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RATIONALE OF COMBINATION ANTIMICROBIAL THERAPY FOR BACTERIAL INFECTIONS

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ABSTRACT

Antimicrobial combination therapy has been used ever since antimicrobials were available. Combinations of antibiotics are often used to take advantage of different mechanism of action which may provide synergy and help in the treatment of serious life threatening infection or to eliminate resistant micro-organisms not responding to a single antimicrobial regimen. In addition, combination therapy may be used to avoid toxicity of certain antibiotics as antimicrobials may be used at lower doses.

The major indications for combination antimicrobial therapy are (a) empirical treatment of life threatening infection (b) teratment of polymicrobial infection (c) prevention of emergence of bacterial resistance and (d) for synergism.

Combination antimicrobial therapy should be considered for the treatment of serious Gram-negative infections caused by Enterobacter cloacae, Pseudomonas aeruginosa, Serratia marcescens and Gram-positive infections caused by Enterococcus spp. and Staphylococcus aureus and also in infections by other organisms resistant to multiple antibiotics.

INTRODUCTION

Combination therapy is often required for empirical coverage of acute infection before the responsible micro-organisms have been identified[1]. Examples include community acquired and nosocomial pneumonia including aspiration pneumonia, sepsis, meningitis and endocarditis[2-5]. However in case of overwhelming sepsis or life theratening meningitis monotherapy is justifiable in the immunocompetent patient when the offend-

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ing pathogen has been identified[6]. It is also indicated in immunocompromised individual such as the febrile neutropenic patient, where pathogen are not easily identified and in case of polymicrobial infections, to cover all potential pathogens isolated[1,2,7,8]. Example of polymicrobial infections requiring combination therapy include complicated intra-abdominal infections, infections ofthe female genital tract, infection of the respiratory tract and in patient with chronic sinusitis. The advent of newer agents such as the broad specturm B-Lactam B-Lactamase inhibitor compounds and new carbapenam agent, allow for single agent therapy with similar coverage spectrum[9].

Indications for clinical use of antimicrobial combinations

1. Synergism

The combination of two different antimicrobials may result in bactericidal activity which is significantly greater than that seen with either agent alone, it is said to be synergistic. If the bactericidal rate of combination is less than that for either drug alone, it is said to be antagonistic.

Though, there are numerous examples of in-vitro synergism, clinically the combinations have been more effective in only a few settings[10,11]. The best example is enterococcal endocarditis. The combination of penicillin with an aminoglycoside achieves good clinical cure rates. Penicillin seems to enhance the uptake of aminoglycoside by the enteococci, hence the synergistic killing of the organisms[12]. Synergistic combination are often sought in infections where the development of resistance/subsequent failure with monotherapy is prevalent, such is the case in the treatment of infective eudocarditis, in which treatment failures and relapses are commonly seen because of poor penetration of antibiotics into the cardiac vegetation, high bacterial density at the site of infection and the development of resistance during therapy[13].

A similar synergism is reported for a combination of penicillinase-resistant penicillin such as oxacillin or nafcillin in combination with gentamicin against S. aureuss[14,15].

A combination of carbenicillin, ticarcillin, mezlocillin, or piperacillin with gentamicin, tobramycin, or amikacin exhibits synergism against majority of strains of Pseudomonas aeruginosa[16,17].

Trimethoprim-sulphamethoxazole combinations inhibit sequential steps in the metabolic pathways of microbes and hence are synergistic[18]. The combination of these two agents is used in treatment of urinary tract infections, typhoid fever, shigellosis, respiratory infections and also certain parasitic infections[19-22].

Synergism has been used to treat fungal infections as it has been observed that amphotericin B damages the envelope of the fungi with a resultant enhanced intracellular penetration of 5-fluorocytosine and other agents[23].

The synergistic effect of combination may also persist for sometime after the dose of the antimocrobials. This phenomenon of presistent suppression of bacterial growth after short exposure to antimicrobials has been referred to as the post antibiotic effect (PAE)[24]. Synergistic PAEs have been observed with combination of β-Lactams and aminoglycosides and by addition of rifampicin to a variety of antibiotic classes synergistic PAE occurs when the PAE produced by the combination is significantly greater than PAE produced by either agent alone[25,26].

2. Synergism and infections in immunocompromised hosts

This is another situtation where synergistic combinations may save the patients life especially in the case of serious infections by Gram negative bacteria[27].

3. Decreased toxicity

Many of the antimicrobials are toxic (e.g. aminoglycoside). Combination therapy leads to a reduction in the dose and probably in a decrease in the toxicity. The problem at the moment is that there is no convincing evidence that combination therapy leads to a sufficient reduction in the dose to reduce the toxicity.

4. Prevention of emergence of resistant organisms

The commonest example is the use of multi-drug therapy in the treatment of tuberculosis. Another emerging area where multiple agents may be used to prevent emergence of resistance is the treatment of HIV positive patients. Another clinical situation where emergence of resistance may be prevented by combination therapy is use of rifampin, in treatment of staphylococcal infection where the use of combination prevents emergence of resistance to rifampin[28].

5. Polymicrobial infections

In majority of infection, even those due to one or two organisms, single agents may be effective. There are still situations where infections may be due to a more broad varitey of agent and combination therapy may be required. The common examples of such situations include intraperitoneal and plevic infections due to mixed aerobic and anaerobic organisms.

6. Initial therapy

This may be in the form of combination therapy to cover a broad spectrum of orgainsms till the results to culture and sensitivity are not available from the laboratory. The situation where such a therapy is usually advocated is neutropaenic patients or patient with serious life threatening infections (meningitis etc.)

LIMITATIONS OF COMBINATION THERAPY

1. Antagonism

Combination antimicrobial therapy may result in antagonism, when bacteriostatic and bactericidal drugs are given concurrently. Well documented clinical example is the combination of penicillin and chlortetracycline in the therapy of pneumococcal meningitis[30]. The fatality rate was 21% when penicillin alone administered, while with the combination the fatality rate was 79%.

Another example of antagonism is the combination of ampicillin, chloramphenicol and streptomycin in the treatment of meningitis. The mortality rate in children treated with ampicillin alone was 4.3% compared to 10.5% with the combination therapy[31].

Another form of antagonism (though classically not an antagonism but an inactivation) is the inactivation of drug when mixed together. For example, if chloramphenicol and erythromycin are mixed together in an infusion they will form insoluble precipitates. Mixing of a penicillin with aminoglycoside may result in the inactivation of the latter (this phenomenon is not observed in vivo as the reaction occurs slowly)[32].

2. Adverse effects

It is obvious that the administration of more than one antibiotic may increase the chance of an adverse drug reaction. Well described adverse reactions with combinations include nephrotoxicity, coagulopathy, diarrhoea, seizures and hypersensitivity reactions.

3. Superinfection

Superinfection is common following broad spectrum antimicrobial therapy. Secondary infection is often caused by resistant bacteria and fungi. Judicious use of antimicrobials as single agent or in combination is prudent to prevent the development of resistance in organisms causing nosocomial infection[33].

4. Cost

The use on combination therapy, especially the newer antibiotics tends to increase the cost of the treatment[34]. This has to considered while initiating combination therapy, more so in developing countries where the patients may not be able to pay for this.

CLINICAL APPLICATIONS OF ANTIMICROBIAL COMBINATIONS

Gram negative bacterial infection

Pseudomonas aeruginosa:

Pseudomonas is a common nosocomial pathogen and because of its extensive prevalence in the hospital setting, patient bocomes easily colonised and at increased risk of developing infection with this organism. The most common site of infection are urinary tract, lung and blood. The advent of antipseudomonal aminoglycoside and pencillin improved patients outcome, however serious pseudomonal infection still causes significant mortality[35]. Bacteremia pneumonia, osteomyelitis and endocarditis resulting from P. aeruginosa can be particularly difficult to cure. Diabetes, drug addiction, cancer, burn, cystic fibrosis, AIDS and patients with urinary catheters are predisposed to pseudomonal infection[36].

Treatment of pseudomonal infections must be based on epidemiological consideration and local susceptibility patterns. Early reports using monotherapy (aminoglycoside) indicated that this was ineffective. It also established the need for vigorous treatment with anti-pseudomonal agents as the infection tends to be aggressive with very high mortality rates.

Recent studies have used ceftazidime as monotherapy, but the disadvantages of such therapy for P. aeuroginosa and other Gram negative infections is the emergence of resistance due to the expression of inducible B-lacatamases[37].

A prospective study of 200 patients of P. aeruginosa bacteremia demonstrated the clear benefit of combination (Piperacillin and Tobramycin) therapy versus monotherapy if treatment is initiated early[38].

The methods of administration of B-Lactam and aminoglycoside is very vital for efficacy and safety. B-Lactam antibiotics kill bacteria in a time dependent fashion i.e. serum concentrations should be kept several fold above the MIC of the infecting organism, and aminoglycosides kill bacteria in a concentration dependant manner i.e. higher concentrations result in increased killing activity. To take advantages of these properties B-Lactam antibiotics can be administered as a continuous infusion and aminoglycoside can be administered once daily or every other day in high doses.

Recently much interest has been generated regarding the combination of fluroquinolones

and B-Lactam. Although this combination is not routinely synergestic, it has never been reported to antagonistic.

In one unique study ciprofloxacin and azlocillin were combined in an in vitro infection model against P. aeruginosa to compare the effect of simultaneous versus staggered dosage regimens[39]. Regimens which were administered simultaneously resulted in the greatest amount of killing, especially in the case of ciprofloxacin resistant strain. This study not only adds information regarding the usefulness of quinolones and B-Lactam combination, but also insight on how to potentially futher enhance killing activity with simultaneous administration. Ceftazidime combined with ciprofloxacin has been recently reported to be successful in treating Pseudomonas infected orthopaedic prosthesis[40].

The current recommendation regarding P. aeruginosa infection with the exception of uncomplicated urinary tract infection, is that it should be treated with combination therapy consisting of antipseudomonal B-Lactam agent with an aminoglycoside dose to achieve high peak serum aminoglycoside concentration 10 to20mg/L.

Enterobacter species

These species are of particular importance due to the fact that resistance often emerges during antibiotic therapy. This phenomenon has been reported during treatment with cephalosporins[41]. The mechanism of resistance is production of B-Lactamases. The current recommendation is combination therapy with a B-Lactam and aminoglycoside when Enterobacter bacteraemia is established.

Acinetobacter, Serratia and Citrobacter species

Acinetobacter, Serratia and Citrobacter species are Gram negative organisms and are generally resistant to all other antibiotics except imipenam and amikacin. Therapy with imipenam and amikacin is synergestic and indicated for serious infections such as pneumonia, complicated UTI, meningitis, bacteremia and endocaarditis.

Gram Positive Bacteria

Staphylococcus aureus

Staphylococcus aureus is the fourth common cause of nosocomial infection S. aureus may develop resistance to B-Lactam agent by alteration in penicillin binding proteins (PBP), hence the name methicillin resistant S. aureus (MRSA) has become commonplace.

S. aureus remains a common cause of endocarditis and much controversy exists regarding optimal therapy[42]. It is generally accepted that Methicillin sensitve S. aureus (MSSA) should be treated with antistaphylococcal penicillin in the absence of penicillin drug alllergy. The question thus arises whether to add an aminoglycoside antibiotic. It is clear from in vitro and animal models that the combination of nafcillin and gentamicin is synergistic against MSSA. However clinical data is inconclusive. The advantages of combination therapy in MSSA are that (a) duration of treatment is decreased, (b) early efficacy and a decreased toxicity and (c) mortality is low.

Interest in the treatment of S. aureus endocarditis was rekindled in the early 1980's because of introduction of fluroquinolone antibiotics, since it might potentially serve as an alternative to vancomycin for patient with MRSA infection and significant penicillin allergy. These antibiotics exhibit potent in vitro bactericidal activity against S. aureus, however wide spread resistance has

now been reported resulting from extensive clinical use.

Addition of rifampicin to ciprofloxacin has resulted in synergy, indifference and antagonism in vitro. Thus the combination is most likely unpredictable clinically. A study in 19 patients of endocarditis with S. areus, treated with ciprofloxacin and rifampicin showed a 100% cure rate[43].

Infections due to MRSA are particularly difficuly to treat. Vancomycin has been the mainstay of treatment in S. aureus endocarditis. Due to large population of bacteria present, vancomycin may fail, since it demonstrates an inocula effect and kills bacteria less effectively at high inocula. The successful addition of rifampicin to vancomycin has been reported in early case reports[44].

Teicoplanin is an investigational glycopeptide that possesses activity against MRSA. Early trials have halted because of failures with low dosages regimens. Trials are currently being conducted with higher dosages to compensate for extensive protein binding. One advantage with teicoplanin is the potential for intramuscular administration, which is not possible with vancomycin.

Quincipristin-dalfopristin is an investigational streptogramin which also exhibitis activity against MRSA. In a novel in vitro infected fibrin clot model, quincipristin-dafloporistin, combined with vancomycin was associated with greater killing activity versus both MSSA and MRSA compared with vancomycin alone[45].

Enterococcal infections

Treatment of enterococcal infection outside of cystitis required combination of a pencillin and an aminoglycosed antibiotic or vancomycin plus aminoglycoside for patient with known history of pencillin allergy. Gentamycin is used in "synergistic doses" to achieve peak serum concentration in the range of 3-5 mg/l[46].

If β-Lactamase producing enterococci is encountered, the use of β-lactamase inhibitor such as ampicillin-sulbactum in combination with an aminoglycoside has been recommended[47].

Recently vancomycin resistant enterococci (VRE) have ben reported[48]. This type of resistance is plasmid mediated and occurs often with E. faecium than E. faecalis. Vancomycin resistance occurs secondary to loss of target affinity. An inducible protein known s VanA is responsible for altering the D-alanine target terminus for vancomycin. The vancomycin minimum inhibitory concentration (MIC) for these isolates generally exceeds 64 mg/L[49].

Unfortunately because of multi drug resistant nature of VRE, there are few treatment options presently available. If the isolate is still B-lactam and amminoglycoside susceptible, the combination of these agent would be preferable treatment options[50]. If the organisms display resistance to the glycopeptide, a triple combination of β-lactam, glycopeptide and aminoglycosides appears to improve the bactericidal activity against glycopeptide resistant strain in animal models.

Recently it has been demonstrated that combination of ceftriaxone plus vancomycin and gentamicin was more effective than benzylpencillin plus vancomycin and gentamicin for experimental treatment of glycoside resistant E faecium endocarditis. Aminoglycoside was essential for bactericidal activity observed.

Ominoprist-dalfopristin has demonstrated promising results against glycopeptide

resistant E faecium infection. The combination is bacteriostatic against glycopeptide resistant E faecium. Recent results have demonstrated a 78% cure rate of VRE infection due to E faecium[51].

Infection caused by E faecium or E faecalis exhibiting Van B type resistance may be treated with teicoplanin.

The combination of teicoplanin with an aminoglycoside against these strains has been shown to be effective in animal model of endocarditis[52].

The use of antimicrobial combinations have certain advantages and disadvantages. The situations where these combinations may be effective are in life threatening infection where the microbe has not been identified and in infections where there is a high possibility of mixed infection like in intra-abdominal infections and in infections by multi-drug resistant organisms. It is also essential that the correct combination be given as there are situations where antagonism instead of synergism may occur. In addition, combination therapy should not be used indiscriminately.

Judicious use of combination can be life saving, but abuse can lead to side effects as well as an increased burden to the patient in the form of increased expenditure, which patients in developing countries can ill afford.

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