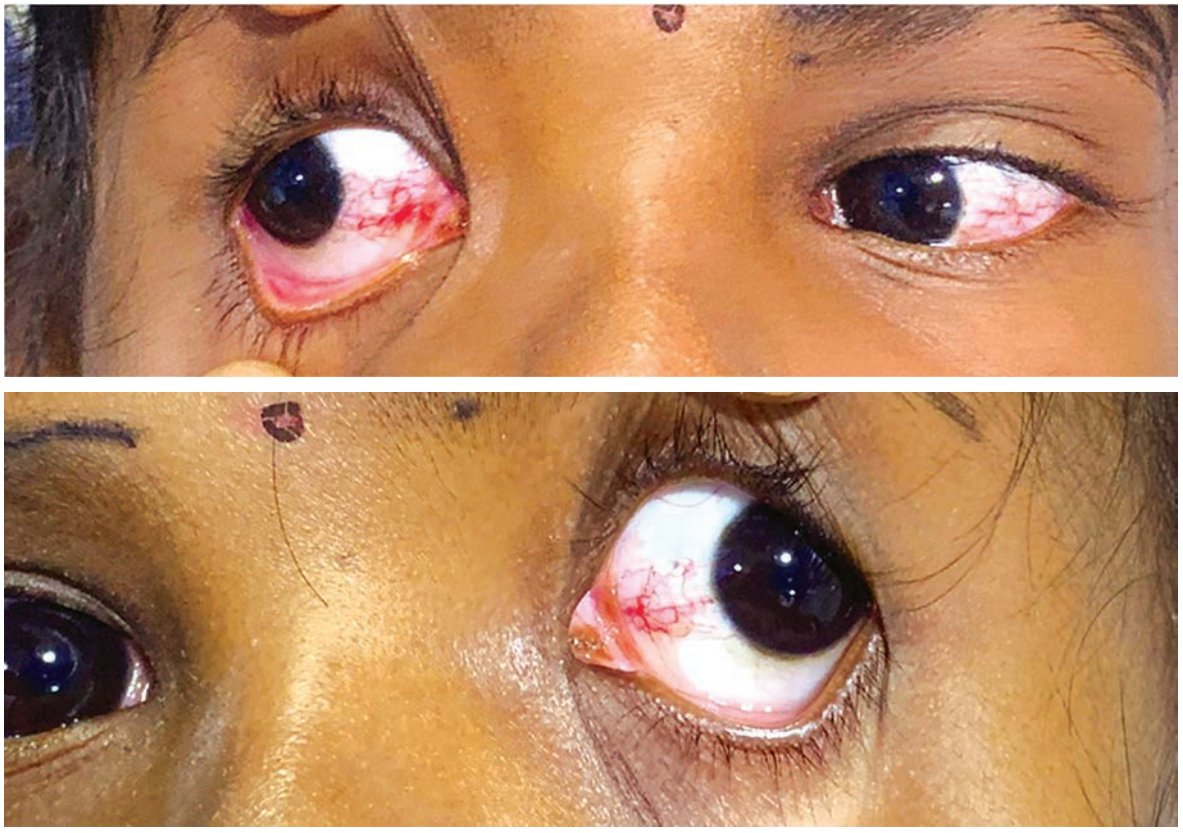
Out of the combined 65 children from the four included chloroquine studies with normal pre-treatment QTc intervals, 13 (20%) experienced clinically defined QTc prolongation (i.e., >440–500 ms). Of the combined 56 patients who were administered hydroxychloroquine across four studies, 5 (8.9%) patients experienced clinically defined QT or QTc prolongation. Such effects were found to be most prominent in the initial days of treatment. While QTc prolongation was reported in the majority of studies analyzed, the isolated medication effect is difficult to establish in the absence of placebo arms and randomization procedures.

Overall, there is a lack of high-quality information on the cardiac rhythm effects of therapeutic HCQ/CQ use in pediatric populations. In this review, pediatric patients treated with HCQ or CQ were at risk of QTc prolongation, particularly in the initial days of treatment (OCEBM Grade C), though the isolated effects of these medications are difficult to establish in absence of a placebo arm. Although hydroxychloroquine and chloroquine may prolong the QT interval in children, there is little evidence to suggest that it commonly prolongs it to a clinically relevant or arrhythmogenic degree with short-term treatment.

Parthasarathy P, Shaikh H, Ryan PM, Mondal T. Does treatment with hydroxychloroquine or chloroquine lead to QTc prolongation in children? Progress in Pediatric Cardiology 2021; 23:101465.

PICTURE QUIZ

This 8 years old girl admitted for pneumonia for the second time. She also has progressive unsteadiness while walking since early childhood. Mother says she has eye redness for a long time and did not show any improvement after applying eye drops. Eye finding is shown below.



QUESTIONS

1. Identify the eye sign and name one associated disorder
2. Name two major clinical features
3. Name two important immunological findings
4. Name two complications

ANSWERS

1. Eye finding – Telangiectasia (healthy white pearly sclera should be seen in between vessels in telangiectasia and not in simple congestion). Underlying disorder - Ataxia telangiectasia

2. a. Progressive cerebellar degeneration with cerebellar signs, b. Recurrent sinopulmonary infections

3. a. Combined immunodeficiency - Decreased IgA, IgG2, IgG4 and IgE, b. Decreased CD4, CD3, increased CD8 and Ti gama / Delta thymic cells

4. a. Lymphoreticular malignancy, Gonadoblastoma, dysgerminoma and adenocarcinoma, b. Fatal varicella

Annexure

Spectrum of antibiotics and clinical indications

B-Lactam antibiotic

Antibiotic Class	Spectrum of activity - Gram +ve	Spectrum of activity-Gram -ve	Common indications
Penicillin	Beta-*Hemolytic streptococci* +++ *Viridans streptococci* ++ *Streptococcus pneumoniae* ++	No activity	Pharyngitis Endocarditis Osteomyelitis
Aminopenicillins Amoxicillin Ampicillin	As above plus *Enterococcus faecalis* +++ *Listeria monocytogenes* +++	*Hemophilus inflfluenz*ae++ *Escherichia coli* + *Proteus mirabilis* +	Pharyngitis Lower respiratory tract infections Genitourinary tract infections Skin/skin structure infections Endocarditis (ampicillin) Osteomyelitis (ampicillin) Prosthetic joint infection (ampicillin)
Aminopenicillins with b-lactamase inhibitors Amoxicillin - clavulanate Ampicillin - sulbactam	As above plusMSSA ++	*Proteus mirabilis* +++. *Hemophilusinflfluenzae*+++ *Escherichia coli* ++ *Moraxella catarrhalis*++ *Klebsiella spp.* ++ *Acinetobacter spp.* + (sulbactam component) Anerobes: *Bacteroides fragilis* +++	Bite wounds (animal/human) Community-acquired pneumonia Intra-abdominal infections Urinary tract infections Diabetic foot infections
Antipseudomonal penicillins Piperacillin - tazobactam	Same as above	*Escherichia coli* +++ *Klebsiella spp.* +++ *Enterobacter spp.* ++ *Citrobacter spp.* ++ *Pseudomonas aeruginosa*++	Bloodstream infections (Gram-negative bacteremia) Intra-abdominal infections Diabetic foot infections Febrile neutropenia Pneumonia,hospital-acquired or ventilator-associated Sepsis and septic shock (broad-spectrum coverage) Urinary tract infections, complicated Skin and soft tissue infection, necrotizing (broad-spectrum coverage)
Cephalosporins *First generation* Cephalexin Cefazolin	*Streptococci* + + + *MSSA* + + +	*Escherichia coli* + + *Klebsiella spp.* + + *Proteus mirabilis* + +	Endocarditis (cefazolin) Osteomyelitis (cefazolin) Skin and soft tissue infections Bloodstream infections, MSSA (cefazolin) Pharyngitis Urinary tract infections, uncomplicated

Antibiotic Class	Spectrum of activity - Gram +ve	Spectrum of activity-Gram -ve	Common indications
Second generation Cefoxitin Cefotetan Cefuroxime	*Streptococc*i + + *MSSA*+ +	*Hemophilus influenzae*+ + *Moraxella catarrhalis*+ + *Proteus spp.* + + *Escherichia coli* + + *Klebsiella spp.* + + *Bacteroides fragilis*+ + (cefoxitin, cefotetan)	Intra-abdominal infections Community-acquired pneumonia (cefuroxime) Skin/skin structure infections Urinary tract infections Pharyngitis
Third generation Cefdinir Cefotaxime Ceftriaxone	S*treptococci* +++ *MSSA* ++	*Hemophilus influenzae*+ + + *Proteus sp.* + + + *Escherichia coli* + + + *Klebsiella sp.* + + + *Serratia sp.* + + + *Citrobacter* + *Enterobacter*+	Intra-abdominal infections (with metronidazole) Gonorrhea (cefotaxime) Community-acquired pneumonia Spontaneous bacterial peritonitis Urinary tract infections Pyelonephritis Meningitis
Antipseudomonal cephalosporins Cefepime Ceftazidime Ceftazidime/ avibactam Ceftolozane/ tazobactam	See third generation, plus *MSSA* + + + Note: ceftazidime, ceftazidime/ avibactam and ceftolozane/ tazobactam have poor coverage of Gram-positive organisms	*Enterobacter*+ + *(cefepime, ceftazidime/avibactam)* *Pseudomonas aeruginosa*+ +	Febrile neutropenia (cefepime) Intra-abdominal infections (with metronidazole) Pneumonia, hospital-acquired or ventilator - associated Urinary tract infections Osteomyelitis Infections by ESBL/KPC - producing Enterobacteriaceae (ceftazidime/tazobactam)
Anti-MRSA cephalosporins Ceftaroline	See third generation, plus *MSSA/MRSA* + + +		Community-acquired pneumonia Skin/skin structure infections
Carbapenems Imipenem-cilastatin Meropenem Doripenem Ertapenem	*Streptococci* + + + *MSSA* + + + *Enterococcus fecalis* (imipenem) + +	Hemophilusinfluenzae+ + + *Proteus spp.* + + + *Escherichia coli* + + + *ESBL Escherichia coli* + + + *Klebsiella spp.* + + + *ESBL Klebsiella sp.* + + + *Serratia spp.* + + + *Enterobacter spp.* + + + *Bacteroidesfragilis*+ + + *Pseudomonas aeruginosa*+ + *(*except ertapenem*)* *Acinetobacter spp.* + + (except ertapenem)	Intra-abdominal infections Febrile neutropenia (except ertapenem) Pneumonia, hospital-acquired or ventilator - associated (except ertapenem) Skin/skin structure infections, necrotizing (broad-spectrum coverage, except ertapenem) Urinary tract infections Osteomyelitis

Antibiotic Class	Spectrum of activity - Gram +ve	Spectrum of activity-Gram -ve	Common indications
Vancomycin	*Streptococci* + + + *MSSA/MRSA* + + + *Staphylococcus epidermidis*+ + + *Enterococcus fecalis*+ + + *Enterococcus fecium* +	No activity	Bloodstream infections *Clostridium difficile colitis* (oral) Endocarditis Osteomyelitis Pneumonia, hospital-acquired or ventilator-associated Sepsis and septic shock Skin/skin structure infections
Lipopeptides Daptomycin	As above, plus VRE, VISA/VRSA	No activity	Bloodstream infections Endocarditis Osteomyelitis
Oxazolidinones Linezolid Tedizolid	Same as above		Enterococcal infections (VRE), including bacteremia (linezolid) Pneumonia, hospital-acquired or ventilator - associated (linezolid) Skin/skin structure infections
Lipoglycopeptides Telavancin Dalbavancin Oritavancin	Same as above		Bloodstream infections, *Staphylococcus aureu*s (telavancin) Pneumonia, hospital-acquired or ventilator-associated (telavancin) Skin/skin structure infections

+ + +- excellent activity; + +,-good activity; +- some activity; MSSA- methicillin susceptible *Staphylococcus aureus*; ESBL- extended spectrum b-lactamases; KPC- *Klebsiella pneumonia* carbapenemase; MRSA- methicillin-resistant *Staphylococcus aureus*; VRE- vancomycin-resistant enterococci; VISA/VRSA, vancomycin-intermediate *Staphylococcus aureus*/vancomycin-resistant *Staphylococcus aureus.*

Source: *Rachel F. Eyler, Kristina Shvets. Clinical Pharmacology of Antibiotics. In: Nephropharmacology for the Clinician. Clin J Am Soc Nephrol 14: ccc–ccc, 2019. doi: https://doi.org/10.2215/CJN.08140718.*

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- Management of anaphylaxis
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- CBC - Your best friend in clinical practice
- Rational antibiotics in gastrointestinal infections
- Fungal infections of the skin
- Approach to inborn errors of metabolism
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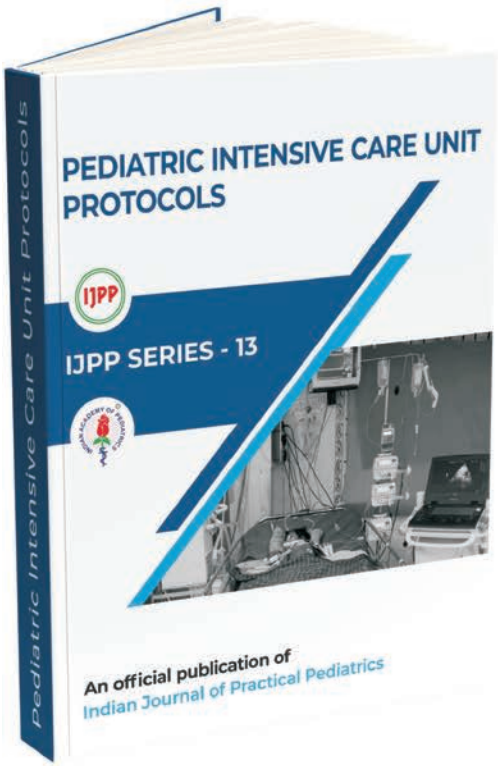

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