REVIEW ARTICLES

ANTIMICROBIAL USE IN OFFICE PRACTICE

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Abstract

There are three indications of antimicrobial use: for treating infections, for prophylaxis and empirical use. In ideal situation, antimicrobials should be used only in case of proven infections. Hence proper diagnosis is the first step towards rational antimicrobial use. Prophylactic use is indicated only in certain selective situations where standard protocols have to be followed. Empirical use is by and large subjective, where it is used mainly by personal experience and intuition. Though this is not the ideal way to use an antibiotic, but it is the most common mode of antibiotic use. It is imperative that antimicrobial resistance is a direct consequence of antimicrobial use. Antimicrobial resistance is crucial and costly for individual and health care system. Moreover the consequence of a single case of antimicrobial resistance is far reaching as microbes are not limited by any boundary. Although awareness of the consequences of antibiotic misuse is increasing, overprescribing remains widespread, driven largely by patient demand, time pressure on clinicians and diagnostic uncertainty. It is much easier to prevent antimicrobial resistance than to treat even a single case. This article will discuss antimicrobial use in common infections encountered in office practice.

Typhoid

Over the years Salmonella typhi has developed resistance simultaneously to all the drugs used in first line treatment (chloramphenicol, cotrimoxazole and ampicillin). (1) By definition this is known as Multi Drug Resistant Typhoid Fever (MDRTF).

Fluoroquinolones are widely regarded as the most effective drug for the treatment of typhoid fever. (2) Ciprofloxacin and ofloxacin are common fluoroquinolones that has been proved to be affective in children and there is no evidence of superiority of either. Fluoroquinolones like ofloxacin or ciprofloxacin are used in a dose of 15mg/kg/day to a maximum of 20mg/kg/day. There is considerable evidence from the long term use of fluoroquinolones in children that neither they cause bone or joint toxicity nor impairment of growth. (2) Fluoroquinolones have the advantage of lower rates of stool carriage than the first line drugs. However, fluoroquinolones are not approved by Drug Controller General of India to be used under 18 years of age unless the child is resistant to all other recommended antibiotics and is suffering from life threatening infection. Rarely some strains of S. typhi have shown reduced susceptibility to fluoroquinolones. Resistance to nalidixic acid is a surrogate marker which predicts fluoroquinolones failure and can be used to guide antibiotic therapy. (2) The resistance to fluoroquinolones may be total or partial. The nalidixic acid resistant S typhi (NARST) is a marker of reduced susceptibility to fluoroquinolones.

Third generation cephalosporins are used in the treatment of enteric fever. (1,2) Of the third generation cephalosporins, oral cefixime has been widely used in children. Amongst the third generation injectable cephalosporins: ceftriaxone, cefotaxime and cefoperazone are used of which ceftriaxone is most convenient. Oral cefixime is used in a dose of 15-20 mg/kg/day in two divided doses. Parenteral third generation cephalosporins include ceftriaxone 50-75mg/kg/day in one or two doses, cefotaxime 40 -80 mg/kg/day in two or three doses and cefoperazone 50-100 mg/kg/per day in two doses.

Recently azithromycin is being used as an alternative agent for treatment of uncomplicated typhoid fever. Azithromycin is used in a dose of 10mg/kg given once daily. Aztreonam and imipenem are also potential third line drugs. (2)

In case of uncomplicated typhoid, oral third generation cephalosporin e.g. cefixime should be the drug of choice as empiric therapy. (2) If by 5 days, there is no clinical improvement and the culture report is inconclusive add a second line drug e.g. azithromycin or any other drug effective against S typhi depending on the sensitivity pattern of the area. For complicated typhoid the choice of drug is parenteral third generation cephalosporin e.g. ceftriaxone (2). In severe life threatening infection, fluoroquinolones may be used as a last resort. Aztreonam and imipenem may also be used. Combination therapy though practiced, needs substantiation with adequate data from studies. (3,4)

Table 1 : Treatment of Uncomplicated Typhoid

SUSCEPTIBILITY	FIRST LINE ORAL DRUG			SECOND LINE ORAL DRUG		
	Antibiotic	**Daily Dose (mg/kg)**	**Days**	**Antibiotic**	**Daily Dose (mg/kg)**	**Days**
Fully sensitive	3rd generation cephalosporin e.g. Cefixime	15-20	14	Chloramphenicol	50- 75	14-21
				Amoxicillin	75-100	14
				TMP-SMX	8 TMP 40 SMX	14
Multidrug resistant	3rd generation cephalosporin e.g. Cefixime	15-20	14	Azithromycin	10-20	14

Table 2 : Treatment of Severe Typhoid

SUSCEPTIBILITY	FIRST LINE ORAL DRUG			SECOND LINE PARENTERAL DRUG		
	Antibiotic	**Daily Dose (mg/kg)**	**Days**	**Antibiotic**	**Daily Dose (mg/kg)**	**Days**
Fully sensitive	Ceftriaxone or Cefotaxime	15-75	14	Chloramphenicol	100	14-21
				Ampicillin	100	14
				TMP-SMX	8 TMP 40 SMX	14
Multidrug resistant	Ceftriaxone or Cefotaxime	15-75	14	Aztreonam	10-20	14

Note: Imipenem are potential second line drug and fluoroquinolones can be used in life threatening infection resistant to other recommended antibiotics.

Relapses occur in 5-10% patients with typhoid fever that have been apparently treated successfully. (5-7). Cultures should be obtained and standard treatment should be administered. (8) Sensitivity to same antibiotics is maintained and these drugs should be given for a period of 5-7days. Tables 1 and 2 depict antibiotics in the management of both complicated and uncomplicated typhoid. (2)

Urinary Tract Infection (UTI)

Children older than 3 months of age with uncomplicated UTI are treated with oral antibiotics for 7 to 10 days. (9, 10) Amoxicillin, co-amoxiclav or an oral cephalosporin is preferred for initial treatment. Following availability of sensitivity reports, treatment may be modified accordingly. Fluoroquinolones should be avoided as first line medication. Their use should be guided by results of urine culture and sensitivity. Nalidixic acid and nitrofurantoin should not be used to treat UTI since they do not achieve therapeutic concentrations in the renal parenchyma and blood streams. (9) The following drugs are recommended for treatment of UTI in children as shown in Table 3.

With adequate and effective therapy, clinical improvement like resolution of toxemia and fever occurs by 48-72 hours. Urine culture is sterile after 48 hours of effective antimicrobials. Ultrasound (USG) abdomen and repeat urine culture should be performed, if there is no clinical improvement after 72 hours of antimicrobial therapy. Maintenance of hydration, antipyretic and supportive therapy should be managed properly during an episode of an acute UTI.

Following the treatment of UTI, prophylactic antibiotic therapy is initiated in children below 2 years of age, until appropriate imaging of the urinary tract is completed. Although the evidence of benefit of long-term low-dose antibiotic prophylaxis for prevention of UTI is not strong, it is the most widely used strategy to prevent UTI in clinical practice. (11) Antibiotic prophylaxis is recommended in infants with UTI pending completion of evaluation, children with vesicoureteral reflux (VUR) and those with recurrent febrile UTI even if the urinary tract is normal. (12, 13) Medications used for prophylaxis are usually given as single bedtime dose (Table 4).

Acute Pharyngo-tonsillitis

Pharyngo-tonsillitis is one of the commonest clinical situations that we come across in day to day practice. It comprises of 40% cases of upper respiratory infections (URI) and nearly 80% of them are viral. (14) It is one of the most common situations for antibiotic misuse.

Table 3. Drugs used in the Treatment of Urinary Tract Infections (9, 10)

Drug	**Dosage (mg/kg/day)**	**Remarks**
Oral		
Amoxicillin, co-amoxiclav	20-40 in 2-3 divided doses	Rapid bacterial resistance
Cefadroxil	30 in 2 divided doses	Ineffective against Proteus spp
Cefaclor	40 in 3 divided doses	
Cephalexin	50-70 in 3 divided doses	
Cefixime	8 in 2 divided doses	Broad spectrum
Ciprofloxacin	10-20 in 2 divided doses	Not first line drugs
Ofloxacin	10 in 2 divided doses	
Parenteral		
Gentamicin	5-7.5	Monitor for renal toxicity. May be given as once daily dose
Amikacin	15-20	
Gentamicin	5-7.5	Monitor for renal toxicity. May be given as once daily dose
Cefotaxime	100-150 in 3 divided doses	
Ceftriaxone	75-100 in 1-2 divided doses	Safe and effective as a single agent

Table 4: Antibiotics for Prophylaxis (9, 10)

Drug	Dosage (mg/kg/day)	Remarks
TMP-SMX	1-2 of TMP	Avoid below 6 weeks age, G6PD deficiency
Nitrofurantoin	1-2	Gastrointestinal upset; avoid below 3 months and with impaired renal functions
Cephalexin	10-12	Use in infants where NFT and cotrimoxazole is contraindicated

Group A beta hemolytic streptococcus infections are self limiting and signs and symptoms subside in 4 to 5 days. However antibiotics are needed for prevention of non-suppurative complications of rheumatic fever. The drugs recommended are Penicillin V 250 mg twice daily in children and thrice or four times daily in adolescents or amoxycillin 40-50mg/kg/day 10 days or benzathine penicillin 6 lakh/12 lakh units deep IM after negative test dose depending upon weight of the child. (15) If the patient is allergic to penicillin, erythromycin ethylsuccinate 40-50mg/kg tid or azithromycin 12mg/kg OD for 5 days or cefaclor 30mg/kg for 10 days are useful.

Acute Otitis Media

Middle ear disease is obviously a major health problem for children. The most common cause of otitis media is Streptococcus pneumoniae, followed by non-typable Hemophilus influenza, Moraxella catarrhails and occasionally Streptococcus pyogenes. (15) The choice of antibiotics is shown in table 5. Alternate antibiotics in non-severe cases are azithromycin or clarithromycin with type 1 penicillin allergy and cefdinir or cefpodoxime in non-type 1 allergy. In treatment failure in a severe case, tympanocentesis plus clindamycin is recommended.

Acute Sinusitis

The bacteriology of acute sinusitis is virtually identical with organisms recovered from children with acute otitis media. Streptococcus pneumoniae, nontypable Haemophilus influenza and Moraxella catarrhalis predominate. (14) Though self-limited in most children, amoxicillin is the drug of choice for effectiveness, cost and safety. Second-line antibiotics are the same as for the treatment of middle-ear disease: amoxicillin-clavulanate, azithromycin, cefaclor and cefuroxime axetil. Therapy should be continued for a minimum of 14 days.

Community Acquired Pneumonia

Community acquired pneumonia is an acute infection of the pulmonary parenchyma in a previously healthy child, acquired outside of a hospital setting. The patient should not have been hospitalized within 14 days prior to the onset of symptoms or has been hospitalized less than 4 days prior to onset of symptoms. Table 6 gives the probable agents at various age groups in order of common prevalence. (14)

Table 6 : Organisms causing pneumoniae

Age	Microbial agent
0-3 months of age	Gram Negative organisms Group B Streptococcus Streptococcus pyogenes Chlamydia Viruses
3 months-5 yrs of age	Streptococcus pneumoniae H. influenzae Viruses Staphylococcus Streptococcus pyogenes Mycoplasma pneumoniae
>5 yrs of age	Streptococcus pneumoniae Chlamydia pneumoniae Viruses Staphylococcus Streptococcus pyogenes H. influenzae Mycoplasma pneumoniae

Empiric therapy should be based on knowing the most likely pathogen in each community. S. pneumoniae is an important causative agent for community acquired pneumonia at all ages. Because it is difficult to distinguish between bacterial, viral, and mixed infections, most children with community acquired pneumonia are treated with antibiotics. Selection of antibiotic is dictated by the age of the child and epidemiological factors and sometimes the

Table 5: Antibiotic selection for acute otitis media (16)

Severity	Initial management with antibacterial agents	Treatment failure at 48-72 hours after initial observation alone	Treatment failure at 48-72 hours after initial management with antibacterial agents
Non severe	Amoxycillin	Amoxycillin	Amoxycillin- clavulanic acid
Severe*	Amoxycillin-clavulanic acid	Amoxycillin-clavulanic acid	Ceftriaxone for 3 days

**Severe disease is defined as explosive onset severe otalgia, toxicity and high fever (>102^{0}F).*

Table 7: Antibiotic therapy in domiciliary patients with pneumonia

AGE	First Line	Second Line	Suspected Staphylococcal disease
Upto 3mo	Usually Severe, treated as in-patients		
3mo- 5yrs	Amoxycillin	Amoxycillin-clavulanic acid OR Chloramphenicol OR Cefuroxime	Amoxycillin+Cloxacillin OR Cefuroxime OR Amoxycillin-clavulanic acid
>5 yrs	Amoxycillin	Macrolide OR Amoxycillin-clavulanic acid OR Chloramphenicol	Amoxycillin+Cloxacillin OR Cefuroxime OR Amoxycillin-clavulanic acid

results of the chest radiography as shown in table 7. The antibiotics should be given for 5-7 days. (17)

Pyogenic Meningitis :

Acute bacterial meningitis is a medical emergency and appropriate antibiotic is the main stay of treatment. Child with suspected meningitis should receive antibiotics ideally after performing lumbar puncture (LP). In cases where LP is contraindicated antibiotics should be given immediately. The choice of antibiotics depends upon the causative organism in that particular age group. Most common organisms include pneumococcus, meningococcus, and H. influenzae type b. (18) In children more than one month of age 3rd generation cephalosporin, ceftriaxone (100mg/kg/24hr given either every 12 hour or as a single dose) or cefotaxime (200mg/kg/24hr given every 6 hour) are recommended for initial therapy. (18) As India has started showing intermediate resistant pneumococci, penicillin is no longer recommended. Vancomycin has role in therapy of penicillin or cephalosporin resistant meningitis in combination with cephalosporin. Monotherapy with vancomycin is not recommended. Vancomycin is used in the dose of 60mg/kg/24 hr, given every 6 hours. In patients who are immunocompromised and where gram negative bacterial meningitis is suspected empiric therapy may start with ceftazidime and aminoglycosides. In patients with cerebrospinal fluid (CSF) shunt, empirical therapy can be done with vancomycin and meropenem. Combination of third generation cephalosporin plus beta lactamase inhibitor has no role in the treatment of pyogenic meningitis.

Pneumococcus or meningococcus which are susceptible to penicillin or ampicillin (MIC <0.6mcg/ml) should be treated with penicillin G or ampicillin. If they are not susceptible to penicillin but susceptible

Table 8: Summary of Treatment with Antibiotics in Bacterial Meningitis in Children (18)

Bacteria	Antibiotic of choice
Listeria	Ampicillin $\pm$ Gentamicin
E. coli	Ceftriaxone or cefotaxime $\pm$ aminoglycoside
Pseudomonas aeruginosa	Ceftazidime or Cefepime $\pm$ aminoglycoside
Staphylococcus aureus - Methicillin sensitive (MSSA) - Methicillin resistant (MRSA)	 Cloxacillin Vancomycin + Rifampicin
Streptococcus agalactie	Penicillin G or Ampicillin + Gentamicin
Enterococcus - Ampicillin sensitive - Ampicillin resistant	 Ampicillin + Gentamicin Vancomycin + Gentamicin

Table 9: Dosages of commonly administered antibiotics for bacterial meningitis in infants and children

Antibiotic	Total daily dose (Dosing interval in hours)
Ampicillin	200 - 300 mg/kg (6)
Cefepime	150 mg/kg (8)
Cefotaxime	200-300 mg/kg (6-8)
Ceftazidime	150 mg/kg (8)
Ceftriaxone	100 mg/kg (12- 24)
Gentamicin	7.5 mg/kg (8)
Meropenem	120 mg/kg (8)
Penicillin G	450,000 units/kg (4-6)
Rifampicin	10-20 mg/kg (12-24)
Linezolid	10mg/kg (12)

to cephalosporin, 3rd generation cephalosporin like ceftriaxone or cefotaxime must be used. Isolates that are not susceptible to penicillin and have a MIC of >1mcg/ml to 3rd generation cephalosporin should be treated with vancomycin plus cefotaxime or ceftriaxone. For S pneumoniae with intermediate resistance to penicillin, cefepime and meropenem may be considered as alternative therapy. However trials with cefepime are not adequate but may be tried in patients who fail with other antibiotic courses. The other organism which might be responsible for bacterial meningitis in children should be treated with antibiotics as summarized in Table 8 and 9.

With adequate antibiotic CSF usually becomes sterile within 24 to 36 hours after initiation of therapy. Repeat lumber puncture after 48-72 hours of treatment is indicated if there is no clinical improvement or when meningitis caused by resistant pneumococcus or gram negative enteric bacilli.

Duration of therapy depends upon the causative pathogen and clinical course. For complicated cases longer course may be needed. For pneumococcus 10-14 days therapy is required, where as meningococcus and H influenzae type b meningitis should be treated for 5-7 days and 7-10 days respectively. (18) If the CSF reports are suggestive of acute bacterial meningitis without any identifiable pathogen patients should continue to receive therapy for 7-10 days. Gram negative bacillary meningitis should be treated for 3 weeks or at least 2 weeks after CSF sterilization. In case of 7 days non responders try to determine the cause by clinical examination, CSF and imaging studies modify duration of treatment accordingly. (19)

Conclusion

It is important to use antibiotics judiciously right from the first contact with a physician. Though empiric antibiotic use is inevitable, but it should be bacteriologically logical. Good antibiotic stewardship involves selecting an opportunity drug and optimizing its dose and duration to cure an infective while minimizing toxicity and conditions of selection of resistant bacterial strains.

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