

Antimicrobial Combinations: An Overview

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ABSTRACT

Anti-microbials are the major contribution of current century to medical sciences. It includes both synthetic as well as naturally obtained agents that attenuate pathogens. Antibiotics (a term commonly used as antibacterial) are the substances produced by fermentation of microorganism which selectively suppress growth or kills microbes in very low concentration. The golden era of antibiotic began after discovery of Penicillin. Antimicrobial are either broad spectrum, extended spectrum or narrow spectrum regarding its activities. Their susceptibility is best predicted by mean inhibitory concentration. Resistance is the major associated problem which may be natural or acquired. In spite of life saving in most of the critical condition, antimicrobial is highly misused and over prescribed in the current scenario of clinical medicine. Combinations of antimicrobials are quite popular in India. The current review highlighting an overview of antimicrobial combinations in Indian context.

Key words: Spectrum, Synergism, Infection, Resistance, Misuse.

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INTRODUCTION

The development of anti-microbial was historical milestone in medical science. Era of antimicrobial began with serendipitous discovery of penicillin by Alexander Fleming. Large number of anti-microbials were synthesized and introduced in world market after the advent of penicillin. Anti-microbials are often over prescribed agent and their unethical recommendation is responsible for grave insult of non-responsiveness. In clinical practice these agents are either used alone or in combination. There combination is sometime required for therapeutic benefits but most of the time they are irrational. An antimicrobial combination in fixed ratio is termed as fixed dose combination or FDC.

Need of anti-microbial combination: Generally, a single agent is sufficient with reference to pathogen but in certain clinical condition their combination will be needed. This is beneficial because -

To achieve synergism: Synergism is the definitive advantage of pharmacological combination. This may manifest in term of MIC of one anti-microbial in context to MIC of other e.g., combination of amoxicillin or ampicillin with beta-lactamase inhibitor like clavulanic acid or sulbactams respectively. Similarly, sulfonamide and trimethoprim both are bacteriostatic when used alone but their combination become bactericidal.

To broaden Antimicrobial spectra - In severe or mixed infection, Beta-lactam and aminoglycoside combination covers both gram positive and negative organism with extended bactericidal action.¹

To prevent emergence of resistance - In some of the clinical condition, combination of two or more anti-microbials are indicated for prolong period. e.g., anti-tubercular's, anti-leprotic and anti-retroviral drugs.

Reduction of adverse drug reaction - This is brought about by either in reduction in dosage or counteracting the side effects by the phenomenon of antagonism.^{1,2}

To improve compliance of user - By combining antimicrobial in same formula. This is more practical when number of antimicrobials are needed in some chronic clinical condition for prolonged time. e.g: 2 to 4 anti-tubercular drugs in same pill.

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Antimicrobial Fixed Dose Combinations [FDCs] and WHO view

FDC is the single formulation of combination of two or more pharmacologically active agent in definite ratio. A rational FDC serve the advantage of phenomenon of synergism or antagonism along with improved compliance, they also enhance therapeutic efficacy and helps in prevention of their resistance.

W.H.O Essential Medicine List {latest edition} mentioned only few antimicrobial combinations for widespread use throughout the world. Some of the rational FDCs of antimicrobial listed in EML are as under^{3,4}

- Amoxicillin + Clavulanic acid
- Ampicillin + Sulbactam
- Imipenem + Cilastin
- Sulfamethaxazole +Trimethoprim
- Isoniazid + Rifampicin
- Artemether + Lumefantrine

Disadvantages of FDCs

Most of the FDC do not follow rational pharmacological basis of combination and will result number of drawbacks -

- i - One antimicrobial can affect bioavailability and MIC of other.
- ii - Combination of bactericidal with bacterostatic.
- iii -Combination of agent with different pharmacokinetic and pharmacodynamics
- iv - Doubtful schedule of dose due to different half-life.
- V - Different spectra of coverage⁵

Problems with FDCs

FDCs are responsible for lots of clinical problems. Some common one is -

- a- FDCs usually does not contain recommended dose, thus marked variable in dose of individual component are quite common.
- b- Causative component may be doubtful during untoward happenings.
- c- Contraindication to one antimicrobial means contraindication of whole preparation.
- d- Patient does not need extra antimicrobial.
- e- Addition of toxicity.⁶

Apart from above mentioned drawback such preparation can result other problem as well such as-

- i- False sense of security to prescribe.
- ii- Patient believe that FDC is more powerful.

- iii- Extra burden of cost i.e., 'FDCs' are usually expensive⁷

Irrational Combination

Only a handful of FDCs are rational and justified, Most of the FDC are irrational but vigorously promoted by pharmaceutical companies.(8) Some Irrational Combination are

- Amoxicillin and Cloxacillin
- Norfloxacin and Metronidazole
- Enalapril and Losartan
- Paracetamol and Nimesulide

Indian Scenario

W.H.O recommended only few FDCs on the basis of their rationality and safety profile. But the Indian scenario is entirely different. Most of the Indian FDCs are irrational. These days our pharmaceutical industries are loaded with antimicrobial combinations. Large number of such preparation are floating in Indian market which are non- scientific. Even some of them disappear after untoward happening. These brands are now highly promoted due to hidden profit. There is addition of number of antimicrobial FDC every year in drug market and most of them are irrational.

Majority of younger generation are interested in prescribing this combination without knowing their long-term safety track. Such combination also makes the prescriber to less vigilant in term of proper diagnosis, confusion of therapeutic aim as well as false sense of superiority e.g. use of ofloxacin and ornidazole combination in amoebic diarrhoea instead of single imidazoles [metronidazole or ornidazole alone]. Similarly, chloroquine is sufficient in responsive malaria but ACT combinations are highly promoted and prescribed.

Other important thing is adjustment of dosing schedule due to different half-life. Most of the time prescriber doesn't know exact amount of component present in combination due to variation among different pharmaceutical products.

Rational Approach

It's therapeutic benefit to use single agent that is most specific for infecting organism. This strategy usually reduces cost of therapy, minimizes toxicity and decreases the emergence of resistant organism. In certain situation a combination of antimicrobials are indicated. There must be certain caution needed while prescribing rational combination of FDCs.

- A- Synergistic combination. [sometime antagonistic]
- B- Cost effective.

- C- Either bactericidal or bacteriostatic.
- D- Similar pharmacological profile in term of pharmacokinetic and pharmacodynamics.
- E- Advantageous to the patient.^{7,8}

Combination at glance

In most cases, combinations are employed to broaden the spectrum in terms of coverage. Clinical indication is only successful, if the combination is not antagonistic in nature. Anti-microbials with static and cidal nature is not as much as effective because such combination antagonizes the counterpart, thereby reduces the efficacy. Therefore, combination should be either static or cidal in nature which enhances the efficacy in term of addition and synergism.⁹ Few examples about FDC of antitubercular and anti-HIV drugs mentioned below.

Rationality for FDC of antitubercular

Tuberculosis is chronic granulomatous disease which require combination of drugs for prolong period. Monotherapy is not recommended because of emergence of resistance. Therefore, WHO recommended fixed dose combination of number of antitubercular drugs.¹⁰ This simplifies the prescription as well as drug supply. FDC of 2,3 and 4 drugs are commonly prescribed. Such combination prevents and limit risk of drug resistance tuberculosis arising as a result of inappropriate drug selection as well as monotherapy.¹¹ Moreover, FDC of Rifampicin and Isoniazid is synergistic and resistance preventing. Most important advantage is ease of administration of number of antitubercular in single preparation thereby increases the patient compliance.¹²

Rationality of FDC of anti-HIV drug

HIV is treated by specific antiretroviral medicine which work by stopping the virus replicating in the body of host.¹³ A combination of different antiretroviral drugs is needed because HIV can quickly adapt and become resistant.¹⁴ Combination of different anti-HIV in single pharmaceutical preparation is advantageous because FDC has not only reduced the risk of resistance but also added the benefits of patient's compliance.¹⁵

CONCLUSION

Antimicrobials are back bone of modern therapy. Usually, single agent is sufficient but in certain clinical situation a combination will be needed. Fixed Dose Combination [FDC] are quite common due to better compliance and other advantage. Rational combination of FDCs is efficacious but irrational is dangerous. These should be prescribed only when dosage is appropriate and rational.¹⁶ A rational FDCs of antimicrobial must follow pharmacological criteria of their combination and approved by competent authority like WHO, FDA and DCGI.

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