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FAQs on Rational Antibiotic Therapy

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Forewords
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CHAPTER 2

Failure of Antibiotic Therapy

Abhay K Shah

Q1. When do we prescribe antibiotic?

Antibiotic is ideally prescribed under following circumstances:

- Proven bacterial infections, as indicated by isolation of an organism in culture or by smear examination
- Near certain bacterial infection e.g. exudative tonsillitis
- Empiric therapy
- Prophylactic use, e.g. urinary tract infection (UTI), rheumatic fever, etc.

Q2. Which are the factors that determine antibiotic response?

Antibiotic response depends on the site of infection, on the pathogen and on the immunological status of the patient.

Although time to response varies for different symptoms and signs, 48–72 hours of adequate therapy are usually needed for improvement in objective signs.

Q3. What are the predictors of antibiotic response?

Response to treatment of an infection can be assessed using clinical, biochemical and microbiological parameters. Sustained defervescence, clinical stability, and improvement of sequential organ function in a 48–72 hours timeframe are the variables that are considered in several studies and seem to better reflect clinical response.

Clinical parameters include improvement in symptoms and signs (e.g. a decrease in fever, tachycardia, respiratory rate, improving sensorium, increasing oral intake, and improving urine output), laboratory values [e.g. decreasing leukocyte count, PCT (procalcitonin) or CRP (C-reactive protein)], organ function markers (reduction or cessation of vasopressors, improvement of hypoxemia among others), and radiologic findings (e.g. improvement in lung opacities). Radiologic improvement can frequently lag behind clinical improvement and routine radiographic follow-up of all infections is not always necessary.

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Q4. Which are the common causes for antibiotic failure?

The common causes for antibiotic failure are as under:

- Wrong diagnosis (noninfectious disease)
- Antibiotic-related issues like dose, duration, dosing interval, etc.
- Antibiotic pharmacokinetic and pharmacodynamic (PK/PD) issues
- Development of infectious complication
- Persistence of inflammation
- Inadequate source control
- Antibiotic resistance
- Host immunosuppression.

Q5. Which are common antibiotic factors responsible for antibiotic failure?

- Wrong drug for a wrong bug, e.g. aminoglycosides for *Shigella* and typhoid fever, vancomycin for gram-negative organisms
- *Inadequate dose and incorrect dosing intervals*: This will fail to achieve desirable concentrations in serum and at the site of infections
- *Lack of bactericidal activity*: In presence of bacteremia one should not use bacteriostatic drug, e.g. clindamycin for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia
- Poor tissue penetration, e.g. in case of acute bacterial meningitis the antibiotic must penetrate blood-brain barrier. Use of beta-lactam/beta-lactamase inhibitor (BL/BLI) like ceftriaxone-tazobactam and piperacillin-tazobactamis useless.

Q6. Which microbial factors are responsible for antibiotic failure?

- Resistant bacteria, e.g. MRSA, extended-spectrum beta-lactamases (ESBL), and multidrug-resistance (MDR) tuberculosis
- *Anaerobes*: Occult abscesses, secondary subacute bacterial peritonitis, and dental infections. These situations need an appropriate anaerobic coverage
- Polymicrobial infections, e.g. intra-abdominal infections, brain abscess, and neutropenic and immunocompromised patients. These situations need broad spectrum coverage with both aerobic and anaerobic coverage
- *Others*:
  - Viral—needs to be treated with specific antiviral if available
  - Leptospirosis–needs to be diagnosed and treated accordingly
  - Rickettsial disease—needs to be diagnosed
- Fungal—needs antifungal drugs
  It should be suspected in a child with certain risk factors like:
  - Immunocompromised host
  - Neutropenic

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- Central venous line
- Receiving antibacterials
- Diabetes mellitus
- Recent corticosteroids.

Q7. What should be our approach in case of antibiotic failure?

Most of the time apparent antibiotic failure results in changing and/or adding a broader spectrum antibiotic, but this will hardly going to be helpful. The most important approach to such antibiotic failure is to analyze the cause of the antibiotic failure by careful evaluation and use of appropriate diagnostic tests to avoid needless, and expensive and potentially dangerous antimicrobial therapy. The important steps would be:

- Maintenance of airway, breathing, circulation, perfusion, nutrition, and euglycemia
- Selection of appropriate antibiotic in correct dose, route, optimum dosing schedule, and duration
- Regular clinical evaluation supported by lab and imaging studies when indicated
- Identification of complication and its remedial measures
- Source control
- Aseptic precautions.

Q8. What is the role of source control in antibiotic failure?

The best recognized example of nonantimicrobial therapy in case of apparent antibiotic failure in the treatment of infections is "source control", namely the use of operative drainage or debridement. This procedure is useful when the organism burden is very high or in the management of abscesses, for which the penetration and activity of antimicrobial agents are often inadequate.

Example: Pleural tapping in complicated pneumonia, removal of subdural fluid in case of acute bacterial meningitis, proper wound care, pus drainage, and debridement of dead tissues in cases of burns, crush injuries, necrotizing fasciitis, etc.

Q9. Which are various mechanisms for antimicrobial resistance?

- Enzymatic degradation of antibacterial drugs, e.g. beta-lactamase and ESBL
- Alteration of bacterial proteins that are antimicrobial targets, e.g. MRSA
- Changes in membrane permeability to antibiotics, e.g. carbapenem-resistance pseudomonas
- Efflux pump, e.g. carbapenem resistance.

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Q10. What is the role of antibiotic combination formulations in antibiotic failure/resistance?

For synergistic activity against a microorganism: Synergy between antimicrobial agents means that, when studied in vitro, the combined effect of the agents is greater than the sum of their independent activities when measured separately. For example, the combination of certain beta-lactams and aminoglycosides exhibits synergistic activity against a variety of gram-positive and gram-negative bacteria and is used in the treatment of serious infections, for which rapid killing is essential (e.g. treatment of endocarditis caused by *Enterococcus* species with a combination of penicillin and gentamicin).

In a critically ill patient, empiric therapy before microbiological etiology and/or antimicrobial susceptibility can be determined.

To extend the antimicrobial spectrum for treatment of polymicrobial infections: When infections are thought to be caused by more than one organism, a combination regimen may be preferred because it would extend the antimicrobial spectrum beyond that achieved by a single agent. For example, most intra-abdominal infections are usually caused by multiple organisms with a variety of gram-positive cocci, gram-negative bacilli, and anaerobes.

To prevent emergence of resistance: The emergence of resistant mutants in a bacterial population is generally the result of selective pressure from antimicrobial therapy. Use of combination therapy would provide a better chance that at least one drug will be effective, thereby preventing the resistant mutant population from emerging as the dominant strain and causing therapeutic failure, e.g. artemisinin-based combination therapy (ACT) for malaria and AKT for tuberculosis.

FURTHER READING

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