DOI: 10.7860/JCDR/2014/8778.4489

Review Article

Internal Medicine Section

Burden of Antibiotic Resistance in Common Infectious Diseases: Role of Antibiotic Combination Therapy

KISHOR C MEHTA[1], RAMESH R DARGAD[2], DHAMMRAJ M BORADE[3], ONKAR C SWAMI[4]

ABSTRACT

Globally, antimicrobial resistance is alarming concern especially in commonly reported disease entities like respiratory tract infection, enteric fever and infections associated with gram-negative bacilli (GNB). Rational use of antimicrobial drugs reported significant decrease in bacterial burden and may also reduce the risk of disease progression. However, at times in particular indication, certain patient and pathogen factor limits the selection and use of specific antibiotic therapy while in some case, due to presence of additional risk factor, aggressive therapy is required to achieve clinical reemission and prevent complications. Delay in start of suitable antibiotic therapy is another imperative factor for treatment failure and rise of drug resistance.

With rapidly increasing antibiotic resistance and decline in new antibiotic drug development, the toughest challenge remains to maintain and preserve the efficacy of currently available antibiotics. Therefore, the best rational approach to fight these infections is to 'hit early and hit hard' and kills drug-susceptible bacteria before they become resistant. The preferred approach is to deploy two antibiotics that produce a stronger effect in combination than if either drug were used alone. Various society guidelines in particular indications also justify and recommend the use of combination of antimicrobial therapy. Combination therapies have distinct advantage over monotherapy in terms of broad coverage, synergistic effect and prevention of emergence of drug resistance.

Keywords: Antimicrobial resistance, Respiratory tract infection, Enteric fever, Gram-negative bacilli, Synergistic effect

INTRODUCTION

Worldwide, antimicrobial resistance is growing concern particularly for respiratory tract infections, enteric fever, and infections associated with gram-negative bacilli (GNB). The important factors responsible for this are misuse of antibiotics and paucity of new and effective antimicrobial agents.

Present armoury of antimicrobials includes a wide variety of drugs and there is continuous investment in the research for new drugs, however, bacteria are rapidly developing resistance to clinically useful antimicrobials and making them ineffective [1]. In India, antimicrobial resistance is far greater problem since many nonqualified persons/practitioners prescribe antibiotics and many times in inadequate dosage/duration, sometime for unindicted therapy. Self medication is also noted. This has resulted in high incidence of antibiotic resistance. This article presents brief overview of antibiotic resistance to commonly reported clinical disease entities in India and role of combination of antibiotics to overcome this resistance.

Is Combination Therapy a Viable Therapeutic Option?

In a review published in 1956, Elek SD stated that "In a way all therapeutic treatment are combined therapy, since the drugs are effective only if body defence of the patient acts in synergy with these drugs".

He also estimated the mathematical chances of success of combination therapy by theory: "If the incidence of a mutants is 1 in a million to one drug and 1 in a million to the other, the odds of a single mutant resistant to both drugs is in a million times a million. In Infection there may well be a few million organisms in the body, but a million times a million bacilli represent about 10 Litres of good laboratory culture of a fast-growing bacillus. Such enormous populations are unlikely to occur and this is the explanation of the success of combined antibiotic treatment in preventing the emergence of resistant mutants" [2].

Decreased toxicity without decreased efficacy
Synergy: 1 + 1 = 4 or more
Initial emergency treatment of seriously ill patients with no time to be wrong: "shotgun therapy"
To prevent and attack mutants bacteria- second antibiotic delays emergence of resistant bacteria, prolonging the effect of the active agents
Mixed infection with each microorganism requiring a different drug
To prevent super-infection by new bacteria
To attack nonsusceptible population
To reach otherwise unaccessible organisms;an uncommon but important consideration

[Table/Fig-1]: Indication for use of multiple antibiotics [3]

In 1975 Levin and Harris published principals of combination therapy [3] [Table/Fig-1].

In a review, Fischbach discussed three different categories of combination therapy; i) inhibition of different targets in different pathways (e.g. combination of drugs in directly observed treatment, short-course (DOTS) regimen for tuberculosis), ii) inhibition of different targets in same pathway (e.g. co-amoxiclav) and iii) inhibition of same target in different ways like action of sulfamethoxazole and trimethoprim on folic acid cycle synergistically lead to inhibition of bacteria [4].

Factors Favouring Rational Antibiotic Combination Therapy [5]

There are certain advantages of rational antibiotic combination therapy [Table/Fig-2].

Broad spectrum activity:

In the era of increased antibiotic resistant, there is high possibility of adequate antibacterial coverage by combining two antibacterial

agents than single agent. In cohort of culture-positive bacterial septic shock ICU patients, combination therapy of β-lactam with other antibiotic (aminoglycosides, fluoroquinolones, or macrolides/clindamycin) reported significant decrease in 28 day mortality (36% versus 29%; p=0.0002), mechanical ventilation-free days (median 10 versus 17; p=0.008) and pressor free days (23 versus 25; p=0.007) compared to β-lactam monotherapy. This is attributed to agents having broad spectrum of activity against Gram-negative organisms causing septic shock. Thus the study clearly highlighted the role of antibiotic combination therapy [5].

Provides broad empiric coverage
Multimodal action (different spectra of activity)
Prevents emergence of drug resistance
Produces synergistic/additive effect depending on the combination
Suitable for management of polymicrobial infection
Decreased toxicity of individual agents
Suitable for initial therapy
Beneficial for patients who are at high risk for treatment failure
Increases compliance to therapy
Reduces mortality

[Table/Fig-2]: Advantages of rational antibiotic combination therapy over monotherapy

Prevention of Drug Resistance: Antibiotic combination therapy permits to explore different molecular targets of individual agents and thereby broaden the spectrum of action. Antibacterial agents with their broad spectra of activity and multimodal action may prevent emergence of drug resistance. Reduced rate of resistance to rifampin and other anti-tubercular agents is noted due to combination treatment [5].

Synergy in action: Synergistic action leading to broader spectrum than the sum of activity of two individual agents has been reported with combination therapy. Combination of ampicillin and gentamicin in Enterococcal endocarditis; penicillin and gentamicin in viridians Streptococcal endocarditis; and vancomycin and gentamicin in Staphylococcal endocarditis are classical examples [5].

Enhance Uptake and Sequential Blockage: Combination also helps in enhancing uptake and inhibition of sequential steps. Combination of β-lactam and aminoglycoside antibiotics provides antimicrobial synergy with increased uptake. This is mediated by β-lactam induced cell wall damage that facilitates passage of aminoglycoside into bacterial cell thereby enhancing bactericidal effect. Sequential blockade with combination of trimethoprim-sulfamethoxazole (Cotrimoxazole) is effective in treating chronic urinary tract infections (UTIs), typhoid fever, and shigellosis caused ampicillin-resistant organisms.

Polymicrobial Infections: Polymicrobial infections are commonly seen in intra-abdominal, pelvic region and uro-genital tract infection. They consist of mixed flora of aerobic and anaerobic microorganism. Antibiotic combination therapies are mainstay of treatment of these polymicrobial infections as seen with common use of ciprofloxacin along with metronidazole. Better coverage including atypical microorganisms was reported in polymicrobial community-acquired pneumonia (CAP) [6].

Empiric Therapy: In patients where the nature of infection is not clear, empiric antibiotic combinations are very useful to initiate the therapy. By using empiric antimicrobial therapy with an agent to which organism is susceptible has been associated with reduction in mortality and improvement in outcomes [7].

Decreased Toxicity and Decreased Mortality: Rational antibiotic combination therapy decrease the concentration/dose required for treatment and thus reduce the dose related toxicity. However there is no data from reported clinical trials that establishes beyond doubt that combination therapy with different agents permits a reduction of the drug dose sufficient to reduce dose-related toxicity. In addition, rational antibiotic combination therapies associated with reduced mortality and were reported to produce better clinical outcome in patient who are at risk for treatment failure [8].

Disadvantages associated with Combination Therapy [5]: There are certain disadvantages of antibiotic combination therapy.

Antagonism: Notably seen in treatment of microorganism like *Enterobacter*, *Serratia*, or *Pseudomonas* with combination therapy where induction of β-lactamase by one agent, renders the second agent ineffective. This is more prominent in immunocompromised patients or in infections where localized host defenses may be inadequate such as meningitis and endocarditis. Antagonism may lead to conversion of bactericidal agent to bacteriostatic.

***Clostridium difficile* Infection (CDI):** Any broad spectrum antibiotic has potential to cause overgrowth of *C. difficile.* Among these, fluoroquinolones have been reported to be an independent risk factor for CDI.

Other Disadvantages of Combination Therapy: Other risks associated with combination therapy are fungal overgrowth, drug drug interactions, drug toxicity, irrational drug use and increase in cost of therapy.

Clinical Studies Favouring Effectiveness of Combination Therapy in Commonly reported Bacterial Infections:

Enteric fever: Emergence of drug resistance is well noted in typhoid fever. Plasmid-mediated resistance to ampicillin, chloramphenicol and/or cotrimoxazole led to the development of multi-drug resistant S. typhi (MDRST) strains. Nalidixic acid resistant S. typhi (NDRST) and fluoroquinolones resistant isolates have also been reported [9]. Sporadic resistance to cephalosporins (including 3rd generation) is possibly due to its usage in areas of high fluoroquinolone resistance particularly South Asia and Vietnam. This has made cephalosporins less useful as a monotherapy over the time [10].

Naik et al., in their non-comparative evaluation study reported that fixed dose combination (FDC) of cefixime and oflaxacin provided rapid clinical cure of enteric fever as assessed by the clinical parameters of fever, hepatosplenomegaly and symptoms. Significant improvement was reported in all parameters from baseline with mean fever defervescence time of 4.9 days which showed clinical improvement in short course of 5 days [11].

In another study on FDC of cefixime and ofloxacin, Faruqui AA assessed the clinical parameters of fever, sleep interference and respiratory rate in typhoid fever patient. They reported that significant improvement in fever reduction, respiratory rate normalization from baseline to day 3 and day 7 of treatment respectively. Study also reported significant reduction in nocturnal awakening (no sleep interference) [12].

Adverse effects reported in both combination studies were the rare cases of nausea, headache and epigastric pain which were of mild to moderate intensity. These adverse events (AE) do not require treatment discontinuation. Both the studies highlighted that fixed dose combination of cefixime and ofloxacin is effective in management of uncomplicated typhoid fever with excellent tolerability and safety. Use of fixed dose combination is also supported by World Health Organisation (WHO) and Indian Association of Paediatrics (IAP) guidelines suggesting cefixime per oral (PO) plus ofloxacin PO for treatment of uncomplicated typhoid fever.

Respiratory tract infections (RTIs): Anti-microbial resistance is most evident in organism causing RTIs [13]. Among the RTIs community-acquired pneumonia (CAP) is a common and potentially serious respiratory tract illness. Most frequently isolated microorganism in CAP is *Streptococcus pneumoniae*. Management of CAP continues to be a challenge for physician even in 21st

Class	Limitation
β-lactam	No activity against atypical pathogen and development of *S. pneumoniae* resistant isolates > 50 %
Macrolides	30.9 % resistant *S. pneumoniae* isolates reported
Fluroquinolones	Increase potential for emergence of resistant strain of gram negative microorganism

[Table/Fig-3]: Individual antibiotic class limitation in RTI management [14]

century due to development of antibiotic resistance especially in *S. pneumoniae* [6].

β-lactam, macrolide and fluoroquinolone class of drugs are mainly involved in RTIs management. However these recommended classes of antibiotic had their certain limitations [Table/Fig-3].

Combinations therapy may help in overcoming individual class limitation as well as to counteract antibiotic resistance of *S. pneumoniae* [6].

Several studies have reported that treatment of respiratory infections (particularly pneumonia) with combination therapy is beneficial and offers better treatment outcome than monotherapy [Table/Fig-4].

In patient with complicated RTI and risk of treatment failure, β-lactam (usually in combination with a β-lactamase inhibitor or combination therapy in management of RTI like CAP, HAP (Hospital Acquired Pneumonia) [Table/Fig-5].

Gram negative infections (*Pseudomonas aeruginosa*): A high mortality rate of 30 – 70% was reported in hospitalized patients with resistant Gram-negative organisms as an important underlying cause. Drug resistance among gram negative organisms is not restricted to β-lactams but also includes quinolones and aminoglycosides. Reported clinical data suggest that in carbapenemase producer, resistance to quinolones and aminoglycosides approaches to 98% and 50% respectively. The last resort agents effective against carbapenemase producers include polymyxins (colistin and polymyxin B), tigecycline, and fosfomycin. However, resistance to these agents has also been reported [5].

Among these, most notable and notorious gram negative microorganism is *Pseudomonas aeruginosa* and posses the ability to express multiple mechanisms of resistance [5].

In patient of *P. aeruginosa* bacteraemia, combination therapy of antipseudomonal β-lactam antibiotics with aminoglycoside reported significantly higher cure rate (72% versus 29%; $p < 0.001$) compared to aminoglycoside monotherapy. Lower mortality rate (27% vs. 47%; $p < 0.02$) was reported with combination therapy compared to monotherapy. Similarly among severely ill patients higher survival

Author	Cohort	Study design	n	Drug Combination	Outcome
Weiss et al., [8]	Pneumococcal bacteremia	Monocenter, retrospective	95	β-lactam plus macrolide	Lower mortality with combination
Dudas et al., [15]	CAP	Multicenter, prospective	2963	β-lactam plus macrolide	Lower mortality and reduced length of stay
Waterer et al., [16]	Pneumococcal bacteremia	Multicenter, retrospective	225	β-lactam plus macrolide	Lower mortality
Lodies TP et al., [17]	CAP	Multicenter, retrospective	845	β-lactam plus macrolide	Lower mortality
Rodrigo C et al., [18]	CAP	Multicenter, retropective	5240	β-lactam plus macrolide	Lower mortality

[Table/Fig-4]: Published clinical studies on combination of antibiotic therapy in-hospitalized patients with CAP

American Thoracic Society (ATS)	British Thoracic Society (BTS)	Infectious Disease Society of America (IDSA)	Canadian Infectious Disease Society (CIDS)
Outpatients with Comorbidities and Previous Antibiotic Therapy			
Cephalosporin or β-lactam/β-lactamases inhibitor plus macrolide or Doxycycline or respiratory quinolone	Preferred: Amoxicillin plus macrolide or amoxicillin-clavulanic acid or cephalosporin (I,II or III generation) plus macrolide Alternative: respiratory quinolone or respiratory quinolone plus benzylpenicillin	Cephalosporin or β-lactam/β-lactamases inhibitor plus macrolide or a respiratory quinolone	Cephalosporin (I,II or III generation) plus macrolide
Cap That Requires Hospitalization			
No risk for *P. aeruginosa* infection: Cephalosporin or β-lactam/β-lactamase inhibitor plus macrolide **or a respiratory quinolone Risk for *P. aeruginosa* infection:** Antipseudomonal β-lactam plus antipseudomonal quinolone or Antipseudomonal β-lactam plus aminoglycoside and macrolide or respiratory quinolone		Cephalosporin or β-lactam/β-lactamase inhibitor plus macrolide or a respiratory quinolone	No risk for *P. aeruginosa* infection: First choice: respiratory quinolone plus III generation cephalosporin or β-lactam/ β-lactamase inhibitor Second choice: Macrolide plus III generation cephalosporin or β-lactam/ β-**lactamase inhibitor Risk for *P. aeruginosa* infection:** Antipseudomonal quinolone plus Antipseudomonal β-lactam/ Antipseudomonal β-lactam plus aminoglycoside and macrolide Antipseudomonal: β-lactam plus a

[Table/Fig-5]: Recommendation by various societies' guidelines on combination of therapy [19,20,21]

macrolide) and respiratory fluoroquinolones are most commonly recommended [19]. Antibiotic combination therapy produces synergistic effects and reduces mortality at high risk for treatment failure, in comparison with monotherapy. Various speciality societies like American Thoracic Society (ATS), British Thoracic Society (BTS), Infectious Disease Society of America (IDSA) and Canadian Infectious Disease Society (CIDS) recommended use of empiric rate (53% vs. 8%; $p < 0.02$) was reported with combination therapy compared to monotherapy [5].

CONCLUSION

In case of drug resistant infection, it is essential to select the appropriate empiric therapy which can completely eradicate target microorganisms without leaving any mutants. Thus the rational

antibiotic combinations therapies are key in the battle against drug resistance bacteria in the area of high prevalence of drug resistance. Drug resistant and multidrug resistant bacteria are major concern in the effective management of infection. Greater morbidity and mortality associated with delays in appropriate and effective antimicrobial treatment.

However combination therapy is not free from disadvantages which may include real or potential as follows: i) Encouragement of shot-gun therapy ii) Failure to provide optimum dose of individual agent iii) Increased drug resistance by providing empirically two agents when organism is susceptible for single agent [22]. Judicious and rational use of antibiotic combination therapy reduces risk of development of drug resistance and improves clinical outcome and can be used whenever required and rational.

REFERENCES

[1] Pena-Miller R, Laehnemann D, Jansen G, Fuentes-Hernandez A, Rosenstiel P, Schulenburg H, et al. When the Most Potent Combination of Antibiotics Selects for the Greatest Bacterial Load: The Smile-Frown Transition. *PLoS Biol.* 2013;11(4): e1001540.

[2] Elek SD. Principles and Problems of Combined Antibiotic Therapy. *Postgrad Med J.* 1956; 32(369): 324–27.

[3] Levin S and Harris AA. Principles of combination therapy. *Bull N Y Acad Med.* 1975; 51(9): 1020–38.

[4] Fischbach MA. Combination therapies for combating antimicrobial resistance. *Curr Opin Microbiol.* 2011; 14(5): 519–23.

[5] Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with Gram-negative bacteria. *Clinical Microbiology Reviews.* 2012;25(3):450–70.

[6] Caballero J and Rello J. Combination antibiotic therapy for community acquired pneumonia. *Ann Intensive Care.* 2011; 1: 48.

[7] Kumar A, Zarychanski R, Light B, Parrillo JE, Maki D, Simon D, et al. Early combination antibiotic therapy yields improved survival compared to monotherapy in septic shock: A propensity-matched analysis. *Crit Care Med.* 2010;38(9):1-9.

[8] Weiss K, Low DE, Cortes L, Beaupre A, Gauthier R, Gregoire P, et al. Clinical characteristics at initial presentation and impact of dual therapy on outcome of bacteraemic *Streptococcus pneumoniae* pneumonia in adults. *Can Respir J.* 2004;11(8):589-93.

[9] Bhutta ZA: Current concepts in the diagnosis and treatment of typhoid fever. *BMJ.* 2006; 333(7558): 78–82.

[10] Brusch JL. Typhoid medication. Available at http://emedicine.medscape.com/article /231135-medication 12 - accessed on 13/11/2013

[11] Naik M, Braganza L, Nair S, Khandeparkar P. Open non-comparative evaluation of fixed dose combination of cefixime and ofloxacin in the treatment of uncomplicated typhoid fever. *Indian Medical Gazette.* 2010: 415-20.

[12] Faruqui AA, Siddique W. Evaluation of efficacy and safety of fixed dose combination of cefixime and ofloxacin (CO_2 Tablet) in the management of typhoid fever. *Indian Journal of Basic & Applied Medical Research.* 2012; 1(4):296-303.

[13] Brook I, Gober AE. Antimicrobial resistance in the nasopharyngeal flora of children with acute maxillary sinusitis and maxillary sinusitis recurring after amoxicillin therapy. *Journal of Antimicrobial Chemotherapy.* 2004; 53: 399–402.

[14] Bruton S. Treating community-acquired bacterial respiratory tract infection: Update on etiology, diagnosis, and antimicrobial therapy. *J Fam Pract*. 2005;54(4):357-64.

[15] Dudas V, Hopefl A, Jacobs R, Guglielmo BJ. Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: A survey of nonteaching US community hospitals. *Ann Pharmacother*. 2000 April;34(4):446-52.(Abstract).

[16] Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. *Arch Intern Med*. 2001 August;61:1837-1842.

[17] Lodise TP, Kwa A, Cosler L, Gupta R, Smith RP. Comparison of ß-lactam and macrolide combination therapy versus fluoroquinolone monotherapy in hospitalized veterans affairs patients with community-acquired pneumonia. ANTIMICROBIAL AGENTS AND CHEMOTHERAPY. 2007 November;51(11):3977–82.

[18] Rodrigo C, Mckeever TM, Woodhead M, Lim WS. Single versus combination antibiotic therapy in adults hospitalised with community acquired pneumonia. Thorax. 2013;68(5):493-95.

[19] Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *CID.* 2007;44(2):S000–000.

[20] The British Thoracic Society guidelines for the management of community acquired pneumonia in adults update 2009. *British Thoracic Society Reports.* 2009;1(3).

[21] Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH. Canadian community-acquired pneumonia working group. Canadian guidelines for the initial management of community-acquired pneumonia: An evidence-based update by the Canadian infectious diseases society and the Canadian thoracic society. CID 2000;31:000–000.

[22] Smith RM, Cope O, Alte RE, Faulkner JM, Hayman JM. Antibiotics in fixed dose combination. *NEJM*. 1960;262(5):255-56.

PARTICULARS OF CONTRIBUTORS:

1. Honorary Physician, Dr. Suchak Hospital, Malad (E) and Vaishanav Seva Samaj Hospital, Kandival (W), Mumbai, India.
2. Honorary Physician, Lilavati Hospital and Research Centre, Bandra (W) and Seven Hill Hospital, Andheri (E), Consulting Physician, Dr. L H Hiranandani Hospital, Powai, Mumbai, India.
3. Assistant Manager, Medical Service, Unichem Laboratories Ltd, Unichem Bhavan, Prabhat Estate, S.V. Road, Jogeshwari (W), Mumbai, India.
4. Head, Medical Services, Unichem Laboratories Ltd, Unichem Bhavan, Prabhat Estate, S.V. Road, Jogeshwari (W), Mumbai, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Onkar C Swami,
Head, Medical Services, Unichem Laboratories Ltd., Unichem Bhavan, Prabhat Estate,
S.V. Road, Jogeshwari (W), Mumbai – 400102, India.
Phone: +91-22-66888333, E-mail: onkar.swami@unichemlabs.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Feb 03, 2014**
Date of Peer Review: **Feb 22, 2014**
Date of Acceptance: **Apr 25, 2014**
Date of Publishing: **Jun 20, 2014**