CHAPTER 2

Rational for Antibiotics – Guidelines

Mangesh Tiwaskar, Tanuja Manohar

AN OVERVIEW OF BACTERIAL INFECTION

Bacteria, ubiquitous in nature, play an important role in maintaining the environment in which we reside. Only a small percentage of the world's bacteria cause infection and disease. Bacteria are grouped as Gram positive and Gram negative based on the characteristics of their cell wall, as observed under a microscope after Gram staining (developed by HC Gram in 1882). Some bacteria which cannot be classified by Gram staining, e.g. Mycobacteria, requires special staining. Bacteria can also be classified as aerobes, obligate aerobes, facultative anaerobes and obligate anaerobes, based on their need for oxygen to grow.[3]

Clinical manifestations of bacterial infections: The human body, which contains about 10^{13} cells, routinely harbors about 10^{14} bacteria called as normal microbial flora. [4] Though all of the human organs are susceptible to bacterial infection, most often microorganisms stay in harmony with the host through mutual or commensal interactions.[3,5] Each bacterial species has a predilection to infect certain organs and not others. For e.g. Neisseria meningitidis usually infects the meninges of the central nervous system causing meningitis or can infect the lungs causing pneumonia, however, it does not cause skin infection.[3]

Infectious disease is the clinically evident illness (viz. signs and symptoms) resulting from the infection, presence and growth of pathogenic bacterial agents in an individual host organism.[5] The list of microorganisms infecting different sites of the human body are mentioned in Figure 1.[6,7,8]

ANTIBIOTICS - A BOON TO MANKIND

Infection was a major cause of morbidity and mortality, prior to the development of antibiotics. The treatment of infections faced a great challenge during those periods.[9] Later in 1928, the discovery of Penicillin, a beta lactam antibiotic, by Alexander Fleming opened up the golden era of antibiotics.[10,11,12] It marked a revolution in the treatment of infectious diseases and stimulated new efforts to synthesize newer antibiotics. The period between 1950s and 1970s is considered the golden era of discovery of novel antibiotic classes, with very few classes discovered since then.[11,13] Table 1 enlists the different antibiotic classes with its mode of action and target infectious microorganisms.[14]

Antibiotics have played a vital role in achieving major advances in medicine and surgery. It has successfully prevented or treated infections that occur in patients with chronic diseases such as diabetes, end-stage renal disease or rheumatoid arthritis, complex surgeries such as organ transplants, joint replacements or cardiac surgery and in patients with chemotherapy treatments.[15] Studies with antibiotics have also shown unexpected non-antibiotic effects that indicate a variety of other biological activities. The results exhibited a significant number of additional therapeutic applications of "antibiotics" as antiviral, antitumor or anticancer agents. In some cases, the alternative administrations have surpassed those of antibiotic activity in importance, such as in the treatment of cardiovascular disease or use as immunosuppressive agents. Unfortunately, the enormous requirement of these valuable drugs had a significant downside.[1]

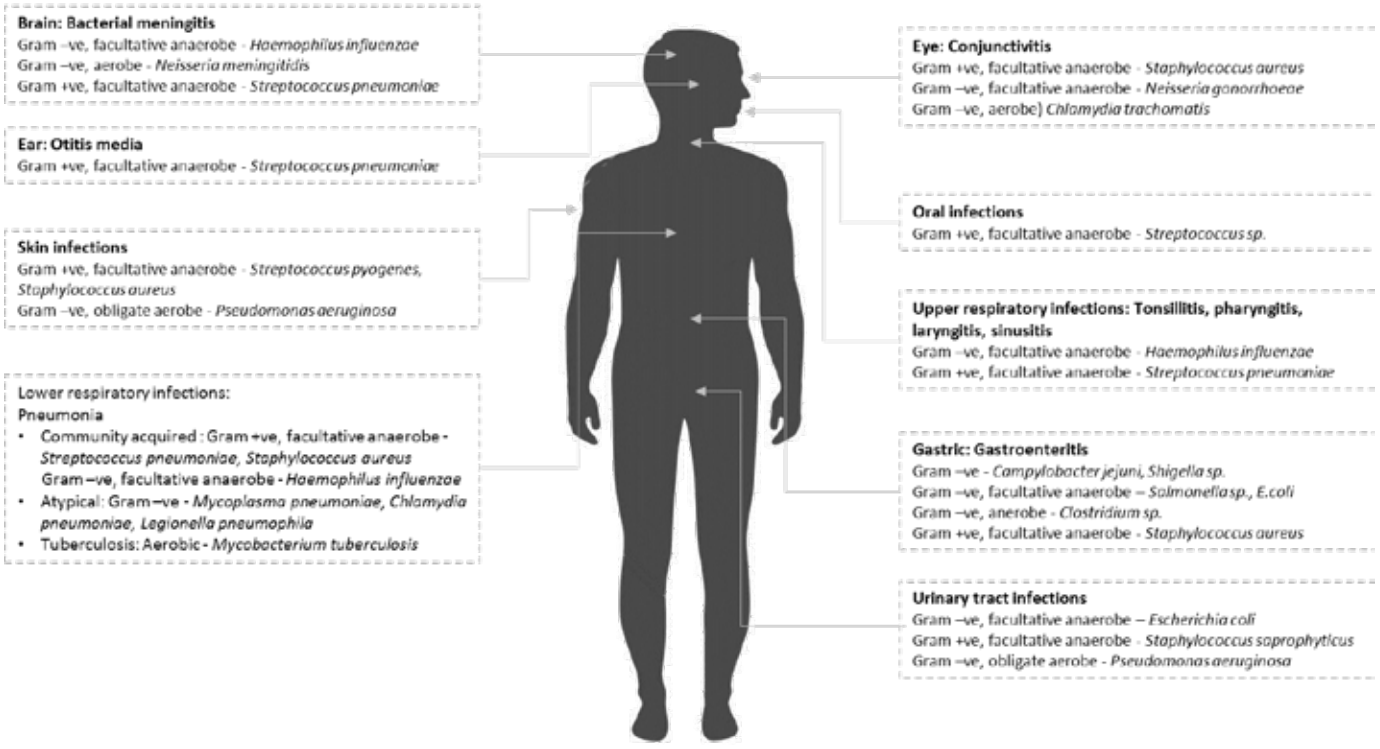
ANTIBIOTIC RESISTANCE - MAGIC BULLETS AND MOVING TARGETS

The successful use of any therapeutic agent is always followed by the potential development of resistance to that agent from the time it is first employed.[1] Alexander Fleming, who won a Nobel Prize for his discovery of Penicillin, had warned about the perils of antibiotic resistance.[16] True to this prediction, resistance began to arise within 10 years of the large scale introduction of Penicillin.[17] Initially, drug-resistant strains appeared in the hospitals, where most antibiotics were being used. Streptococcus pyogenes resistant to Sulfonamide emerged in military hospitals in the 1930s while Penicillin Resistant Staphylococcus aureus confronted London civilian hospitals shortly after the introduction of Penicillin in the 1940s. Similarly, Streptomycin-resistant Mycobacterium tuberculosis appeared in the community soon after the discovery of this antibiotic.[18] Over the years, more and more microorganisms, exposed to more and more antibiotics, eventually developed resistance to nearly all antibiotics that have been developed.[19] (Table 2 enlists the resistance mechanisms of commonly used antibiotics[1]) As a result, the optimism during the initial period of antibiotic discovery was tempered by the appearance of therapeutic resistant bacterial strains.[18]

FACTORS INTENSIFYING ANTIBIOTIC RESISTANCE

Irrational use of antibiotics contributes to dramatically increasing antibiotic resistance. Irrational antibiotic use is a worldwide problem that causes significant mortality, morbidity and increased health-care costs.[20] Following are some of the factors that drive antibiotic resistance:

Clinical over-prescription and public misconceptions:



Gram –ve - Gram negative organism, Gram+ve - Gram positive organism

Fig. 1: Overview of bacterial infections[6,7,8]

Table 1: Mode of action and target of antibiotic classes

Antibiotic class; example	Mechanism of action	Activity or target species
Sulfadrugs; Prontosil	Inhibition of dihydropteroate synthetase	Gram +ve bacteria
β-lactams; Penicillin	Inhibition of cell wall biosynthesis	Broad-spectrum activity
Aminoglycosides; Streptomycin	Binding of 30S ribosomal subunit	Broad-spectrum activity
Chloramphenicols; Chloramphenicol	Binding of 50S ribosomal subunit	Broad-spectrum activity
Macrolides; Erythromycin	Binding of 50S ribosomal subunit	Broad-spectrum activity
Tetracyclines; Chlortetracycline	Binding of 30S ribosomal subunit	Broad-spectrum activity
Rifamycins; Rifampicin	Binding of RNA polymerase β-subunit	Gram +ve bacteria
Glycopeptides; Vancomycin	Inhibition of cell wall biosynthesis	Gram +ve bacteria
Quinolones; Ciprofloxacin	Inhibition of DNA synthesis	Broad-spectrum activity
Streptogramins; Streptogramin B	Binding of 50S ribosomal subunit	Gram +ve bacteria
Oxazolidinones; Linezolid	Binding of 50S ribosomal subunit	Gram +ve bacteria
Lipopetides; Daptomycin	Depolarization of cell membrane	Gram +ve bacteria
Fidaxomicin (targeting Clostridium difficile)	Inhibition of RNA polymerase	Gram +ve bacteria
Dairylquinolines; Bedaquiline	Inhibition of F1F0 – ATPase	Narrow-spectrum activity (Mycobacterium tuberculosis)

Gram+ve – Gram positive organism, S – Svedbergs unit, DNA – Deoxyribonucleic Acid, RNA – Ribonucleic Acid

Source: Kim Lewis14

Table 2: Modes of resistance of commonly used antibiotics

Antibiotic class (examples)	Mode(s) of resistance
β-Lactams (Penicillins, Cephalosporins, Penems, Monobactams)	Hydrolysis, efflux, altered target
Aminoglycosides (Gentamicin, Streptomycin, Spectinomycin)	Phosphorylation, acetylation, nucleotidylation, efflux, altered target
Glycopeptides (Vancomycin, Teicoplanin)	Reprogramming peptidoglycan biosynthesis
Tetracyclines (Minocycline, Tigecycline)	Monooxygenation, efflux, altered target
Macrolides (Erythromycin, Azithromycin)	Hydrolysis, glycosylation, phosphorylation, efflux, altered target
Lincosamides (Clindamycin)	Nucleotidylation, efflux, altered target
Streptogramins (Synercid)	C-O lyase (type B streptogramins), acetylation (type A streptogramins), efflux, altered target
Oxazolidinones (Linezolid)	Efflux, altered target
Phenicols (Chloramphenicol)	Acetylation, efflux, altered target
Quinolones (Ciprofloxacin)	Acetylation, efflux, altered target
Pyrimidines (Trimethoprim)	Efflux, altered target
Sulfonamides (Sulfamethoxazole)	Efflux, altered target
Rifamycins (Rifampin)	ADP-ribosylation, efflux, altered target
Lipopeptides (Daptomycin)	Altered target
Cationic peptides (Colistin)	Altered target, efflux

Source: Davies J and Davies D[1]

Table 3: Resistance mechanisms of P. aeruginosa

Upregulation efflux pumps	Resistant to antibiotics
MexEF-OprN	Carbapenems and Fluroquinolones
MexCD-OprJ	Fluorquinolones and some β-lactams
MexAB-OprM	Sulfonamides, β-lactams, Cephalosporins, Fluoroquinolones, Macrolides, Novobiocin, Tetracycline & Chloramphenicol
MexXY-OprM	Aminoglycoside

Adapted from : Fair RJ et al[21]

There are a plethora of ways by which humans have inadvertently escalated the evolution of resistance.[21] Inappropriate prescriptions and over use of antibiotics contributed to the promotion of bacterial resistance.[15] Worldwide, it has been evaluated that half of all medicines are prescribed, dispensed or sold inappropriately, and that half of all patients fail to take their medicine properly.[20] An estimated two-thirds of global antibiotic sales occur without any prescription, while studies in Indonesia, Pakistan and India show that over 70% of patients are prescribed antibiotics. A vast majority - up to 90% - of injections are estimated to be administered unnecessarily.[22] The determinants of irrational antibiotic use are mentioned below: [20,22,23,24]

- Very short consultation time - does not allow proper diagnosis
- Prescription of antibiotics for non-bacterial infections: Clinicians prescribe antibiotics to patients with non-bacterial infections, a practice that has important repercussions
- Polypharmacy - Too many medicines are prescribed per patient (Lack of trust in or delayed lab results, fear of clinical failure)
- Antibiotic injections are used where oral formulations would be more appropriate
- Prolonged prophylactic therapy
- Prolonged empiric antimicrobial treatment without clear evidence of infection
- Failure to narrow antimicrobial therapy when a causative organism is identified
- Prescriptions do not follow clinical guidelines
- Patients self-medicate inappropriately
- Patients do not adhere to prescribed treatment

Antibiotic overprescribing is associated with other problems, apart from spreading resistance, viz. Increased medicalization of self-limiting infectious conditions, increase of more severe diseases, length of disease, risk of complications, mortality rate, healthcare costs, risk of adverse effects and re-attendance due to infectious diseases.[25]

Misuse by the food Industry: The use of antibiotics in animal feed stocks has also aggravated the spread of resistance. Especially, their use for non-curative reasons such as prophylaxis, metaphylaxis and growth promotion accounted for up to 50% of all antibiotic consumption in the early 2000s.[21]

Diminished pharmaceutical investment: Antibiotic development is no longer considered to be an economically wise investment for the pharmaceutical industry as they are not as profitable as drugs that treat chronic conditions, such as diabetes, psychiatric disorders, asthma or gastroesophageal reflux.[15] Additionally, regulatory hurdles have also muted the interest of major pharmaceutical companies.[21]

Human independent resistance: Though there is a pronounced human contribution to the evolution of bacterial resistance, there is also resistance that occurs in nature in the absence of human interference.[21] Bacteria can be either intrinsically resistant to certain antibiotics or can also acquire resistance to antibiotics.[26]

The legacy of the past decades in terms of antibiotic use and misuse has added to the development of bacterial resistance towards multiple drugs.[18]

SUPERBUGS AND SUPER-RESISTANCE

Many of the bacterial pathogens related with the epidemics of human disease, subsequent to antibiotic use, have evolved into multidrug-resistant (MDR) forms. The term "superbugs" refers to microorganisms with heightened morbidity and mortality due to multiple mutations conferring high levels of resistance to the antibiotic classes specifically recommended for their treatment.[1]

Staphylococcus aureus (MRSA, VISA and VRSA): S. aureus, a Gram positive, facultative anaerobic pathogen with both hospital and community acquired strains, is one among the most notorious superbugs.[1,21] Following the discovery of Penicillin, it seemed that S. aureus infections were controllable; however, it proved to be a short-lived one. The landmark discovery and introduction of Methicillin was anticipated to be a sure defense against the penicillinases, but the appearance of Methicillin-resistant S.aureus (MRSA) within 3 years inexorably led to other multiantibiotic-resistant variants.[1] MRSA is resistant to certain antibiotics, such as Methicillin, Dicloxacillin, Oxacillin, Cloxacillin, Nafcillin and closely related classes of drugs, such as Cephalosporins. The use of more powerful drugs than necessary for less serious infections could be a cause of MRSA expansion.[27] The development of resistance has led to the frequent use of Vancomycin to treat MRSA infections. This greatly increased selective pressure has resulted in the emergence of MRSA isolates with reduced susceptibility to Vancomycin (Vancomycin intermediate Staphylococcus aureus - VISA strains) and to the appearance of Vancomycin-resistant S. aureus (VRSA strains) with high-level resistance to Vancomycin.[28]

Resistant Enterococci Including VRE: Resistant Enterococci primarily comprises of two species, E. faecalis and E. faecium, both of which are Gram-positive, facultative anaerobic, opportunistic pathogens. Both E. faecalis and E. faecium have high levels of resistance rates (30–50%) against the aminoglycosides Gentamicin and Streptomycin.[21]

Streptococcus pneumoniae: S. pneumoniae is a Gram-positive, aerotolerant, anaerobic, opportunistic pathogen. It has a polysaccharide capsule that makes it naturally resistant to phagocytes. About 40% of strains are no longer susceptible to Penicillin, and its Penicillin resistance often correlates with resistances to Macrolides, Sulfamides, older Tetracyclines and early generation Cephalosporins. The strain is also resistant towards the third-generation antibiotics.[21]

Clostridium difficile: C. difficile is a Gram-positive, obligate anaerobic, spore forming opportunistic pathogen. C. difficile can be community acquired, but has a particularly high rate of acquisition in hospitals. Patients hospitalized for over four weeks have an approximately 50% chance of contracting C. difficile, a known causative agent for antibiotic associated diarrhoea.[21] A study by Pepin J et al.[29] showed that administration of fluoroquinolones emerged as the most important risk factor for Clostridium difficile-associated-diarrhea caused by a hypervirulent strain of C. difficile.

β-lactam and Quinolone Resistant Enterobacter: Enterobacter is a genus of Gram-negative, facultative anaerobic, opportunistic pathogens. They are mainly known to exhibit antibiotic resistance through expression of an extensive variety of extended spectrum β-lactamases (ESBLs) and Carbapenemases including, Klebsiella pneumoniae Carbapenemase, Oxacillinases and several metallo-β-lactamases (MBLs).[21]

MDR Pseudomonas aeruginosa: P. aeruginosa is a gram-negative, facultative anaerobic, opportunistic pathogen. It naturally has a host of siderophores (Fe3+ carriers) and pigments that allow it to evade the innate immune system. Furthermore, it has particularly discriminating outer membrane porins that make its outer membrane impermeable and thus naturally resistant to many antibiotics. It has a high propensity to form biofilms that can increase resistances to antibiotics by 100 to 1000 fold. P. aeruginosa also has an extremely comprehensive efflux pump system. Upregulation of the efflux pumps results in resistance to an array of antibiotics.[21] (Table 3)

Resistant Escherichia coli: Antibiotic resistance of E. coli has risen rapidly due to horizontal gene transfer. ESBL positive strains in bacteraemias have shown high cross resistance to Cephalosporins, Fluoroquinolones and Gentamicin. E.coli strains in multiple continents have also acquired the New Delhi Metallo-β-lactamase-1 (NDM-1) enzyme from Klebsiella pneumoniae, which confers a broad resistance to all β-lactams including Carbapenems except for Monobactam and Aztreonam.[21]

MDR Acinetobacter, MDR and Pan-drug-resistant Klebsiella pneumoniae, Resistant Neisseria Gonorrhoeae & Mycobacterium tuberculosis (MDR-TBTB and XDR-TBTB) are the other vital resistant bacteria dominating the headlines of alarming resistance.[21]

The growing numbers of antimicrobial-resistant pathogens place a significant burden on healthcare systems and have important global economic costs. It results in high mortality and morbidity rates, increased treatment costs, diagnostic uncertainties and lack of trust

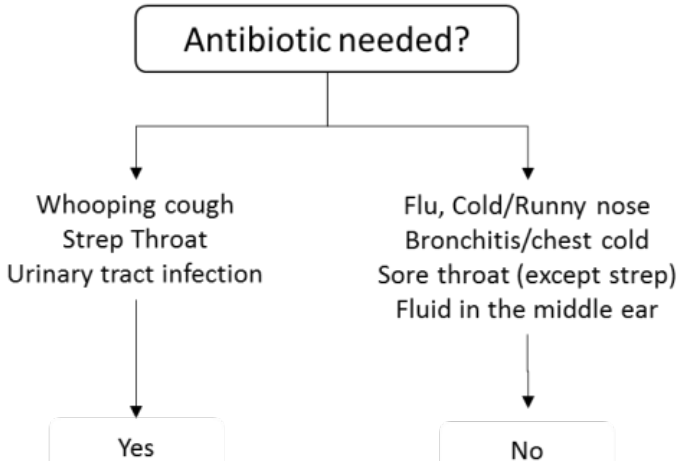


Fig. 2: Common illness which requires Antibiotic therapy[38]

in orthodox medicine.[30] Considering the complications associated with increasing antibiotic resistance, its high time to promote judicious and optimized use of antibiotics worldwide.

GUIDELINES FOR ANTIBIOTIC STEWARDSHIP

The rise of antibiotic-resistant bacteria, which represents a serious threat to public health, can be overcome by promoting the optimized use of existing antibiotic agents and preventing transmission of drug-resistant organisms through control of infection.[31,32] Rationalizing the use of antibiotics is an important patient safety and public health issue in addition to being a national priority.[33] The following guidelines can help clinicians to ensure appropriate use of antibiotic therapy.

Evaluate the infection by clinical diagnosis: The communication occurring within the consultation influences the treatment decision both for and against antibiotic prescription.[34] Initial clinical diagnosis of an infection should always precede the clinician's decision to prescribe antibiotics.[35] The clinician should always consider whether or not antibiotic therapy is even necessary for the patient by weighing the benefits (efficacy, rapid recovery and comfort of patient) against the risks (antibiotic resistance, adverse effects) and costs of treatment. At the same instance, clinician should also keep in mind that many infections are self-limiting and that most of the patients just require supportive therapy to deal with the symptoms.[36] It is of utmost importance to highlight that a clinician should never prescribe antibiotics for non-bacterial infections such as cold, flu & sore throats. Antibiotics tackle bacteria and hence should be restricted for the treatment of bacterial infections only.[37,38] (Figure 2)

Select an appropriate antibiotic therapy: Following a proper clinical diagnosis, a clinician should decide whether to direct a patient to a definitive therapy or an empirical therapy or a prophylactic therapy.

Definitive therapy: When the etiology of the infection is known, the clinician should proceed with definitive therapy. Firstly, the clinician should confirm the bacterial infection by advising for a microbiological testing (staining of secretions/fluids/exudates, culture and sensitivity, serological tests and other tests).[39] Microbiological testing helps to identify the specific etiologic agent and provides information about the in-vitro activity of antimicrobial drugs against the microorganisms identified.[40] It also assists the clinicians to decide whether the patient should be prescribed antibiotics, as they are often under pressure from patients who believe they need antibiotics. A negative microbiology test report can make it easier for the clinician to refuse unnecessary prescription of antibiotic. Additionally, if the patient needs treatment immediately, the test results can help in choosing the most appropriate agent.[41]

Empirical therapy: Clinician should reserve empirical therapy for critical patients, where time is inadequate for identification and isolation of the infection causing bacteria.[39] Empiric prescribing is based on the clinicians working knowledge or experience of what is most likely to be the pathogen causing the patient's condition. E.g. certain elements of the presenting illness (such as site of infection) can help the clinician to predict a broad group of pathogens such as: skin and soft tissue: Gram positive cocci, urinary tract: Gram negative bacilli, intra-abdominal: Gram-negative, Gram-positive and anaerobic organisms.[35] Therefore, a common approach can be prescribing a broad-spectrum antibiotic agent as initial empiric therapy with an intention to cover multiple possible pathogens commonly associated with the specific clinical syndrome.[23]

Simultaneously, the clinician should ensure that the samples for microbiological testing are collected before starting the empirical therapy.[42] Once microbiological results have aided in identifying the etiological agent, every attempt should be made by the clinician to narrow the spectrum of the antibiotic.[23]

Prophylactic therapy: Antibiotic prophylaxis should be prescribed to susceptible patients to prevent specific infections that can cause definite detrimental effects.[39] Susceptible patients include pre-surgical patients, immunocompromised patients and patients with traumatic injuries.[23] The selection of an antibiotic for prophylaxis should be based on known or likely target pathogens, for a short duration of time. A single dose of antibiotic should be recommended for surgical prophylaxis. Long-term prophylaxis should be administered only when the benefits outweigh the risk of resistance selection or propagation.[42]

Criteria for choosing an antibiotic drug: Appropriate antibiotic selection is vital to facilitate successful treatment of infections and minimize the development of antibiotic resistance.[43] Once the etiology of an infection is known, the clinician should recommend a most narrow spectrum antibiotic which is cost-effective and least toxic for the shortest duration possible.[36] While prescribing an antibiotic, clinicians should consider the following treatment guidelines:

EFFICACY

- Narrow spectrum or broad spectrum: The spectrum of the antibiotic selected by the clinician should be the narrowest to cover known or likely pathogens. For instance, patients undergoing procedures associated with high infection rates, those involving implantation of prosthetic material and those in whom the consequences of infections are serious should receive perioperative antibiotics. The prophylactic antibiotic(s) should cover the most likely organisms and be present in the tissues when the initial incision is made, with adequate serum concentrations maintained during the procedure. In such situations, a single dose of a Cephalosporin (such as Cefazolin) administered within 1 hour before the initial incision is appropriate for most surgical procedures; this practice targets the most likely organisms (i.e., skin flora), while avoiding unnecessary broad-spectrum antimicrobial therapy.[23]

  However, in scenarios where the causative agent is not known and a delay in initiating therapy would be life-threatening or risk serious morbidity, broad spectrum antibiotics, based on the likelihood of the pathogen(s), should be prescribed.[44] Clinician should also make it a point to de-escalate the regimen as soon as the etiological agent is known.[35]

- Monotherapy or combination therapy: In order to evade antagonism between drugs and undesirable side effects of several antibiotics, it is prudent to use a single agent wherever possible in antibiotic treatment.[44] However, there are situations when the use of an antibiotic combination is desirable. The situations are:

- To achieve synergistic effect against the infection: Synergy of antimicrobial agents infers that the combined effect of the agents is greater than the sum of their independent activities when measured separately. For instance, in the treatment of serious infections for which rapid killing is essential, the combination of certain β-lactams and aminoglycosides exhibits synergistic activity against a variety of Gram-positive and Gram-negative bacteria (e.g. combination of Penicillin and Gentamicin to treat endocarditis caused by Enterococcus species). The addition of Gentamicin to Penicillin has been shown to be bactericidal, whereas Penicillin alone is only bacteriostatic and Gentamicin alone has no significant activity.[23]

- Combination therapy also shortens the course of antibiotic therapy, e.g. combination of Penicillin or Ceftriaxone with Gentamicin for 2 weeks results in more rapid clearance of the infecting microorganism as compared to Penicillin or Ceftriaxone alone for 4 weeks.[23] Other combinations that act synergistically are as follows: β–lactam antibiotic + β–lactamase inhibitor, β–lactam antibiotic + Glycopeptide (Vancomycin/Teicoplanin) and Sulphamethoxazole + Trimethoprim.[44]

- When critically ill patients require empiric therapy before bacteriological diagnosis: Combination therapy can be used in hospital-associated infections to ensure that at least 1 of the administered antibiotic agents will be active against the suspected organism(s). E.g. if a patient hospitalized for several weeks develops septic shock and the blood culture reports the growth of Gram-negative bacilli, it would be appropriate to provide initial therapy with 2 agents that have activity against Gram-negative bacilli, particularly P. aeruginosa, which is both a common nosocomial pathogen and frequently resistant to multiple agents. Thus in this scenario, a combination of an antipseudomonal β-lactam with a fluoroquinolone or aminoglycoside could be advisable.[23]

- To extend antibiotic spectrum during polymicrobial infections: When infections are caused by polymicrobes (more than one organism), a combination therapy can be preferred as it would extend the antimicrobial spectrum beyond that achieved by a single agent. Most intra-abdominal infections are usually caused by multiple organisms with a variety of Gram-positive cocci, Gram-negative bacilli and anaerobes. Antimicrobial combinations, such as a third-generation Cephalosporin or a Fluoroquinolone plus Metronidazole, can be used as a potential treatment option in these cases and can sometimes be more cost-effective than a comparable single agent (e.g., a Carbapenem).[23] Bronchiectasis, peritonitis, urinary tract infections and otitis media are the conditions considered as polymicrobial infections.[39]

- To prevent the development of bacterial resistance with long term therapy: The development of resistant mutants in a bacterial population is the result of selective pressure from antibiotic treatment. While combining antibiotics with 2 different mechanisms of action, the chance of a mutant strain being resistant to both antimicrobial agents is much lower than the chance of it being resistant to either one. Additionally, use of combination therapy prevents the resistant mutant population from emerging as the dominant strain and causing therapeutic failure. This is the reason why, combination therapy is considered as a standard for the treatment of infections like tuberculosis and the human immunodeficiency virus, where treatment duration is prolonged, resistance can emerge relatively easily and therapeutic agents are limited.[23]

- Efficacy at the site of infection & tissue penetration – An antibiotic which is effective at the infected site and exhibits adequate target tissue penetration should be the preferred therapy.[45] Antimicrobial

concentrations attained at some sites (namely, ocular fluid, cerebrospinal fluid (CSF), abscess cavity, prostate and bone) are often much lower than serum levels. For example, first- and second-generation Cephalosporins and Macrolides are not recommended for central nervous system infections as they do not cross the blood-brain barrier. Fluoroquinolones are preferred oral agents for the treatment of prostatitis because they achieve high concentrations in the prostate. Daptomycin, an excellent bactericidal agent against Gram-positive bacteria, is inactivated by the lung surfactant, hence it is not useful for the treatment of pneumonia.[23,35] The tissue penetration profile of a few antibiotics are mentioned in the table below.[35]

- Bactericidal vs bacteriostatic therapy: An antibiotic that is able to kill an organism instead of inhibiting its growth is preferred in few clinical settings. These include infections where the site of infection is not easily penetrated, e.g. in infections such as meningitis, endocarditis and osteomyelitis. Immunocompromised patients, in particular neutropenic patients, are also usually recommended for "cidal" therapy.[46]

DOSAGE, ROUTE OF ADMINISTRATION AND DURATION

- The clinician should consider pharmacokinetic and pharmacodynamic factors in determining the drug dose.[47] The dosage should be high enough to ensure efficacy and minimize the risk of resistance selection, and low enough to minimize the risk of dose related toxicity.[42]

- The clinician should ensure the most appropriate route of administration in antibiotic treatment. Oral/enteral route of administration should be preferred in patients with mild-to-moderate infections.[35] When using oral therapy for invasive infections (such as pneumonia, pyelonephritis, or abscesses), clinicians should select an agent that has excellent absorption and bioavailability (i.e., the percentage of the oral dose that is available unchanged in the serum). Examples of antibiotics with excellent bioavailability are Fluoroquinolones, Doxycycline, Linezolid, Trimethoprim-Sulfamethoxazole and Metronidazole.[23] Clinicians should reserve intravenous antibiotics for severe infection or for certain sites such as the CSF, bacteraemia, endocarditis and bone & joint infections.[35] New microbiological or other information (e.g. fever defervescence for at least 24 hours, marked clinical improvement; low C-reactive protein) should often permit a switch to oral antibiotic(s), or switch to an intravenous narrow spectrum alternative or cessation of antibiotics (if no infection is present).[44]

- Antibiotic treatment should generally be continued for a maximum of 5 days or a shorter period if this is clinically appropriate; however, some specific conditions require a longer course of therapy (viz. endocarditis, osteomyelitis etc.)[48]

Table 4: Tissue penetration profile of few antibiotics

Infection site	Ampicillin	Co-amoxi-clav	Ceftriaxone	Aminogly-cosides	Ciprofloxa-cin	Co-trimoxa-zole	Ertapenem	Meropenem	Vancomycin	Linezolid	Daptomycin
CSF	Good (in high doses)	Poor	Good (in high doses)	Poor	Good (in high doses)	Good	Poor	Good (in high doses)	Poor	Good	Poor
Lung	Good	Good	Good	Poor	Good	Good	Good	Good	Fair	Good	Poor
Soft tissue	Good	Good	Good	Fair	Good	Good	Good	Good	Poor	Good	Good
Urinary	Good	Fair	Good	Good (if normal GFR)	Good	Good	Good	Good	Good	Good	Good

CSF – Cerebrospinal Fluid, GFR – Glomerular Filtration Rate

Source: Wasserman S et al[35]

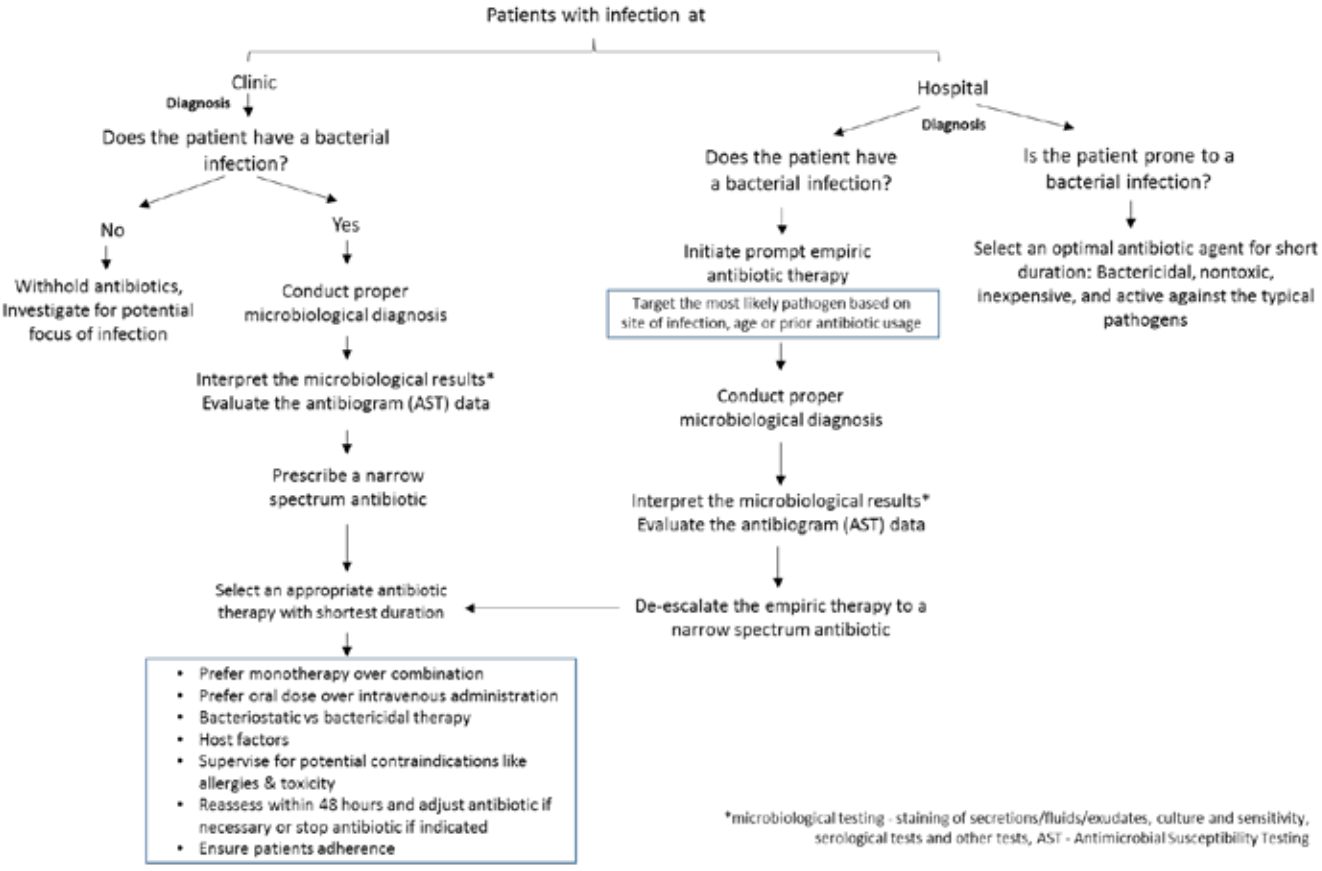


Fig. 3: Summary algorithm for rationale prescription of antibiotic therapy

PATIENT FACTORS

The clinician should consider the age of the patient, immune status, pregnancy and lactation, associated conditions like renal and hepatic function, epilepsy etc. while choosing the antibacterial agent.[49]

- Age: Patients at both extremes of age handle drugs differently, primarily due to differences in body size and kidney function.[39]
- Hepatic and renal function: Usually, dose is reduced to prevent accumulation and toxicity in patients with reduced renal or hepatic function. However, sometimes doses might need to be increased to avoid underdosing young healthy patients with rapid renal elimination or those with rapid hepatic metabolism due to enzyme induction by concomitant use of drugs such as Rifampin.[23]
- Pregnancy and lactation: Human studies on safety of antibiotics in pregnancy and lactation are scarce, hence clinicians should prescribe it with utmost caution.[23] Drugs with known toxicity or unestablished safety like Tetracyclines, Quinolones, Streptomycin, Erythromycin and Clarithromycin are contraindicated in all trimesters while Sulfa, Nitrofurantoin and Chloramphenicol are contraindicated in the last trimester. Drugs with limited data on safety like Aminoglycosides, Azithromycin, Clindamycin, Vancomycin, Metronidazole, Trimethoprim, Rifampicin and Pyrazinamide should be used with caution when benefits overweigh the risks. Penicillins, Cephalosporins and Ethambutol are safe in pregnancy. In lactating mothers, Sulfa, Tetracyclines, Metronidazole, Nitrofurantoin and Quinolones are contraindicated.[39,49]
- Allergy or intolerance - Clinicians should routinely obtain an evaluation of history of antibiotic allergy or intolerance.[23]
- Recent antibiotic use - Eliciting a history of exposure to antimicrobial agents in the recent past (approximately 3 months) can also help the clinician in selecting an antimicrobial therapy. Because the causative microorganism for a current episode of infection emerged under the selective pressure of a recently used antimicrobial agent, it is likely to be resistant to that drug and/or drug class, and an alternative agent should be used.[23]

MONITORING RESPONSE TO THERAPY

The need for an antimicrobial therapy should be reviewed on a daily basis by reviewing laboratory evidence.[44,35] Response to therapy depends on the nature and sensitivity of the agent, specificity of the drug, bioavailability and dosage. Longer the doubling time of the organism, longer the time it takes to respond. Thus a Streptococcal pneumonia can respond within 24-48 hours, but tuberculosis may take 28 weeks to respond. The clinician should wait for the adequate period before changing the drug (e.g. Streptococcal pneumoniae infections 24-48 hours; E. coli 24-48 hours; Salmonella

typhi 4-7 days; Mycobacterium tuberculosis 2-8 weeks etc.). Drugs should be changed midway only when there is absolutely no response or there is no expected response and the sensitivity report also suggests resistance.[49] Since non-compliance is also one of the causes for treatment failure,[50] the clinician should ensure patient adherence to the therapy. Treatment should be continued until all pathogens are eliminated from the tissues or until the infection has been sufficiently controlled for the normal host defenses to eradicate it.[51]

Additionally, clinicians should work together with patients to ensure safe antibiotic use. Clinicians should remind patients to avoid sharing of medications with anyone, to take antibiotics as prescribed and to discard unused medication.[36]

An example of the rationale usage of antibiotic is summarized in the algorithm below. (Figure 3)

Taking everything into account, it is important for the clinician to implement the "7D's of optimal antibiotic therapy: right Drug, right Dose, appropriate Direction (route of administration), De-escalation to pathogen-directed therapy, and right Duration of therapy, watch for and consider Drug to drug interaction, always evaluate for possible immune Deficiency" to optimize antibiotic use in clinical settings.

CONCLUSION

Antibiotics, the magic bullets, have represented a great revolution for humankind. The discovery of antibiotics has determined a new era in the treatment of infectious diseases and in the quality of life.[53] However, extravagant use of antibiotics has resulted in the rise of multi-drug resistant bacteria- the so called "superbugs". Infections caused by these emerging superbugs require urgent action as these infections tend to last longer, can increase the risk for complications and may even cause death. Therefore, it is essential to use antibiotics in an optimal manner to prevent this rapidly growing issue. Only appropriate use of existing antibiotics can limit the spread of these superbugs. Antibiotics being a shared resource, should be preserved as a last weapon to treat patients and should be used only when the need is obligatory.

REFERENCES

1. Davies J, Davies D. Origins and Evolution of Antibiotic Resistance. *Microbiol Mol Biol Rev* 2010; 74:417–433
2. Megha MJ. Current scenario of antibiotic resistance and latest strategies to overcome it. *IJCH* 2014; 26:218–221
3. Doron S, Gorbach SL. Bacterial Infections, overview. In: Hamer D, editor. Griffiths J, Maguire JH, Heggenhougen HK, Quah SR. Associate editors. Public Health and Infectious Diseases.UK. Elsevier Inc.; 2010. p.3-7
4. Davis CP. Normal Flora. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996
5. Kumar SV, Damodar G, Ravikanth S, Vijayakumar G. An overview of infectious disease. *Indian Journal of Pharmaceutical Science & Research* 2012;2:63-74
6. Available at https://medschool.creighton.edu/fileadmin/user/medicine/MMI/Files/Bacteria_Table.pdf, viewed on August 27, 2016.
7. Patras K. Polymicrobial Infections: Perhaps The Rule, Not The Exception. 2013, Available at http://schaechter.asmblog.org/schaechter/2013/08/polymicrobial-infections-perhaps-the-rule-not-the-exception.html, viewed on August 27, 2016.
8. Pathogen Regulation Directorate. Pathogen safety data sheet-Infectious substances. 2011, Available at http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/myco-pneu-eng.php, viewed on August 27, 2016.
9. Runcie H. Infection in a pre-antibiotic era. *J Anc Dis Prev Rem* 2015; 3:125.
10. Antibiotics: One of the Greatest Discoveries of the 20th Century, Available at http://www2c.cdc.gov/podcasts/media/pdf/Antibiotics_Short.pdf, viewed on August 27, 2016.
11. Minikel E. Chemical biology 16: infectious disease.2015; Available at http://www.cureffi.org/2015/11/05/chemical-biology-16/, viewed on August 27, 2016.
12. Caramia G, Ruffini E. Proper antibiotic therapy- From penicillin to pharmacogenomic. *Minerva Pediatrica* 2012; 64:225-237.
13. Aminov RI. A brief history of the antibiotic era: lessons learned and challenges for the future. *Frontiers in Microbiology* 2010;1:1-7.
14. Kim Lewis. Platforms for antibiotic discovery. *Nature Reviews Drug Discovery* 2013; 12:371–387.
15. Ventola CL. The Antibiotic Resistance Crisis, Part 1: Causes and Threats. *P T* 2015; 40:277–283.
16. Bushak L. A brief history of antibiotic resistance: How a medical miracle turned into the biggest public health danger of our time, Available at http://www.medicaldaily.com/antibiotic-resistance-history-373773, viewed on August 27, 2016.
17. Rosenblatt-Farrell N. The Landscape of Antibiotic Resistance. *Environmental Health Perspectives* 2009; 117:A244–A250.
18. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. *Nature Medicine Supplement* 2004; 10:S122-S129.
19. Nanotechnology solutions to combat superbugs 2013, Available at http://www.nanowerk.com/spotlight/spotid=32188.php, viewed on August 27, 2016.
20. Kathleen Anne Holloway. Promoting the rational use of antibiotics. *Regional Health Forum* 2011; 15:122-130.
21. Fair RJ, Toi Y. Antibiotics and Bacterial Resistance in the 21st Century. *Perspect Medicin Chem* 2014; 6:25–64.
22. Rational use of medicines. The World Medicines Situation;2004, Available at http://apps.who.int/medicinedocs/en/d/Js6160e/10.html, viewed on August 27, 2016.
23. Leekha S, Terrell CL, Edson RS. General Principles of Antimicrobial Therapy. *Mayo Clin Proc* 2011; 86:156–167.
24. Global Antibiotic Resistance Partnership (GARP) - India Working Group. Rationalizing antibiotic use to limit antibiotic resistance in India. *Indian J Med Res* 2011; 134:281–294.
25. Llor C, Bjerrum L. Antimicrobial resistance: risk associated

with antibiotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf* 2014; 5:229–241.

26. Blair JMA, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJV. Molecular mechanisms of antibiotic resistance. *Nature Reviews: Microbiology* 2015; 13:42-50.
27. Navidinia M. The clinical importance of emerging ESKAPE pathogens in nosocomial infections. *Journal of Paramedical Sciences* 2016; 7:43-57.
28. Gardete S & Tomasz A. Mechanisms of vancomycin resistance in Staphylococcus aureus. *J Clin Invest* 2014; 124:2836–2840.
29. Pépin J , Saheb N, Coulombe MA, Alary ME, Corriveau MP, Authier S et al. Emergence of fluoroquinolones as the predominant risk factor for Clostridium Difficile associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005; 41:1254-60.
30. Santajit S, Indrawattana N. Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens. *BioMed Research International* 2016;2016(Article ID 2475067):8 pages,
31. Nathwani D, Sneddon J. Practical guide to antimicrobial stewardship in hospitals. Available at http://bsac.org.uk/wp-content/uploads/2013/07/Stewardship-Booklet-Practical-Guide-to-Antimicrobial-Stewardship-in-Hospitals.pdf, viewed on August 27, 2016.
32. Antibiotic Resistance Threats in the United States. 2013; Available at http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf#page=6, viewed on August 27, 2016.
33. Core Elements of Hospital Antibiotic Stewardship Programs, Available at http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html, viewed on August 27, 2016.
34. Cabral C, Ingram J, Lucas PJ, Redmond NM, Kai J, Hay AD, Horwood J. Influence of Clinical Communication on Parents' Antibiotic Expectations for Children With Respiratory Tract Infections. *Ann Fam Med* 2016; 14:141-147.
35. Wasserman S, Boyles T, Mendelson M. A pocket guide to antibiotic prescribing for adults in South Africa 2014; Available at http://www.fidssa.co.za/Content/Documents/SAASP_Antibiotic_Guidelines_2015.pdf, viewed on August 27, 2016.
36. Modern Approaches to Managing Bacterial Infections. In: Tindall WN, Sedrak MM, Boltri JM. Patient-Centered Pharmacology: Learning System for the Conscientious Prescribe; Unit 2, Chapter 17, p 312-313.
37. Balzer D. Mayo Expert Discusses Antibiotics Overuse and Misuse. Available at http://newsnetwork.mayoclinic.org/discussion/mayo-expert-discusses-antibiotics-overuse-and-misuse/, viewed on August 27, 2016.
38. Antibiotics Aren't Always the Answer. Available at http://www.cdc.gov/features/getsmart/, viewed on August 27, 2016.
39. Chaudhury RR & Sharma S. General principles of chemotherapy with particular reference to antimetabolites. In: Talwar GP, Hasnain SE, Sarin SK (editors). Textbook of Biochemistry, Biotechnology, Allied and Molecular Medicine, 4th edition; PHI learning Private Limited;2016. p 1468-1476.
40. Washington JA. Principles of Diagnosis. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996.
41. Kolmos HJ, Little P. Should general practitioners perform diagnostic tests on patients before prescribing antibiotics? *BMJ* 1999; 318:799–802.
42. Moulds R, Rao G, Tevita S, Waqanibete I, Tikoduadua L, Wata T et al. Antibiotic Guidelines 2011; 3rd edition. Available at http://www.health.gov.fj/wp-content/uploads/2015/04/Antibiotic-Guidelines-3rd-edition-2011.pdf, viewed on August 27, 2016.
43. Marcia Frellick. Clinicians and Antibiotic Prescribing: Should They Know Better? 2015; Available at http://www.medscape.org/viewarticle/837039, viewed on August 27, 2016.
44. National Treatment Guidelines for Antimicrobial Use in Infectious Diseases 2016; version 1, Available at http://www.ncdc.gov.in/writereaddata/linkimages/AMR_guideline7001495889.pdf, viewed on August 27, 2016.
45. General antibiotic prescribing pitfalls. Available at http://www.jbpub.com/physicianspress/antibioticpitfalls.htm, viewed on August 27, 2016.
46. Ernst EJ. Infectious Diseases: Introduction. In Richard A, Quan DJ, Herfindal ET, Gourley DR, Zeind CS, Hudson JQ, Gourley GK et al. Textbook of Therapeutics: Drug and Disease Management; 8th edition, Lippincott Williams & Wilkins;2006. Chapter 72; p 1851.
47. Introduction to Pharmacokinetics and Pharmacodynamics. In: DiPiro JT, Spruill WJ, Wade WE, Blouin RA, Pruemer JM. Concepts in Clinical Pharmacokinetics. 5th edition, 2010; p 1-18.
48. Catchpole C. In: Worcestershire Acute Hospitals NHS Trust. 2013; Titled as 5 day Stop/ Review Date Policy for Antimicrobial Prescriptions, viewed on August 27, 2016.
49. Kakkilaya BS. Rational Medicine. 2008, Available at http://www.rationalmedicine.org/antibiotics.htm, viewed on August 27, 2016.
50. Kardas P. Patient compliance with antibiotic treatment for respiratory tract infections. *J Antimicrob. Chemother* 2002; 49:897-903.
51. General principles of the treatment of infection. In Davey P, Wilcox M, Irving W, Thwaites G. Antimicrobial Chemotherapy; 7th edition. Oxford University Press. 2015; Chapter 13:p 137-138.
52. Doron S, Davidson LE. Antimicrobial Stewardship. *Mayo Clin Proc* 2011; 86:1113–1123.
53. Cascioferro S, Schillaci D. The Future of Antibiotic: From the Magic Bullet to the Smart Bullet. *J Microb Biochem Technol* 2014; 6:e118.