

## ‘Rationale’ of Antibiotic Therapy – Think before you Ink !

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**I**n September 1928, Sir Alexander Fleming returned to his laboratory after a month away with his family, and noticed that a culture of *Staphylococcus aureus* he had left out had become contaminated with a mold (later identified as *Penicillium notatum*). He also discovered that the colonies of staphylococci surrounding this mold had been destroyed. He later said of the incident: “When I woke up just after dawn on September 28, 1928, I certainly didn’t plan to revolutionize all medicine by discovering the world’s first antibiotic, or bacteria killer. But I suppose that was exactly what I did.” He at first called the substance mold juice, and then named it penicillin, after the mold that produced it.

As we are celebrating the Rational Antibiotic Day on 28th September and a week thereafter, here is a mnemonic **RATIONALE** to fit in some aspects of rational prescribing practices:

- R** - Reasoning for prescription, Right dose, route, duration;
- A** - Academically updated decisions;
- T** - Training of mind, residents, parents, pharmacists;
- I** - Instructions to parents;
- O** - Organism search;
- N** - Noting down the diagnosis;
- A** - Antibiotic Policy;
- L** - Local sensitivity pattern; and
- E** - Ethical considerations, Economic condition of the patient

**R** – Reasoning behind our prescription. Prescribing an antibiotic is a three step process. (i) Is the fever because of infection or of non-infectious origin; (ii) If because of infection, is it viral or bacterial (or protozoal); and (iii) If bacterial, what is the likely organism. **R** also stands for **R**ight dose, frequency, route and duration. A Pediatrician can refer to a handy guidebook of antimicrobial therapy for the exact dose and use a calculator rather than giving a blanket dosing of 1 tsp tid! The prescription should be in legible handwriting so that the pharmacist doesn’t dispense cephalixin for cefixime! **R** also stands for adverse **R**eaction to a particular antibiotic. This should be clearly mentioned at the top of the letterhead.

**A** – Academically updated decisions. The pediatrician must be aware of the IAP guidelines for the management of infectious diseases. The routine use of Beta Lactam-Beta Lactamase inhibitor (BL-BLI) combinations should be avoided as they are more expensive, are likely to have more adverse effects, and may cause accidental under-dosing of the ceftriaxone component. Ceftriaxone is the drug of choice for the treatment of enteric fever, and there is no benefit of using ceftriaxone-tazobactam/cefotaxime-sulbactam (the *tam-tam* antibiotics!) upfront as salmonella has rarely been shown to produce resistance through beta-lactamases. Many ‘obsessed’ pediatricians feel that every caesarian delivery is an indication for antibiotics! Some of them are AGOs (Ampi-Genta-Obstetricians) while some are CMOs (Cefotaxime-Mikacin-Obstetricians)! While treating neonates with sepsis, use of third generation cephalosporins should be avoided as it potentiates development of extended-spectrum beta-lactamases. The addition of ampicillin/amoxicillin does not improve the anti-staphylococcal activity of cloxacillin, and in fact may worsen diarrhea. Fixed dose combinations of anti-amebic medicines (like Metronidazole/Tinidazole) with antibiotics (like Norfloxacin or Ciprofloxacin) are irrational. There are very few situations where combinations are rational, as in life-threatening infections with unknown organisms, antibiotics used for synergistic actions, and anti-tubercular therapy. For treating infections in immunocompromised children, antibiotics used should be bactericidal and not bacteriostatic.

**T** – Training. First is the **T**rainning of mind about 3 ‘O’s; the **O**rgan involved, the causative **O**rganism and the available therapeutic **O**ption. In reality, very few of us train our minds to follow the Standard Operating Procedure for prescribing an antibiotic. The process of training the mind for choosing proper antibiotics is described in **Box 1**. These steps may appear cumbersome for a busy practitioner but they are essential in the beginning of practice or whenever a new drug comes in the market or when there is significant antibiotic resistance. Next is the **T**rainning of subordinates and resident doctors about rational antibiotic practices.

**BOX 1** PROCESS OF TRAINING THE MIND FOR CHOOSING AN ANTIBIOTIC

1. Make a precise clinical diagnosis from the symptoms, signs and investigations. In a case of pyogenic meningitis, symptoms could be fever, irritability, altered sensorium, refusal of feeds, vomiting and convulsions; signs could be those of raised intracranial tension and meningeal irritation; and investigations will be CSF examination, blood counts and blood culture.
2. Consider possible etiologic agents:- *S. pneumoniae*, *H. influenzae* and *N. meningitidis*. Target the most likely ones after consideration of age, past history of trauma, etc.
3. Specify the therapeutic objectives, such as sterilization of CSF at the earliest by use of bactericidal drugs, clinical cure, prevention of relapse, and prevention of early and late complications.
4. Make an inventory of effective group of drugs. Choose the most appropriate and effective group based on the criteria of efficacy, safety, suitability and cost.
5. Choose an appropriate antibiotic from the chosen group.
6. Decide route of administration, dosage schedule and standard prescribed duration.
7. Write a legible prescription with name, age, sex, weight, diagnosis, drug's generic name, dose, route, frequency and duration of treatment with other supportive drugs and treatment measures with signature and date.
8. Give relevant information, instructions and warnings.
9. Monitor and review the therapeutic response, and choose an alternative in case of intolerance, allergy or other adverse drug reactions or poor *in vivo* response (midcourse correction).

Training the parents is also important, who sometimes pressurize the doctor to prescribe antibiotics for rapid relief. They should be explained about irrationality of antibiotics in viral infections, and when antibiotics are necessary, why it is important to follow all directions and finish the entire prescription even when child starts to feel better. Pharmacists should be trained to refrain from selling without valid prescription

**I – Instructions.** It is expected that a pediatrician gives time and speaks up about irrationality of antibiotics in viral infections, and when antibiotics are necessary, why it is important to follow all directions and finish the entire prescription even when child starts to feel better. More the written instructions, lesser the space available for writing medicines!

**O** – efforts to search the **O**rganism, by developing a culture of sending cultures. One should remember that *in vitro* sensitivities do not always result in clinical cure; e.g., aminoglycosides cannot cure enteric fever even though the report always shows sensitivity of salmonella to all of them. Sometimes an injectable antibiotic is marketed for oral use by simply adding the suffix O. One should know that the spectrum of these antibiotic preparations may differ.

**N** – **N**oting down a working diagnosis. Clinical differentiation between bacterial and viral infection, although difficult is still possible with reasonable certainty most of the times [1]. Children with viral infections usually have fever, runny nose, red eyes, red throat, hoarse voice, loose stools or rash. Fever in viral infections may be high at onset and tends to reduce by the third or the fourth day. The child is comfortable and not sick in the inter-febrile period. If you clinically diagnose and write provisional diagnosis as viral infection, your hands should shake while writing an antibiotic. These 'shake hand situations' include acute watery diarrheal (which is mostly viral) and bronchiolitis.

**A** – **A**ntibiotic policy. **Box 2** enlists the steps to be followed for any patient who requires antibiotics. Findings of the audits will drive improvement in antibiotic use. Even practicing pediatricians can have monthly meetings and have prescription audits of the colleagues' prescriptions (without disclosing the names!). **A** also stands for **A**voiding double standards *i.e.* writing one in private clinic, using a different one in a general hospital, and speaking totally different in conferences!

**L** – knowledge of **L**ocal sensitivity pattern through ongoing research. The research need not be in the institutes alone; it could be a part of Pediatric Research in

**BOX 2** CLINICAL PATHWAY FOR ANTIBIOTIC USE

1. Does the patient need an antibiotic?
2. Document the site of infection and possible microorganism.
3. Send appropriate cultures
4. Choose the antibiotic from the antibiotic policy after checking for allergy risks.
5. Some antibiotics should be prescribed after getting an infectious disease consult. These include carbapenems, colistin, linezolid, teicoplanin, vancomycin, voriconazole, amphotericin B
6. Follow the clinical response and de-escalate antibiotics.
7. Infection control team should fill antibiotic audit form and conduct regular department-wise audits.

Office Setting. **L** also stands for **L**earning to increase our Minimum Intelligence Concentration (MIC!).

**E** – Empiric antibiotic therapy. On many occasions, it is difficult to identify the organism, and hence selection of an antibiotic is an ‘educated guess’ which should depend on the system involved and the prevalent behavior of the organism (drug sensitivity and disease epidemiology). There are some classical presentations of bacterial infection in office practice, and a short course of an antibiotic is rational without attempt at bacterial isolation. Some examples are acute tonsillitis, acute otitis media with bulging eardrum in infant, acute bacillary dysentery, acute suppurative lymphadenitis and pyoderma. Patient with acute onset of fever and no localizing signs prove to be a challenge for need for empiric antibiotic therapy. Pediatricians must train themselves to decide about the safety of waiting for natural progress to arrive at definite diagnosis. Close observation and daily follow-up may be necessary to ensure this [1]. **E** also stands for giving consideration to the **E**conomic condition of the patient. If efficacy and safety are equal, one can use the cheaper alternative. More expensive does not mean better. Cloxacillin is still better than vancomycin for methicillin-sensitive *S. aureus*. **E** also stands for **E**thical considerations. Doctors are so busy with the work that they hardly find time to search for the accurate information regarding efficacy, safety, suitability and cost of drugs, and they often resort to ‘Academic Gurus’ in the form of medical representatives. They focus the brighter side and conceal the negative points. The pediatrician starts using the new antibiotic just for the sake of novelty. This tendency results in rapid emergence of resistance to the newly introduced antibiotic. It also unnecessarily taxes parents to pay for a new drug. The safety profile of many of these drugs is known only in the long run.

It is our bounden duty to use antibiotics with precision after great thought and clear rationale. One must not forget that the three most important principles in medicine are diagnosis, diagnosis and diagnosis [2]. We should respect the antibiotics. We should think before we ink. Pediatricians have a great responsibility to use antibiotics properly. Misuse of antibiotics can have disastrous consequences, not only for the patient in question, but by promoting bacterial resistance can pose a threat to the entire community [3]. Potential risks, cost and community effects of empirical antibiotic therapy should always be

weighed against probable benefits. We have to be rational as a group, not in isolation. Busy pediatricians are likely to become members of one of two societies. The first is the ‘No Guilt’ society. As there is no punishment for their unnecessary use, the members of this society use antibiotics without any remorse. The second is the ‘No Shame’ society. Trainee pediatricians who have not been sufficiently guided against the hazards of the unjustifiable use of antibiotics have no feelings of shame while penning them down. Though a challenge, we have to vacate the halls where these two societies hold their meetings and form a new one, based on sound scientific principles and rigid moral standards – A Rational Antibiotic Society.

Let me end with a story of a person who was very proud that he could hit exactly in the center of a circle with an arrow. While on travel in the countryside, he came across many circles on a wall with an arrow hit in the center. Curious to meet the competitor, he found out the person with this extraordinary talent and asked for the secret of this art. The talented archer told him, “My dear, I shoot the arrow first and then draw the circle around it!” Dear friends, we should not hit antibiotics first and then keep rationalizing the use. We should **HIT** following the proper sequence of **H**istory, **I**vestigations and **T**reatment. Let us ensure that we do not get infected with the Human Irrationality Virus (**HIV**) out of **H**abit, **I**gnorance and **V**arying factors like pressure from pharma, our ego and callous disconcern about antibiotic resistance. Until recently, recognition of new resistant clones was balanced by the promise of newer and more potent antibiotics. Today fewer new classes of antibiotics are under development, and clinicians are facing limitations in their ability to treat some serious bacterial infections. Let us be rational every day and enjoy **REM** sleep daily by developing a **R**ational **E**thical **M**indset.

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