

Original Research Article

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Doxycycline and Co-trimethoxazole: A new combination for treatment of MDR *Acinetobacter baumannii*. Does it work?

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ABSTRACT

Acinetobacter baumannii has proven to be an increasingly important and demanding species in health care-associated infections. The drug-resistant nature of the pathogen and its unusual and unpredictable susceptibility patterns make empirical and therapeutic decisions even more difficult. Most of the published and running studies for treatment of multidrug-resistant *Acinetobacter baumannii* (MDR-AB) depends on the usage of older class of antibiotic (Colistin) either alone as a single therapy or in combination with another antibacterial agents. The fact that new strains of *Acinetobacter baumannii* started to show resistance to colistin obliged the investigators to search for other alternatives for treatment. The aim of this study was to assess the effect of combination of Doxycycline and co-trimethoxazole in the cure of nosocomial MDR-AB infection in critically ill patients and its effect on the patients outcome. The study was done on 50 adult critically ill patients who developed nosocomial isolated MDR-AB in the Critical Care Medicine Department of Alexandria University in Egypt and received combination of Doxycycline 100 mg twice daily With trimethoprim-sulphamethoxazole (co-trimethoxazole) in a dose of 80 mg Trimethoprim/400 mg Sulphamethoxazole twice daily for 1 week. patients who are allergic to the antibiotics used or those who did not continue 7 days treatment were excluded from the study. Approval of local ethical committee as well as consent from patients relatives were obtained. culture and sensitivity was repeated after 1 week treatment. The microbiological cure rate was 60 % as 30/50 patients were cured. The bestcure rate was in surgical site infection with 88.9 % (8/9) while the cure in pneumonia was 56.7 % (17/30). Two cases with blood stream infection were not cured while (5/9) patients from those who had more than one site infection were cured. The total 30 days mortality was 20 % (10/50) while the mortality related infection was 12 %. We concluded that combination of Doxycycline and co-trimethoxazole can be used in the treatment of nosocomial MDR-AB infection resistant to colistin or incases with contraindications or unavailability of colistin especially in surgical site infection and to less extent in pneumonia. However, further larger studies are needed to validate the results of this study.

Keywords

Doxycycline and co-trimethoxazole, *Acinetobacter baumannii*, MDR-AB infection,

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Introduction

The genus *Acinetobacter* was first isolated and described in 1911 by a Dutch microbiologist, several changes was introduced into the taxonomic classification of *Acinetobacter* species. *Acinetobacter*, family Moraxellaceae, consists of gram-negative bacilli that initially encompassed a heterogeneous collection of non-pigmented, oxidase-positive, and oxidase-negative gram-negative rods. It currently comprises gram-negative coccobacilli that are non-motile, non-fermentative, non-spore forming, strictly aerobic, catalase-positive, and oxidase-negative. ⁽¹⁾*Acinetobacter* classified as an opportunistic pathogen of relatively Low pathogenicity. The organism can survive under dry conditions. Colonization in the lung is facilitated by the ability of *Acinetobacter* species to adhere to human bronchial epithelial cells using fimbria. ^(1,2)

Acinetobacter baumannii has also been isolated from a number of sites in the hospital: as environmental surfaces, equipment including mechanical ventilators and dialysis machines, air ventilation systems, water sources, hands of healthcare workers, respiratory, and gastrointestinal tracts secretions, wounds of hospitalized patients. ^(2,3) Members of the genus *Acinetobacter* first began to be recognized as significant nosocomial pathogens during 1970. Nosocomial transmission is responsible for the vast majority of *Acinetobacter* infections. ⁽³⁾

Although wide variations exist in different countries, there has been a general trend of increasing incidence of *Acinetobacter* infections. *Acinetobacter* was the fourth most frequently isolated respiratory pathogen, accounting for 9.6 percent of

isolated bacterial species. Higher rates of *Acinetobacter* as a cause of nosocomial infection (27 to 35 percent of isolates) have been reported. ^(4,5) In addition to sporadic infections, *Acinetobacter* has the potential of causing outbreaks in the hospital setting. Two important factors that contribute to the propensity for outbreaks are antimicrobial resistance and tolerance of desiccation. ⁽³⁾ Most outbreaks have occurred in adult ICUs, although other hospital wards that house patients with weakened immunity are also at risk, including intensive care nurseries and burn units. Transient hand colonization among healthcare workers can contribute to outbreak dissemination. ^(5,6)

Treatment of bloodstream infection due to *Acinetobacter* consists of antibiotic therapy and intravascular catheter removal. Empiric antibiotic therapy should be selected based on local susceptibility patterns; in general, it should consist of a broad-spectrum cephalosporin, a combination beta-lactam/beta-lactamase inhibitor (eg, a combination including sulbactam), or a Carbapenems – either alone or in combination with an antipseudomonal fluoroquinolone or an aminoglycoside. Carbapenems monotherapy is reasonable in institutions where Carbapenems resistance rates are low; there is no evidence for improved outcome with combination therapy. ⁽²⁸⁻³⁰⁾ In the setting of resistance to the above agents, therapeutic options are limited; options include colistin, polymyxin B, and Tigecycline (only for secondary bacteremia). In one report, treatment with colistin did not reduce mortality in patients with bacteremia due to multidrug-resistant *Acinetobacter*. These findings highlight the poor outcome of such patients, regardless of whether treatment for bacteremia is initiated. ^(7,8)

The challenges of treating multidrug-resistant bacteria continue to be at the forefront of the clinician's practice in caring for hospitalized patients. *Acinetobacter baumannii* has proven to be an increasingly important and demanding species in health care associated infections. The drug resistant nature of the pathogen and its unusual and unpredictable susceptibility patterns make empirical and therapeutic decisions even more difficult. The association of *A. baumannii* with pneumonia, bacteremia, wound infections, urinary tract infections, and meningitis has been well described⁽⁹⁾. Risk factors associated with colonization or infection (which can be difficult to distinguish) include prolonged hospitalization, intensive care unit admission, recent surgical procedures, antimicrobial agent exposure, central venous catheter use, prior hospitalization, nursing home residence, and local colonization pressure on susceptible patients⁽¹⁰⁻¹¹⁾.

The particular resistance pattern displayed by *Acinetobacter baumannii* strains is a result of the combination between its intrinsic resistance and acquisition of resistance genetic determinants over time, most probably due to extensive use of broad spectrum antimicrobials. The lack of uniformity in the use of antibiotics in different geographical areas is likely to result in different resistance rates noted all over the world⁽¹²⁾.

Most of the published and running studies for treatment of multidrug-resistant *Acinetobacter baumannii* depends on the usage of older class of antibiotic (Polymyxins) either alone as a single therapy or in combination with another antibacterial agents. The polymyxins include colistin or polymyxin E and polymyxin B, and this class of drug has been a savior for the treatment of highly drug-resistant gram-negative bacteria. Colistin is most

commonly used in the United States, and it is administered intravenously as a pro-drug known as colistimethate sodium (CMS). A wide range of observational studies have now been published on the clinical efficacy and toxicity of colistin for treating modern day gram-negative bacteria⁽¹³⁾. Efficacy

ranges from ~55% to 80% depending on the

study and appears to be equal to that of other antibiotics in similar populations. Nephrotoxicity and neurotoxicity remain as key concerns for increasing use in an era of multidrug-resistant pathogens⁽¹⁴⁾.

The problem of associated side effects of colistin especially that critically ill patient have higher incidence of renal impairment which could be aggravated with its usage and the fact that new strains of *Acinetobacter baumannii* started to show resistance to colistin obliged the investigators to search for other alternatives for treatment. Another major local problem in Egypt is the non availability of colistin in the market which was the triggering point to our team to conduct this research in a trial to test the efficacy of possible alternatives available in the Egyptian market.

The aim of the work was to test the efficacy of combination Doxycycline and cotrimoxazole antibiotics in the treatment of *Acinetobacter* infection in critically ill patients and its effect on the patient's outcome.

Materials and Methods

The study was a Prospective Randomized Interventional Trial conducted on 50 adult patients admitted to the Critical Care Medicine Department of Alexandria University Main Hospital in Egypt with

multiple drug resistance (MDR) *Acinetobacter baumannii* (AB) diagnosed from culture and sensitivity test who received combination of doxycycline 100 mg twice daily with Trimethoprim-sulphamethoxazole in a dose of 80 mg / 400 mg twice daily (modified according to renal functions) for 7 days.

Patients not tolerating enteral route feeding, Patients with history of drug allergy to Doxycycline or co-Trimoxazole, Patients who do not complete one week therapy with Antibiotics and Patients who received treatment for infections other than *A. baumannii* were excluded from the study.

Informed consent was taken from all patients or their next of kin. The study was approved from the local ethical committee of the Faculty of Medicine. Follow up culture and sensitivity was repeated after 1 week coverage of antibiotics. Total cure rate as well as cure rate in different subgroups according to the source of infection was followed. Also the mortality related to infection was recorded.

MDR AB was defined as *Acinetobacter baumannii* that is concomitantly resistant to all the agents of four antibiotic classes (fluoroquinolones, aminoglycosides, cephalosporins, and beta-lactam/beta-lactamase inhibitor combinations)⁽¹⁵⁾. The microbiological response was considered positive if the organism could not be isolated in repeated samples during or after the course of Antibiotic treatment, and negative if cultures were persistently positive with the same organism 7 days after treatment initiation. Death attributable to primary infection was defined as occurring without resolution of signs and symptoms of infection and with no other cause identified.⁽¹⁶⁾

Results and Discussion

Table I showed the source of infection in the 50 patients included in the study, 30 of them had respiratory tract infection, 9 patients with surgical site infection, 2 patients with blood stream infection and 9 patients had mixed infections involving more than one site.

Table II showed the total cure rate which was 30 out of 50 patients with a cure rate of 60% while 20 patients did not show cure. The overall total mortality was 10 out of 50 patients (20%) while the infection related death was only 4 patients (8%).

Table III showed the cure rate for each category of infection. The highest cure rate was in the surgical site infection 8 out of 9 patients were cured (88.9%) while respiratory tract infection subgroup showed a cure of 17 out of 30 patients (56.7%). The 2 patients with blood stream infection did not show any cure with a cure rate of 0%. In patients with mixed infections 5 out of 9 patients were cured with a percentage of (55.6%)

A significant amount of time and energy has been devoted to studying combination therapy for the treatment of *A. baumannii* infection. Much of the current information is derived from in vitro or animal studies. There are surprisingly limited data from comparative studies involving human *A. baumannii* infections⁽¹⁷⁾. Petrosillo et al produced a nice review on colistin versus combination therapy; they found only 4 relevant clinical studies and only 1 study demonstrates statistical significance with respect to mortality, favoring monotherapy. The heterogeneity of combinations and infections studied, as well as the small numbers of patients involved, makes interpretation very difficult⁽¹⁴⁾.

Few published data support the use of doxycycline as a treatment for *Acinetobacter baumannii*. Goel et al ⁽¹⁸⁾ tested the Antibiotic sensitivity pattern of gram negative bacilli isolated from the lower respiratory tract of ventilated patients in the intensive care unit. The sensitivity pattern of *Acinetobacter* for doxycycline was tested in 38 patients revealing 33.3% sensitivity, 64.1% intermediate sensitive organisms while only 2.6% of *Acinetobacter* strains were resistant to doxycycline. In another study done by Vila G et al ⁽¹⁹⁾ testing the In vitro antimicrobial production of beta-lactamases, aminoglycoside modifying enzymes, chloramphenicol acetyltransferase and susceptibility of clinical isolates of *Acinetobacter baumannii*. Antimicrobial susceptibility testing was performed on 54 epidemiologically unrelated clinical isolates of *Acinetobacter baumannii* by using a standard agar dilution technique. On the basis of the in vitro activities, imipenem and doxycycline were the most active agents by 100% sensitivity to Imipenem and 97% sensitivity to doxycycline. This was in contrast to a study done by Hernandez et al ⁽²⁰⁾ who studied the effect of doxycycline and other antibiotics alone or in combination for treating lung and blood stream infection of *Acinetobacter baumannii* in experimental models of mice. No cure rate was seen out of 7 models with lung infection treated with doxycycline alone with only 2 out of 7 (28.5%) cured from blood stream infection. With the addition of Amikacin to doxycycline in another 22 models, 3/11 (27%) of pneumonia models were cured and 11/11 (100%) of blood cultures came to be negative for *Acinetobacter baumannii*. This result denotes clearly the importance of giving the doxycycline as a combination therapy with other antibacterial for treating such serious gram negative infections and that is we had done in our study by the addition of trimethoprim-sulfamethoxazole

(co-trimoxazole) to the doxycycline.

Although the usage of co-trimoxazole for treating *Acinetobacter baumannii* can't be considered as a common or routine practice, yet, some data support a possible curative effect especially when used in combination with other agents. Popescu G.A et al ⁽¹²⁾ studied the antimicrobial resistance for *Acinetobacter baumannii* strains, 147 strains of *Acinetobacter baumannii* were analysed. The main specimen which provided the *Acinetobacter baumannii* isolates was tracheobronchial aspirate (68 strains, 46.25%). Less often, other positive samples were: wound secretions (24 strains, 16.32%), sputum (18 strains, 12.24%), urine (9 strains, 6.12%), blood cultures (8 strains, 5.44%), removed foreign material (7 strains, 4.76%), deep collections (4 strains, 2.72%), cerebrospinal fluid (4 strains, 2.72%), other pathologic products (5 strains, 3.4%). The analysis of *Acinetobacter baumannii* strains' susceptibility for the entire study period revealed a very low susceptibility rate, under 50% for most of the investigated antibiotics (Tobramycin: 44.45%, Carbapenems: 19.18%, Amikacin: 18.86%, trimethoprim-sulfamethoxazole: 13.77%, fluoroquinolone: 10.89%, Ampicillin-sulbactam: 9.58%). Colistin was the only one to prove a high activity (99.06%) against these strains. It might be reasonable to claim that the trimethoprim-sulfamethoxazole is not a good choice for treatment but we have to consider that the study tested only the effect of single agent antibiotic which is definitely different from the effect of combinations. Moreover, in the absence of colistin, the results showed that the effect of all other antibiotics is ranging from 10 to 20% which means that there is no clear superiority to test a combination of any antibiotics over the others. In another study done by T Karsligil et al ⁽⁶⁹⁾, the susceptibility of *Acinetobacter baumannii* to trimethoprim-sulfamethoxazole was 47/136 strains which

represents 34.5% sensitivity.

emergence of resistant isolates and to strengthen the efficacy of treatment itself.

The rationale of combination therapy in *A. baumannii* infections is to reduce the

Table.1 Source of Infection

	Source of infection	
	No	%
Surgical site	9	18.0
Blood	2	4.0
Respiratory tract infection	30	60.0
Mixed infection	9	18.0

Table.2 Cure Rate and Mortality

	Cure rate and mortality	
	No	%
Cure		
No	20	40.0
Yes	30	60.0
30 days Mortality		
No	40	80.0
Yes	10	20.0
Mortality related to infection	4	8.0

Table.3 Relation Between Cure and Site of Infection

Site of infection	Cure			
	No (n = 20)		Yes (n = 30)	
	No	%	No	%
Surgical site infection	1	11.1	8	88.9
Blood stream	2	100.0	0	0.0
Respiratory tract infection	13	43.3	17	56.7
Mixed infection	4	44.4	5	55.6

Unfortunately, there are no well designed clinical trials comparing treatment regimens for MDR *Acinetobacter* infections⁽⁹⁾. There is still much debate about the role of combination therapy versus monotherapy for gram negative infections. The results of earlier studies and meta-analyses are difficult to interpret, but more recent

evidence is starting to clarify this issue. For empirical treatment, combination therapy improves the likelihood that a drug with in vitro activity against the suspected organism is being administered (often defined as appropriate therapy). This effect is more pronounced in institutions with a greater prevalence of multidrug resistant organisms.

The antibiotics selected for the combination, however, need to be tailored to local susceptibility data. To our Knowledge, no available data about using the combination studied in the treatment of *Acinetobacter baumannii* (Doxycycline plus cotrimoxazole)⁽²¹⁾.

The cure rate in the current study is quite reasonable in the soft tissue surgical site infection which may be related to better penetration power and I think that this positive result deserves more validation by applying it to larger patients sample especially when there is evidence of colistin resistance. Although the cure rate was zero in blood stream infection but we should interpret this result cautiously as the number of treated patients was only two which make it impossible to reach any strong conclusion and still the use of the combination study can be tried when the colistin is not available. The results related to cure in the respiratory tract infection exceeding the 50% cure rate cannot be considered bad as the maximum cure rate with the use of colistin as a standard treatment is not far away from this number, I think also that using higher concentration of the two antibiotic used would allow higher penetration power to the lung tissue and definitely will be reflected in the form of higher cure rate but this is can be applied in patients when the risk of serious side effects on them is not very high.

The main limitation related to the relatively smaller number of patients and heterogeneity of infection sites in the current study makes the validation of the results difficult but still it provides a new window for exploring more probable combinations for better cure of *Acinetobacter baumannii* infections in critically ill patients.

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