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INTRAVENOUS MINOCYCLINE FOR TREATMENT OF MULTIDRUG-RESISTANT ACINETOBACTER BAUMANNII INFECTIONS

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ABSTRACT

A baumannii is intrinsically multidrug resistant. Only few antibiotics are active against this organism. Among Acinetobacter species, A. baumannii and other closely related species are commonly implicated in nosocomial infections. These organisms are usually multidrug resistant and therapeutic options to treat A. baumannii infections are very limited An intravenous formulation of minocycline has recently available for clinical use. Intravenous minocycline has high activity against Acinetobacter species .U.S. Food and Drug Administration (FDA) has also approved a supplemental new drug application for a new formulation of MINOCIN® (minocycline) for Injection and indicated for the treatment of infections due Acinetobacter species bacteria. Minocycline is an old drug that has the potential to become a important part of armamentarium against emerging infection such as CA-MRSA and A. Bumannii.

KEYWORD: Minocycline, Minocycline Combination therapy, intravenous, Acinetobacter baumannii.

INTRODUCTION

Acinetobacter has undergone significant taxonomic modification over the last 30 years. Its most important representative, Acinetobacter baumannii, has emerged as one of the most troublesome pathogens for health care institutions globally.

Treatment options of multidrug-resistant Acinetobacter baumannii infections are extremely limited. The need for new treatments for serious infections caused by MDR strains of A. baumannii has become critical, especially given the lack of new antibacterial development within the pharmaceutical industry. Minocycline intravenous is active against in many MDR strains of Acinetobacter. Minocycline a tetracycline derivative was introduce in the 1960s, the IV formulation of the drug was voluntarily withdrawn form the US market in the 2005 but reintroduced in May 2009.[8] Minocycline and doxycycline are both available by intravenous infusion and minocycline is approved by the FDA for use in Acinetobacter infections. There is an accumulating amount of literature reporting successful use of minocycline intravenous for treatment of serious MDR Acinetobacter infections, particularly for nosocomial pneumonia. These results, coupled with the generally favourable tolerability of minocycline intravenous, support its use as a viable therapeutic option for treatment of MDR Acinetobacter infections.[1]

Acinetobacter baumannii

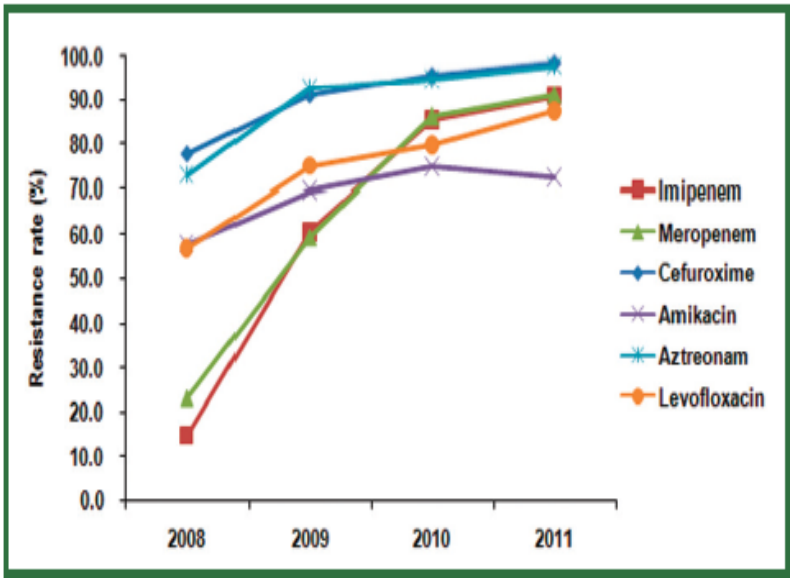
Family:	**Moraxellaceae**
Genus:	**Acinetobacter**
Species:	**A. baumannii**

Acinetobacter baumannii is a typically short, round, rod-shaped Gram-negative bacillus , affecting people with compromised immune systems, and is becoming increasingly important as a hospital-derived nosocomial infection.

Acinetobacter baumannii is a pleomorphic aerobic gram-negative bacillus commonly isolated from the hospital environment and hospitalized patients. A baumannii is a water organism and preferentially colonizes aquatic environments. This organism is often cultured from hospitalized patients' sputum or respiratory secretions, wounds, and urine.. A baumannii has

always been a multidrug-resistant organism inherently resistant to multiple antibiotics A baumannii is a multi-resistant sensitive to relatively few antibiotics. A investigation report of Hospital of Nanjing Medical University on changes in resistance of Acinetobacter baumanni (A. baumannii) to different antimicrobial agents and the association of resistance rates with several independent factors shows.[11]

Rapid increase of imipenem and meropenem resistance in A.buminnii . The secular trend of resistance to 4 other agent are shown for comparison.[11]



Trends in resistance (R%) of A. bauminnii to antibiotic , 2008 to 2011.[11]

Table 4. The resistance rate (R%) of *A. baumannii* to antibiotics stratified by patients' gender, 2008 to 2011.

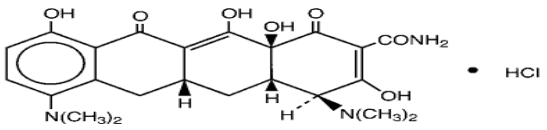
Antibiotics	Male (n=2,095)	Female (n=693)	P
Cefuroxime	94.5	92.7	0.188
Ceftazidime	89.1	86.7	0.093
Cefotaxime	97.5	95.8	0.053
Cefepime	85.1	81.8	0.119
Cefperazone/sulbactam	56.2	48.5	<0.001
Piperacillin/tazobactam	86.9	83.2	0.055
Amoxycillin/clavulanate	90.3	86.6	0.006
Imipenem	77.9	72.6	0.017
Meropenem	78.1	72.9	0.017
Amikacin	70.9	71.7	0.475
Aztreonam	89.2	84.4	0.001
Levofloxacin	80.5	78.4	0.109

Intravenous minocycline

- **General information**

Minocycline for injection, a sterile formulation of a semisynthetic derivative of tetracycline . Minocycline has a longer half-life, better oral absorption and ability to overcome most tetracycline resistance mechanism. Minocycline has a greater partition coefficient at neutral pH and therefore has enhances lipophilic properties. This increased lipophilicity enhances minocycline penetration into various tissues compared with other tetracycline.

Its structural formula is



$C_{23}H_{27}N_3O_7$•HCl M.W. 493.94

Each vial, dried by cryodesiccation, contains minocycline HCl equivalent to 100 mg minocycline. When reconstituted with 5 mL of Sterile Water for Injection USP the pH ranges from 2.0 to 2.8.

- **INDICATION**

Minocycline is indicated for the treatment of infections caused by the following Gram-negative bacteria if bacteriologic testing indicates appropriate susceptibility to the drug

Escherichia coli.

Enterobacter aerogenes.

Shigella species.

Acinetobacter species. [4]

- **PHARMACOLOGY AND PHARMACOKINETIC**

MOA; Inhibits protein synthesis and thus bacterial growth by binding to 30S and possibly 50S ribosomal subunits of susceptible bacteria.

ABSORPTION	DISTRIBUTION	METABOLISM	ELIMINATION
90-100%	Crosses placenta; enters breast milk Protein bound: 70-75%	Liver (partially)	Feces and urine

- **PREGNANCY CATEGORY**

Category D: Lactation: Enters breast milk, some manufacturers say do not nurse; however AAP considers nursing compatible due to calcium chelation of drug and prevention of its absorption; long-term safety of prolonged exposure unknown[7]

Minocycline Intravenous for Acinetobacter Pneumonia infection (Clinical Study Reports)

In a retrospective case series conducted, seven critically ill trauma patients with VAP caused by A. baumannii isolates that were resistant to all antibiotics tested except for doxycycline or minocycline. Patients were treated with IV doxycycline or minocycline for an average of 13.5 (range 9-20) days. Doxycycline or minocycline was successful in six of seven patients.[2] Study of the in vitro and in vivo antibacterial activities of tigecycline , Minocycline, Polymyxin B and other 11 common antimicrobial agents, alone or in combination, against multi-drug resistant Acinetobacter baumannii showed high sensitivity to tigecycline (98% inhibition), polymyxin B (78.2% inhibition), and minocycline (74.2% inhibition). However, the use of these antimicrobial agents in combination with other antimicrobial agents produced synergistic or additive effects. The combination of minocycline with either rifampicin or amikacin is more effective against multi-drug resistant A. baumannii than single-agent tigecycline or polymyxin B. [5]

Antibiotics	RIF	TZP	C	FOS	E	MNO	AMK	IMP/CS	PB
PB	+	+	+	+	+	−	−	−	−
TIG	+	−	+	+	+	+	+	−	−
MNO	+	−	+	+	+	−	+	−	+
FOS	−	−	+	−	+	−	+	+	−
C	−	−	−	−	−	−	−	+	−

PB, Polymyxin B; TIG, Tigecycline; MNO, Minocycline; FOS, Fosfomycin sodium; C, Chloramphenicol; RIF, Rifampicin; TZP, Piperacillin/tazobactam sodium; E, Erythromycin; IMP/CS, Imipenem/cilastatin sodium; AMK, Amikacin; "+" represents the combination of two drugs; "–" represents the non-combination of two drugs.

In another retrospective analysis, Consecutive isolates from 67 patients with MDR-A. baumannii were tested to determine susceptibilities to tetracycline, minocycline, tigecycline, ampicillin/sulbactam, imipenem/cilastatin, and colistin. Patients receiving minocycline from September 1, 2010, to March 31, 2011 were analyzed for demographics, penicillin allergy, clinical and microbiologic response, length of stay (LOS), infection-related LOS, and mortality. Minocycline was susceptible to 32 (48%) of 67 A. baumannii isolates. Of the imipenem/cilastatin- and ampicillin/sulbactam-resistant isolates, minocycline was susceptible to 18 (38%) of 47. Five patients received minocycline in combination with

ampicillin/sulbactam or colistin for pneumonia (n = 3), bacteremia (n = 1), and skin and soft tissue infection (n = 1). The median treatment duration, LOS, and the infection-related LOS were 10, 34, and 21 days, respectively. All patients had microbiologic cure, and 4 had clinical response. Minocycline showed clinical utility for MDR-A. baumannii infections. Antimicrobial Stewardship Programs should consider minocycline for MDR-A. baumannii infections and monitor patient outcomes. [3]

The emergence of extensively drug-resistant Acinetobacter baumannii (XDRAB) is a serious threat to hospitalized patients. In a invitro study Fourteen XDR-AB clinical isolates were collected.. Susceptibility testing was carried out according to the standards of the Clinical and Laboratory Standards Institute. Activities of drug and drug combinations were investigated against four selected strains and analysed by mean survival time over 12 hours in a time-kill study. The time-kill studies indicated that the minimum inhibitory concentration (MIC) of colistin (0.5 or 0.25 μg/mL) completely killed all strains at 2 to 4 hours, but 0.5×MIC colistin showed no bactericidal activity. Meropenem (8 μg/mL), minocycline (1 μg/mL) or rifampicin (0.06 μg/mL) did not show bactericidal activity. However, combinations of colistin at 0.5×MIC (0.25 or 0.125 μg/mL) with each of the above were synergistic and shown bactericidal activities against all test isolates. A combination of meropenem (16 μg/mL) with minocycline (0.5×MIC, 4 or 2 μg/mL) was synergetic to all test isolates, but neither showed bactericidal activity alone. The $MST_{12\ h}$ values of drug combinations (either colistin- or minocycline-based combinations) were significantly shorter than those of the single drugs. This study indicates that combinations of colistin/meropenem, colistin/rifampicin, colistin/minocycline and minocycline/meropenem are synergistic in vitro against XDR-AB strains.[10]

How effective is minocycline for MDR Acinetobacter baumannii

Several studies have suggested that >90% of recent A. baumannii isolates have susceptibility to minocycline . Due to the apparent in vitro activity and favorable pharmacokinetic profile, anecdotal reports have supported intravenous combinations using minocycline in serious MDR Acinetobacter infections. However, comparative studies with a larger number of patients are required to confirm its efficacy.

CONCLUSION

As we know bacteria are the champions of evolution and Acinetobacter baumanni is readily multidrug resistant, we should treat it cautiously. Minocycline is an old, safe, second-line

antimicrobial agent that has drawn attention over the last few years as a possible therapeutic option against multidrug-resistant Acinetobacter baumannii (MDR-AB) Minocycline and Its's combination is an option we got as a drug of tetracycline group to treat the new culprit so we must protect it from resistance by use it rationally.

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