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Strategies of Treatment for Extensively Drug-Resistant *Acinetobacter baumannii* Infections: Single Centre Experience

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Abstract

Objective: To describe treatment strategies employed in hospitalized patients at the "General Hospital Dr. Manuel Gea González" with infection by Extensively Drug-Resistant (XDR) *Acinetobacter baumannii*.

Methodology: A retrospective analysis was carried out from January 1st 2012 to December 31st, 2014. Clinical data were collected, as well as group and doses of antimicrobial agents administered.

Results: 39 patients were enrolled, the main infectious diagnosis was hospital acquired pneumonia (HAP) in 64%, followed by skin and soft-tissue infections (SSTI) in 23%. Thirty patients (77%) received tigecycline, while 83% of these received high doses. Thirty three percent of patients receiving meropenem had high dose. Twenty-nine patients (74.3%) received colistin and, from these, 61.5% was given a loading dose. Concerning the combined therapy, the following distribution was observed: 19 patients (48.7%) had triple therapy: meropenem, colistin and tigecycline (MCT), and 20 patients (51.3%) had double therapy including combinations of meropenem-colistin (MC), meropenem-tigecycline (MT) and tigecycline-colistin (TC). The sole adverse effect with the use of tigecycline was nausea in 20%. Twenty five percent of patients receiving colistin required dose adjustment after 5 days due to acute kidney injury (AKI). Outcomes: overall mortality was 33.3%, the mean of hospital stay at the intensive care unit (ICU) was 12.8 days (SD ± 16.2), while the total days of stay were 41 (SD ± 25.9). The lowest mortality (25.3%) was observed in the group receiving triple therapy (MCT), although this was no statistically significant.

Conclusions: Triple combination therapy showed a trend to decreased mortality. The use of tigecycline at high doses and colistin at loading dose did not determine unfavorable clinical outcomes. It is necessary to perform randomized studies comparing different therapeutic strategies.

Keywords: XDR-*Acinetobacter baumannii*; Combined therapy; Colistin multidrug resistant infections

Introduction

Acinetobacter baumannii is a microorganism of great clinical relevance, is considered one of the most frequent nosocomial pathogens in recent years. Although is considered a low virulent microorganism, the treatment has been a challenge due to the high resistance rates that exhibits towards the available antimicrobial agents [1,2]. It can be isolated from the skin, oral cavity, and gastrointestinal tract in healthy hosts.

The presences of this microorganism have been documented in medical equipment within hospitals, such as humidifiers, ventilators, mattresses and other surfaces. There are at least 21 strains, in the clinical practice, the genospecies 1 (*A. colcoaceticus*), 2 (*A. baumannii*), and 13 (*A. baumannii-colcoaceticus*) represent about 80% of the pathogens resulting in nosocomial infections [1,3].

Infection foci that have been reported are the lung, urinary tract, blood, central nervous system, and peritoneum. The rate of bacteremia reported at the ICU (intensive care unit) is 1.6% and it is usually documented following long-term stays, with a mean value of 26 days [2]. The overall mortality rate in patients with bacteremia by XDR *A. baumannii* at the ICU has been reported of 43%.

The mortality attributable to the infection is variable and difficult to determine because patients usually have other comorbidities; a critical condition, long-term hospital stay and multiple organ system failure; these may influence poor outcomes [4,5].

The objective of the treatment is to achieve clinical cure with a subsequent decrease in mortality. Early start of appropriate antimicrobial therapy have been demonstrated a significant reduction in mortality [6].

Optimal antimicrobial treatment is a challenge due to the high resistance of the microorganism and the difficulty to determine the *in vitro* susceptibility for some antimicrobials such as colistin and tigecycline [2].

Tigecycline is a broad-spectrum antimicrobial agent with *in vitro* activity against Gram-positive, gram-negative and multidrug-resistant (MDR) pathogens. Only *Pseudomonas aeruginosa* and species of the genus *Protea* exhibit *in vitro* resistance. Said it is approved to treat complicated intra-abdominal infections and skin and soft tissue

infections (SSTI). Up to 78% of circulating strains of XDR *A. baumannii* have *in vitro* susceptibility to tigecycline [2-7] .

It has been postulated that tigecycline cannot reach it pharmacodynamics objective using standard doses in clinical samples with a minimal inhibitory concentration (MIC) between 1-2 mcg/mL [8]. Two systematic reviews reported that high dose (HD) of tigecycline had significantly less ICU mortality and better clinical outcomes than standard doses [9,10]. Other studies reported higher rates of clinical resolution and microbiological eradication using HD of tigecycline strategy in patients with ventilator associated pneumonia (VAP) [11,12]. Other studies could not demonstrate clinical efficacy with the use of tigecycline,in fact, they showed lower microbiological eradication and high mortality rates (up to 41%) [13,14].

Colistin is another option of treatment for *A. baumannii* infections. Colistin (*polymyxin E*) has been available since 1960 and was replaced in 1970 due to its nephrotoxicity and neurotoxicity. There are several clinical studies about colistin effectiveness to treat complicated infections by XDR microorganisms (*A. baumannii, P. aeruginosa, K. pneumoniae*). Strategies to improve the bioavailability of colistin are related to a loading dose (LD) and the administration of prolonged infusions [15,16].

Drugs that have typically shown susceptibility to XDR *A. baumannii* are colistin, rifampicin, and tetracyclines. In the presence of MDR *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* colistin have shown synergic effect in combination with other antimicrobials such as carbapenems, rifampicin, tigecycline, amynoglycosides, fosfomycin and levofloxacin [2,3].

The highest synergy rate reported recently is 67.4% (95% CI, 27.3-91.9) for tigecycline in combination with colistin [17]. In Turkey, Timurkaynak et al. [18] analyzed 25 strains of MDR *A. baumannii* and tested 5 of them for synergy with combinations of antibiotics. The combination of colistin with rifampicin showed synergy in 100% of strains.

In 2016 Gram negative bacteria resistant to colisitin have emerged as an important public health issue. Although for resistant *enterobacteria* new antimicrobial are available, *Acinetobacter* have no different options. A promising strategy for treating XDR *A. baumannii* infections is the triple antimicrobial combination [19].

Objective

To describe treatment strategies for patients hospitalized at the General Hospital Dr. Manuel Gea González in Mexico City, Mexico, with infection by XDR *A. baumannii*, including: High-doses (HD) of tigecycline, loading-dose (LD) of colistin, and combined therapy.

Methodology

A retrospective analysis was carried out in patients hospitalized with infections by XDR *A. baumannii* from January 1st 2012 to December 31st, 2014. Clinical data were collected, as well as group of antibiotics, doses and time of administration. XDR was defined as resistance to all the groups of active antibiotics with exception of 2 or less categories. Acute kidney Injury (AKI) was defined as an increase of creatinine twice its baseline value 72 hours after the beginning of the antimicrobial.

To determine severity of disease we used Quick Secuential Organ Failure Assessment (q-SOFA) score. It uses three criteria, assigning one point for high respiratory rate (≥ 22 breaths/min), low systolic blood pressure (≤ 100 mmHg), and altered mental status. This score predicts mortality for patients with suspected sepsis [20-27].

Doses of antibiotics were defined as follows: standard dose (SD) tigecycline: LD of 100 mg followed by 50 mg bid (twice a day); HD tigecycline: LD of 200 mg followed by 100 mg bid; HD meropenem: 2 gms for every 8 hours and LD colistin: 5 mg per kilogram with a maximum dose of 300 mg. Subsequent doses of colistin were 150 mg twice a day.

Combined therapy was classified as triple therapy if the patient received together meropenem, colistin and tigecycline (MCT) and double therapy if the patient received any of the following combinations: meropenem-colisitn (MC), meropenem-tigecycline (MT) or colistin-tigecyclinie (CT). Clinical parameters were collected at the beginning of antimicrobials and after 72 hours.

Strains were analyzed in the automatic equipment Microscan® (Beckman Coulter) during the year of 2013. In 2014 the automatic system VITEK 2® (bioMérieux) was introduced and included susceptibility tests to colistin and tigecycline.

Infectious syndromes Hospital acquired pneumonia (HAP), SSTI, abdominal sepsis, osteomyelitis, otitis media, urosepsis, and peritonitis) were defined according to the 2005 CDC (Centers for Disease Control and Prevention) criteria for disease definition [20].

Results

Thirty nine patients were enrolled in the study, 70% were male with a mean of age of 49.4 years old (SD ± 17.5). The major comorbidities were diabetes mellitus (43.5%), hemiplegia (25.6%), chronic kidney disease (25.6%) and obesity (12.8%) (Table 1).

Variable	Mean ± SD/ Total (%)
Men	27 (70)
Age	49.4 (DE ± 17.5)
Diabetes mellitus	17 (43.5)
CKD	10 (25.6)
Hemiplegia	10 (25.6)
Morbid obesity	5 (12.8)
Steroids use	4 (10.2)
Immunosupresant drugs*	3 (7.6)

*Methotrexate (predominantly)

CKD: Chronic kidney disease; CHF: Chronic heart failure; COPD: Chronic obstructive pulmonary disease; HIV: Human Immunodeficiency Virus; SD: standard deviation

Table 1: Baseline characteristics of the studied patients.

The most common hospital admitting diagnoses were SSTI (30.7%), multiple contusions (15.3%) and urosepsis (10.2%) (Table 2).

The most common isolation site of *A. baumannii* were bronchial sample, related to HAP in 64%, followed by skin swab, related to SSTI in 23% (Table 3).

Variable	Mean ± SD/ Total (%)
SSTI	12 (30.7)
Stroke	4 (10.2)
Urosepsis	4 (10.2)
Multiple contusions	6 (15)
CAP	3 (7.6)
Abdominal surgery	2 (5.1)
Abdominal sepsis	1 (2.5)
Osteomyelitis	1 (2.5)
CSOM	1 (2.5)
Tuberculosis	1 (2.5)
Mucormycosis	1 (2.5)
Influenza	1 (2.5)
SBP	1 (2.5)
Empiema	1 (2.5)
SSTI: Skin and soft tissue infections; CAP: Community acquired pneumonia; CSOM: Chronic suppurative otitis media; SBP: Spontaneous bacterial peritonitis. SD: Standard deviation	

Table 2: Diagnosis at hospital admission.

Variable	Mean ± SD/ Total (%)
HAP	25 (64)
SSTI	9 (23)
Abdominal sepsis	2 (5.1)
Osteomyelitis	1 (2.5)
CSOM	1 (2.5)
UTI	1 (2.5)
HAP: Hospital acquired pneumonia; SSTI: Skin and soft tissue infections; CSOM: Chronic suppurative otitis media; UTI: Urinary tract infections. SD: Standard deviation	

Table 3: Infectious diagnosis with isolation of XDR A. baumannii. For HAP the samples collected were bronchial aspiration; for skin and soft tissue infections predominantly were swabs; in abdominal sepsis were peritoneal fluid or drainage from intra-abdominal collections; for osteomyelitis bone sample were collected.

The various therapeutic strategies are shown in (Table 4) Figure 1.

HD tigeciclyne: loading dose of 200 mg, followed by 100 mg twice a day; SD tigecycline: loading dose of 100 mg, followed by 50 mg twice a day. HD meropenem 2 gms three times per day. LD colistin: 5 mg/kilo with a maximum dose of 300 mg. Triple therapy is a combination of colistine, tigeciclyne, meropenem.

Variable	Mean ± SD*/ Total (%)
Total patients with tigecycline	30 (77)
HD tigecycline	25 (83)
SD tigecycline	5 (17)
Total patients with meropenem	35 (90)
HD meropenem	12 (34)
Total patients with colistin	29 (74)
LD colistin	24 (82)
Triple therapy	18 (46)
Double therapy MC	9 (23)
Double therapy MT	8 (21)
Double therapy CT	4 (10)
HD: high doses; SD: standard doses; LD: loading doses; MC: meropenem-colistin; MT: meropenem-tigecycline; CT: colistin-tigecycline *SD standard deviation	

Table 4: Treatment strategies applied to the patients including double and triple therapy, high doses and loading doses.

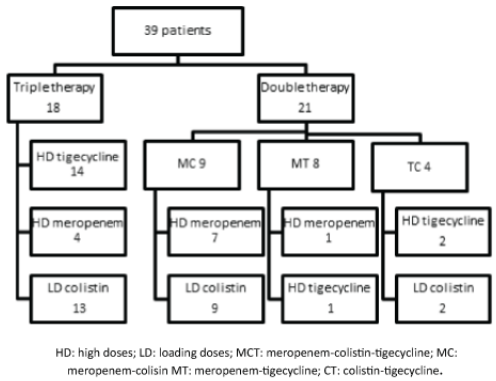

Figure 1: Distribution of treatment strategies including double and triple therapy, meropenem and tigecycline in high doses and colistin in loading doses.

The sole adverse effect reported with the use of tigecycline was nausea in 6 patients (20%), however any patient required suspension of the medication, only antiemetic therapy was required. Eight patients (25%) receiving colistin required dose titration after 5 days due to the presence of AKI, of these 4 normalized renal function and 4 died. The overall mortality was 33.3% (13 patients), the mean value for the days of stay in the ICU was 12.8 days (SD ± 16.2), and the total days of hospitalization were 41 (SD ± 25.9). 77% of patients had a q-SOFA scale equal or over 2 points. Mortality with the triple therapy was of 25.3%, mortality with double therapy was as follows: MC 40%, MT 37.5%, and TC 25%. Mortality in patients receiving tigecycline at high doses was 33.3% (Table 5).

Variable	Mean ± SD/Total (%)
Death	13 (33.3)

Death with MCT	5 (27.7)
Death with MC	4 (44.4)
Death with MT	3 (37.5)
Death with CT	1 (25)
Stay longer than 30 days with MCT	14 (77)
Stay longer than 30 days with MC	5 (55)
Stay longer than 30 days with MT	2 (25)
Stay longer than 30 days with CT	1 (25)

Table 5: Clinical outcomes including death, invasive mechanical ventilation, admission to ICU and stay longer than 30 days.

Outcomes after 72 hours of admission reveals absence of fever in 66% of patients; absence of leukocytosis and withdrawal of vasopressors in 59% and 56.5% of patients respectively (Table 6).

Figure 2 compares these outcomes between the triple and double therapy, any statistically significant difference was found. 77% of patients had a q-SOFA scale equal or over 2 points.

Variable	Mean ± SD/ Total (%)
Abscense of fever	26 (66.6)
Abscense of leukocytosis	23 (59)
Thrombocytosis	3 (7.6)
Thrombocytopenia	7 (17.9)
Vasopressors withdrawal	22 (56.5)
Acute kidney injury	18 (46)

Table 6: Clinical outcomes 72 hours after admission.

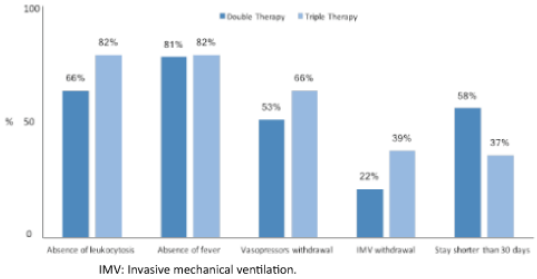

Figure 2: Comparative of clinical outcomes after 72 hours of admission double versus triple therapy.

When we compared the mortality rates between the different treatment strategy groups, we found that CT and MCT combinations had the lowest rates (25% and 28% respectively) compared with MC and MT combination groups (Figure 3). Mortality with triple therapy (MCT) was 25% compared with overall and dual therapy (40%) with no statistical significance (p=0.70) (Figure 4). HAP caused 69% of deaths, followed by abdominal infections 15%, SSTI and urosepsis 8% each one respectively (Figure 5).

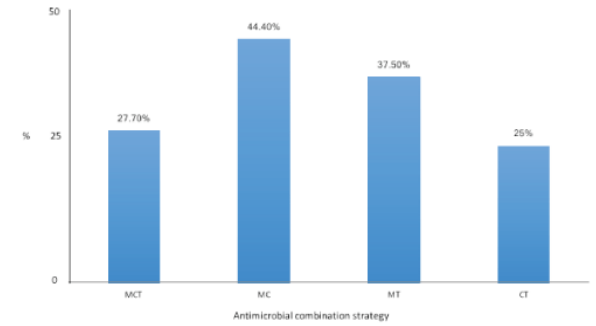

Figure 3: Mortality with the different therapeutic strategies.

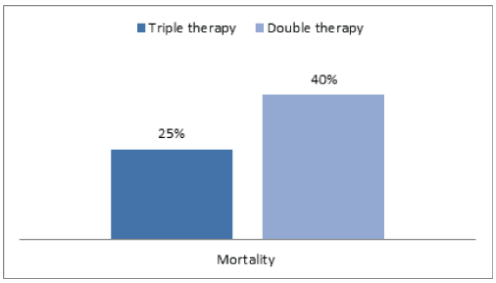

Figure 4: Mortality comparing triple vs double therapy.

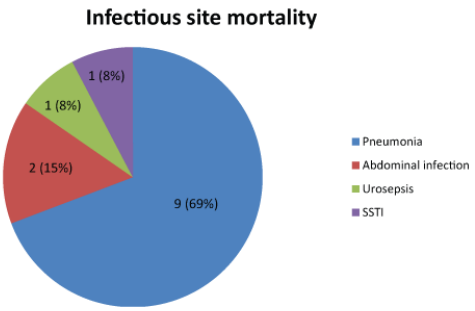

Figure 5: Mortality per infectious site. SSTI: Skin and soft tissue infections.

Comparing the stay at the ICU, HAP was 79% vs. 11% of patients with SSTI. Concerning the q-SOFA scale, 96% of patients with pneumonia and 33% of patients with SSTI had a score equal or over 2. Regarding antimicrobial agents administered to the HAP group, 50% received the triple therapy, 25% received MC, and 21% received MT. The combination of antimicrobial agents used in the group of SSTI was mainly MT in 44%, followed by MC in 33% and 22% had triple therapy.

Discussion

Several *in vitro* studies have shown a clear advantage of using combined therapy to treat XDR *A. baumannii*. The microbiological

explanation for this strategy is that the use of colistin increase permeability of the outer membrane, allowing penetration and increasing activity of the drug with which it is combined. Several combinations have been tested and the results of most of them show synergy and even the ability to prevent drug-resistant strains. In a systematic review and meta-analysis, Ni Wentao et al. analyzed 70 published studies and 31 conference proceedings for *in vitro* studies with strategies of combined therapy with polymyxins and 28 different antimicrobial agents used against *A. baumannii*. In addition to synergy, it was also observed that the combination with carbapenems or rifampicin was efficient to prevent the development of resistance to colistin, as well as a synergy of more than 50% for colistin-resistant strains [21].

In our study general mortality was lower than that reported in the literature. Due to the multiple comorbidities, severity of the disease and stay at ICU, it was difficult to determine the infection associated mortality per se. There was mild improvement shown in mortality for the triple therapy, although this result was not statistically significant. The mortality and clinical outcomes changed with the infectious site, HAP patients had a higher mortality and higher scores in the q-SOFA scale compared with SSTI patients.

It is difficult to determine the specific cause that resulted in lower mortality in our study because there was no access to certain relevant data on the medical records to assess in a more objective way the baseline clinical condition of patients, such as APACHE II and q-SOFA. Due to the sample size, no statistically significant differences were seen for the different therapeutic strategies. However, a trend towards decreased mortality was observed in the triple therapy group compared to the other strategies.

When assessing the adverse effects associated to the administration of HD of tigecycline and LD of colistin, no serious alterations were observed that required discontinuing antimicrobial agents. Since a high percentage of the patients included in the study were under sedation with invasive mechanical ventilation, the presence of nausea with high doses of tigecycline was not a frequently reported adverse effect. AKI associated with the use of colistin did not exceed that reported in the literature with the use of this antimicrobial agent.

Our study did not shown increased mortality in the tigecycline group, which may be explained by the use of higher doses and by the combination with other antimicrobials. In the last five years at our center, we justified the use of combined therapy because susceptibility to colistin and tigeciclyne was unknown in the routine laboratory, and because the use of VITEK system for identifying *A. baumannii* resistance have error rate of 7.2% [22].

Despite *in vitro* studies of synergy combining two or more antimicrobials have shown promising results clinical trials have not been able to demonstrate improvement in clinical outcomes. There are two randomized clinical trials and one observational study that evaluated combinations of colistin with rifampicin or fosfomycin and all failed to prove difference in mortality [23]. However since 2017 CLSI (Clinical & Laboratory Standards Institute) guidelines emphasize that colistin should generally be given at maximum recommended doses and used in combination with other agents [24].

In 2006, hetero-resistance was reported for the first time in *A. baumannii*, which is defined as the occurrence of resistance to colistin of a subpopulation from a susceptible strain (MIC<2 mcg/l). Available reports provide rates ranging from 18% to 100% of hetero-resistance in strains [25]. Rodríguez et al. [26] showed that *in vitro* combinations of colistin with rifampicin have synergistic activity in hetero-resistant strains and prevents the development of resistant mutants to colistin.

Reasons that support the use of combined therapy at this moment are: microbiological synergy, and lack of an accurate test for detecting colistin resistance. With the results obtained at our Centre, the availability of automatized systems for susceptibility tests and knowledge about pharmacokinetics it is possible to propose an algorithm of treatment for rationalize and optimize the use of antimicrobials in agreement with the infectious site and MIC of the microorganism (Figure 6). This strategy let us adjust the treatment to the clinical and microbiological condition of each patient. Our strategies are directed to improve survival of patients, better clinical outcomes and prevention of the emergence of resistant *A. baumannii* strains.

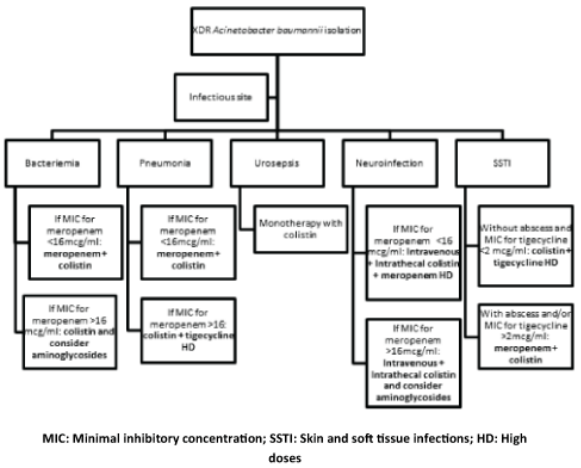

Figure 6: Proposed algorithm for treatment of infections caused by XDR *A. baumannii* taking on account site of infection and MIC of antimicrobials.

Conclusion

XDR *A. baumannii* is a threatened microorganism that implies outbreaks at ICU and high rates of mortality in hospitalized patients. The combinations of antimicrobials are the cornerstone of treatment of *A. baumannii*.

We conclude that LD colistin, HD tigecycline and HD meropenem used in combined therapy when we don´t know susceptibility was safe and the mortality was similar or lowest to the reported in the literature. In the case of colistin and tigecyline we recommend its use with double therapy taking into account the minimum inhibitory concentration and the site of infection. In the emergence of XDR microorganism is important to consider the availability of old antimicrobials that could contribute to the treatment of this infections besides the new betalactamics combined with betalactamse inhibitors drugs.

In case of presence of XDR microorganisms it is important not only focus on therapeutic protocols but also in taking preemptive actions for avoid it´s dissemination. In the real world the management of resistant strains is becoming a frequent hospital issue, to ignore the susceptibility of the drugs that are being used confer a future risk of therapeutic failures or resistance. More studies must be done for a

better understanding of *in vivo* combination of antimicrobials for the treatment of infections related to *A. baumannii*.

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