Review article

Antibiotic resistance, genotype and clinical significance of *Acinetobacter Baumannii* in Saudi Arabia

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Abstract:

Background: In Saudi Arabia, due to its dynamic population and annual hajj pilgrimage, there is influx and efflux of millions of visitors every year, especially to Makkah dan Madinah, providing an international hub for the exchange of microbes. It is rather a common interest to understand the molecular epidemiology and clinical significance of multidrug resistant organisms in this country. Acine*tobacter baumannii* in particular, is one of the most common Gram negative bacteria isolated in the Kingdom. This organism is responsible for ventilator associated pneumonia, blood stream infections, urinary tract infections and skin infections. ***Objective*:** In this manuscript we aim to review the literature available on the antimicrobial resistance, genotypes and clinical significance of*A. baumannii* acquisitions in Saudi Arabia. ***Methodology:*** The literature was reviewed systematically using PubMed with a combination of the terms '*Acinetobacter*' AND 'Saudi Arabia'. Reference lists of relevant articles were searched to identify further material. We only included studies with plausible data. ***Main observations*:** In Makkah itself, there are significant increase in carbapenem resistant *Acinetobacter* from 14% in 2004-2005, 46% in 2005-2006, 63% in 2011 to 90% in 2015. Recent publication from Madinah indicated, beside resistant to carbapenem approaching 90%, an alarming resistant rate to the last resort antibiotic, polymyxin is also observed at 24% of 379 tested strains. In a study in Makkah, the most predominant sequence types being ST 195 and ST557, which in the worldwide clonal complex 2. ***Conclusion:*** These resistant rate and sequences type indicated intermingling of the resistant superbugs occurred. With limited treatment option, effective infective control measures and antibiotic stewardship programs are the key element to contain these resistant isolates from spread.

Keywords: Antimicrobial resistance; genotypes; clinical significance; *Acinetobacter baumannii*; Saudi Arabia.

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Introduction:

Acinetobacter baumannii is a Gram negative coccobacilli that is responsible for many nosocomial infections, primarily in immunocompromised patients. This organism is intrinsically tolerant to dry surfaces, which contributes to its persistence in hospital environments and transmission.[1] Moreover, it is inherently resistant to several antibiotics and has capability to acquire resistance to other antibiotics via various mechanisms, leaving the clinician with relatively few treatment options.[2]Among common infections caused by this organism are ventilator associated pneumonia (VAP), catheter associated blood stream infections, surgical site infections and

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urinary tract infections.[2]

The incidence of carbapemen-resistant *A. baumannii* (CRAB) has been on the rise around the world and in the Gulf region. Treatment options are becoming limited with the only reliable possibilities seem to be polymyxins in combination with other agents, with a few new agents in the development pipelines.[3] The studies in Saudi Arabia and the Middle East region on the molecular characterization and antibiotic profile of *A. baumannii* are scarce.[4,5] In this manuscript we aim to review the literature available on the antimicrobial resistance, genotypes and clinical significance of *A. baumannii* acquisitions in Saudi Arabia. The literature was reviewed systematically using PubMed with a combination of the terms '*Acinetobacter*' AND 'Saudi Arabia'. Reference lists of relevant articles were searched to identify further material. We only included studies with plausible data. In this review, MDR is defined as organisms that *in vitro* show non-susceptible to >1 agent in ≥ 3 antimicrobials, extreme dug resistant, (XDR) as organisms non-susceptible to ≥ 1 in all but ≤ 2 categories of antibiotics and pandrug resistance (PDR) is defined as bacteria that are resistant to all current clinically available antibiotics.[6]

Prevalence of *Acinetobacter* in Saudi Arabia

The Kingdom of Saudi Arabia is divided into 13 administrative regions (Figure 1). It is located in Western Asia with land area of approximately 2,150,000 km^2, it is the largest country in the Middle East. The area of Saudi Arabia formally consisted of mainly four distinct regions: Hejaz, Najd and parts of Eastern Arabia (Al-Ahsa) and Southern Arabia (Asir) with population more than 34 million in 2019, mainly located in the big cities.[7,8] In addition to that, two cities i.e. Makkah and Madinah hosts annual mass religious gatherings of up to 3 million Muslims from all over the world namely "Hajj pilgrimage" where the transmission of infectious diseases is high. This makes Saudi Arabia a potential center for the exchange of MDR strains from around the world.[3-8]

Figure 1: The administrative regions in the Kingdoms of Saudi Arabia. The city in the map where reports on *Acinetobacter* are available.

It is difficult to estimate the true prevalence of *Acinetobacter* infections and its resistant rate in Saudi Arabia in the limited of large multicentre studies.[9] One big nationwide study involve 24 hospitals by Ziad *et al*., 2012 indicated *A. baumannii* contributed 25.3% of non-fermenting Gram-negative bacteria in Saudi Arabia. Only 5.4% resistant to imipenem in this 2009 study.[10] Another multicenter study at national level took place for six months between January and June 2012 which indicated *A. baumannii* contributed 32.7% to the isolated Gram negative bacilli.[11] However the number of isolates were only 242. There are a few other reports from different hospitals in Saudi that are summarized in Table 1. There is no specific pattern of prevalence observed from 1998-2018 studies (Table 1).

Table 1: Prevalence of *Acinetobacter* reported from Saudi Arabia

Year of study	Place of study (no of isolates)	Location of study	Prevalence	Proportion of resistance	Reference
1998-2004	Dhahran(476)	Whole hospital	Approximately 5% of total isolates	35.8% of *Acinetobacte*r were MDR	[12]
2001	Jeddah (499)	Whole hospital	34% of GNB	NA	[13]
2004-2005	Makkah (1626)	Whole hospital	7.4% of total isolates	14% resistant to imipenem	[14]
2005-2006	Makkah (1137)	Whole hospital	10.8% of GNB	45.9% resistant to imipenem and 28% resistant to meropenem	[15]
2009	Riyadh (1210)	Intensive care unit	19.4% of total isolates	97.0%of *Acinetobacter* were MDR	[16]
2009	Nationwide (8908)	Whole hospital	25.3% of non-fermenting GNB	5.4% resistant to imipenem	[10]
2010	Taif (170)	Whole hospital	12% of respiratory isolates	NA	[17]
2010-2012	Hofuf (758)	Intensive care unit	31.9% of total isolates	91.7% of *Acinetobacter* were MDR	[18]
2013	Riyadh (1307)	Whole hospital	NA*	Tigecycline resistance rates 9.7% and colistin 1.8%	[19]
2010-2013	Jeddah (1176)	King Abdul Aziz university hospital	4.2% (2010) to 12.3% (2013)	NA	[20]
2011	Makkah and Jeddah (72)	Whole hospital	NA	62.5% resistant to imipenem	[21]
2012	Nationwide (242)	Whole hospital	32.7% of GNB	100% resistant to carbapenem	[11]
2012-2014	Makkah (107)	Intensive care unit	NA*	94% of *Acinetobacter* were MDR	[22]
2013	Riyadh (457)	Intensive care unit	26.5% of total isolates	NA	[23]
2013	Najran (125)	Whole hospital	54.5% of GNB	7.4% of *Acinetobacter* resistant to imipenem. 0% resistant to colistin	[24]
2014	Dammam (565)	Intensive care unit (Rectal swab screening)	8.3% of the samples	74.5% of *Acinetobacter* sp. were carbapenem resistance	[25]
2014-2015	Asir (94)	Whole hospital	NA*	69% of *A. baumannii* were MDR. 36.2% were PDR (susceptible only to colistin)	[26]
2015	Makkah (374)	Whole hospital (during Hajj)	7% of the total isolates	90% were resistant to imipenem and 64% resistant to meropenem	[27]

Year of study	Place of study (no of isolates)	Location of study	Prevalence	Proportion of resistance	Reference
2015	Al Ahsa (4532)	Whole hospital	20% of total isolates	20% resistant to imipenem and 44% resistant to meropenem	[28]
2016	Asir (105)	Intensive care unit	NA*	98.1% were MDR but all were susceptible to colistin	[29]
2016	Riyadh (56)	Oncology unit	18% of GNB	81.8% were resistant to meropenem and 73.7% resistant to imipenem	[30]
2016	Madinah (6840)	Whole hospital	5.5% of total isolates	89.2% resistant to imipenem	[31]
2016-2018	Bisha Province (290)	Intensive care unit	27.2% of GNB	97.5% were MDR and 4.0% were resistant to colistin	[32]

GNB – Gram negative bacilli, NA – Not available

* The prevalence of *Acinetobacter* infections were not available because these studies solely on *Acinetobacter* spp.

Mechanism of resistance

A. baumannii is intrinsically resistant to several antibiotics. These include penicillins, cephalosporins, nitrocefin and chloramphenicol.[33] In addition it also easily acquires resistant to the few others that exhibit inherent activity. For example, resistant to cephalosporins is often associated with the up-regulation of a chromosomal ampC gene by insertion sequences, predominantly ISAbaI.[34] While β-lactam resistance appears to be frequent, the underlying mechanisms are little studied in Saudi Arabia.[35] The mechanism of β-lactams resistance can be attributed to [36,37,38]

(a) Up-regulation of the chromosomally- mediated blaOXA-51-like beta-lactamase gene.

(b) Acquisition of further OXA-carbapenemases.

(c) Acquisition of class B metallo-carbapenemase.

(d) Other mechanisms such as class A ESBLs of the TEM, CTX-M, VEB, PER, and GES families,

(e) Changes to penicillin-binding proteins, alterations in porin proteins, and up-regulation of efflux pumps.

(f) A second mechanism for carbapenem resistance is the efflux pump that generally has three components and is present in the cytoplasmic membrane. The efflux pump in *A. baumannii*is responsible for aminoglycoside, quinolones, tetracyclines, chloramphenicol, erythromycin, trimethoprim resistance.

Antibiotic resistance among *Acinetobacter* in Saudi Arabia

The rise in antimicrobial resistance in Saudi Arabia has been highlighted recently.[39] Several factors that attributed to emergence and spread of MDR bacterial in Saudi have been identified. These include unoptimized use of antibiotics, improper use of antibiotics, possible use of antibiotics as a growth promoter in poultry sector and intermingling of microorganism during pilgrimages. The prescription of carbapenem is almost ten times higher in Riyadh compare to the prescription in the US. More than 98% and 77% of the pharmacists in the Eastern province and Riyadh respectively ready to dispense antibiotic without prescription.[40] The compliance to hand hygiene practice is known to prevent the spread of MDR nosocomial outbreak.[40] The introduction of antibiotic stewardship program over a period of two years from 2012 to 2014 were able to reduce all monitored MDR infections from 2012 to 2015. These programs also could reduce the dispensation and prescription of restricted antibiotics by 67% and 75% respectively.[41]

The earlier reports from Riyadh indicated a bold increase in the prevalence of resistant of *A. baumannii* in a whole hospital study.[42] Resistance to meropenem for example, increased from 12% in 2005, 35% in 2006, 47% in 2008 to 55% in 2009.[42] The studies in intensive care settings indicated the resistant rate were high from the first available report in 2009.

Except one rectal screening study in Dammam in 2014,[25] the studies in intensive care units indicated the MDR *Acinetobacter* are always more than 90% (Table 1).

A few whole hospital studies in Makkah indicate the increasing trend of carbapenem resistant from 14% in 2004-2005,[14] 46% in 2005-2006,[15] 63% in 2011[21] to 90% in 2015[27] (Figure 2). The proportion of resistant to carbapenem of whole hospital studies in Makkah in 2015 [27] and Madinah in 2016 [31] are almost similar to MDR in whole hospital of other places (Table 1). In fact, probably high resistance rate among *Acinetobacter* was influenced by hajj in Makkah study,[27] but no specific analysis on the influence of hajj season in Madinah study.[31]

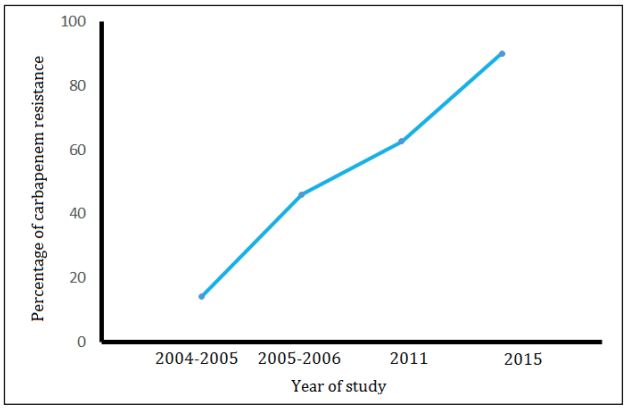

Figure 2: The proportion of *Acinetobacter* resistant to carbapenem in Makkah from 2004 to 2015.

Awareness needs to be created in both physicians and patients globally to ameliorate the prescription and usage of antibiotics to avoid an alarmist future.[39,41] Besides that, infection prevention and control also plays a very important role to prevent the spread of MDR organisms. Active surveillance is able to prevent the spread of resistant bacteria. The antibiotic stewardship guidelines also being suggested to restrict the irrational use of antibiotics in Saudi Arabia.[39]

Penicillins

Between 1998 and 200486% of *A. baumannii* isolates across Saudi Arabia were found to be resistant to ampicillin.[12] Although sulbactam has inherent activity against some *Acinetobacter* strains, 63% of isolates from a Riyadh ICU in 2009 were resistant to ampicillin/sulbactam.[16] The resistant rate against piperacillin/tazobactam in fact higher at 93%.[16] A recent study reports overall, a high resistance was observed for β-lactam antibiotics.[27] In 2018 a study from Madinah, Saudi Arabia reported 99.21% and 97.63% resistance for amoxycillin/clavulanate and piperacillin respectively.[31]

Cephalosporins

Acinetobacter is resistant to first and second-generation cephalosporins inherently.[43] Whereas third generation cephalosporins have some activity, 86% of *Acinetobacter* isolates in Riyadh in 1994 and 2009 were resistant to ceftriaxone.[9] On the other hand, studies from Riyadh, Al-Khobar, Al-Medina, found resistant to cefotaxime to be 50%, and 88% for ceftazidime. [12,16,44,45] Some more recent studies found resistance rates to be high. One of the studies reported it to be 75% in isolates from across the Kingdom in 2009 for ceftazidime. The rates of resistance ranged from 58% in the Eastern region, to 72.5% in Asir and to up to 95.8% in Hail.[10] In addition, a high resistance was noted for ceftazidime with *A. baumannii* species 77%.[27] More recently further increase in resistance rates has been reported to be up to 99.21%, 99.74%, 98.42% for cefotoxin, cephalothin and ceftazidime respectively.[31]

Carbapenemresistance

Initially the resistance rates of 3–11% were noted for imipenem 1998 to 2006 in the Eastern region.[12,46] In 2009 a nationwide survey of 2228 *A. baumannii* isolates reported 5.4% isolates resistant to imipenem, with the highest rate of 13.1% in the Eastern region.[10] Whilst carbapenemsresistance is frequent in Saudi Arabia, Alsultan*et al.* implicated genes for VIM, OXA-23, OXA-40, OXA-89, OXA-66 carbapenemases, novel chromosomal OXA-51-like beta-lactamases in the etiology of carbapenem-resistant.[45,47]

Later studies in Saudi Arabia indicated carbapenem resistant *A. baumannii* appears to have risen seriously over the years. Between 2006-2012, a decrease in susceptibility to meropenem and imipenem from 64-81.2% in 2006 to 8.3-11% in 2012 which is a major cause for concern.[53] In 2014 a study done in Dammam Saudi Arabia reported 32.6% of the *A. baumannii* isolated to be carbapenem resistant with underlying mechanism related to blaOXA-23.[4] Whereas higher rates of carbapenem resistance or intermediate resistance in 69% of *A. baumannii* isolates have also been reported with concomitant bla VIM gene detection in 94%, while bla OXA-23-like genes in 58% in Eastern District of Saudi Arabia.[54] High rates of resistance have also been reported in the southern

region of Saudi Arabia citing a new threat in the hospitals reporting 69% multi drug resistant isolates.[26] A study in Riyadh has found 76.3 % prevalence of the PER-1 resistance gene in *A. baumannii* clinical isolates.[56] Most *A. baumannii* strains were found to be resistant to imipenem 90.5%, meropenem 90.5%, and doripenem 77.4%.[57] The acquisition of resistant to carbapenems in *A. baumannii*has been attributed to a number of mechanisms including the expression of OXA-type A and metallo-β-lactamase.[58] More specifically reports on isolates from the Arabian gulf exhibit that carbapenem resistance phenotype in *A. baumannii* is mostly because of the expression of OXA enzymes, and in particular OXA-23 .[40] It is particularly noteworthy that the imipenem resistance rate has increased to 89.18% in 2018.[31]

Aminoglycosides

Aminoglycosides resistance in *A. baumannii* has increased with time in the Saudi Arabia studies from the 1980s to the early 2000s reported resistance rates of 40%,[12,46,59,60] whereas recent reports suggest that over 75% of the isolates are now resistant to gentamicin and amikacin, with 47% resistant to netilmicin. Resistant to amikacin and gentamicin was highest in Makkah region (around 90%) and lowest in the Eastern region (around 60%).[10,16,61] In 2012 the reported rate of resistance for amikacin was 76,9% and for gentamicin was 77.8%.[10] More recent studies from 2016-2018 have reported resistant to amikacin to be 67% and 83.7% respectively.[27,29]

Polymyxin resistance

Colistin is a cationic polypeptide and a member of the polymyxin family is the last resort in the battle against multi drug resistant *A. baumannii.* Previously, colistin resistance was not reported and in 2013 a study from Najran, Saudi Arabia reported 100% (all 68 isolates) of the isolates to be susceptible to colistin.[6324] Up until 2015 all isolates of *A. baumanni* were found to be sensitive to colistin.[64] In a study conducted in a hospital is Asir region of Saudi Arabia 98.1% of *Acinetobacter*species were found to be multidrug resistant but 100% were sensitive to colistin, whereas 74.5% were sensitive to trimethoprim and sulfamethoxazole.[62] In spite of the above colistin with or without rifampin appears to be the best available .[3]

In another study 74% of isolates were found to be multidrug-resistant, 50% of which were extensively drug resistant, sensitive to colistin and resistant to all other drugs of choice. Almaghrabi found that, the most effective antibiotic with high spectrum to treat *A. baumannii* is colistin followed by combination of trimethoprim and sulfamethoxazole.[6526]

Saeed *et al*. studied the resistant to colistin and tigecycline in *A. baumannii* in Riyadh, as these are now the most-frequently-used agents against carbapenem-resistant *A. baumannii* and reported no colistin resistant isolate.[16]Baadani*et al.* at Riyadh, found resistance rates to colistin and tigecycline of 1.8 and 9.7%, respectively in 2010–2011.[19] One national study found that 13.2% of the 68 *A. baumannii* isolates in 2009 were resistant to colistin.[10] Some other studies reported some resistant to colistin (4.6%) which is higher than the reported prevalence in North America and Europe, which according to the SENTRY program range from 2.7% in Europe and 1.7 % in Latin and North America.[66-68] A recent study from Madinah has reported 24% resistant to colistin which is remarkably high in contradiction with a study from south west region reporting only 4% resistance.[31,32]

Common sequence types and common resistance genes in Saudi Arabia

In Saudi Arabia the common identified sequence types for *A .baumannii* were ST195, ST208, ST436, ST450 and ST499.[70] In another study in Makkah, Alyamani*et al.*, 2015 found beside ST195, the most predominant sequence types being ST557, in which both are belonging to worldwide clonal complex 2.[22]

Another study by Aly *et al.* in 2014 revealed four main sequence types ST2, ST19, ST20 and ST25, in addition to ST194–ST197 singletons. In the same study exploration of genetic diversity of class D oxacillinase in a tertiary care hospital in Riyadh reported that OXA-51-like and OXA-23 genes were carried on all 253 tested isolates. OXA-58 and OXA-40 gene were also detected in some isolates. Further sequence based typing produced four groups OXA-66 (62.3 %), followed by OXA-69 (19.1 %), OXA-132 (7.6 %) and OXA-51-like genes (10.3 %), including OXA-79, -82, -92, -131 and -197. Moreover, a high prevalence (81.4 %) of OXA-66 and OXA-69-like genes in *A. baumannii* was identified.[71] A similar study in Asir region of Saudi Arabia found that all studied isolates [n=108], from different sources such as respiratory, wound and urinary tract infections possessed the blaOXA-51-like gene. Whereas 85.7% had blaOXA-23-like, 5.4% blaOXA-40-like and 3.6% blaOXA-58-like genes. Moreover, ISAba1 element was consistently

found upstream of the blaOXA-23 in 71.4% of the isolates.[66] Another study on *A. baumannii* showed a radical decrease in susceptibility to carbapenems. The main carbapenem resistance mechanism was found due to class D-OXA-type enzymes (OXA-23 and OXA-24/40) with carbapenemase activity.[29]

Moreover, a study from Riyadh spanning from February to June 2001 reported universal presence of *blaTEM*, *blaADC*and *blaOXA-51* like genes, whereas *blaOXA-23*, *blaPER*, *blaGES*and *blaOXA-24*were present in only 60.0%, 49.1%, 34.5% and 3.6% of isolates, respectively. Secondly, genes for SHV, CTX-M, VEB, KPC, OXA-58 and metallo-β-lactamases were absent.[72]

Clinical significance

A. baumannii is an important cause of nosocomial infections in hospitals around the world. Especially in the case of MDR *A. baumannii*, which is more associated with higher mortality and outbreaks. These latter outbreaks mostly caused by strains susceptible only to colistin.[73-75] *Acinetobacter* species were also significantly associated with late-onset ventilator associated pneumonia in an adult intensive care units in Saudi Arabia.[76]

Saudi Arabia faces several obstacles that result in the emergence and spread of multidrug-resistant bacteria. A multi-sectorial approach is required to cater the problem of antimicrobial resistance such as infection control and prevention programs, raising awareness as well as antibiotic stewardship programs.[39] A systematic literature review showed a considerable hike in the rate of carbapenem-resistant gram negative bacteria in Saudi Arabia over the last decade.[40] According to a study done by Aly *et al.* from January1990 through April 2011, the most prevalent microorganism was*Escherichia coli* (10073, 44%), followed by *Klebsiella pneumoniae* (4709, 20%),*Pseudomonasaeruginosa* (4287, 18.7%), MRSA (1216, 5.4%) and *Acinetobacter* (1061, 5%).[45,51,77] In Saudi Arabia prevalence of digestive tract *Acinetobacter* colonization of intensive care unit patient was reported to be 8.3% (47/565).[52]

Many factors such as un-optimized use of antibiotics, overuse of antimicrobial agents, over the counter prescription, mass migration during hajj and a high expatriate population from the Indian sub-continent may be responsible for the rise in the resistant isolates in Saudi Arabia.[40,78] In Makkah region in Saudi Arabia, the most frequent site of infection was found to be the respiratory tract having 77.3% of related cases.[79]

Moreover, apart from a high prevalence of antimicrobial resistance in *A. baumannii*diverse sequence types have been reported and are suggestive that new extended-spectrum β-lactamase producing strains are continually emerging contributing to increased antimicrobial resistance.

Conclusion

Acinetobacter infections are among significant problems faces in Saudi's hospitals. The resistance against clinically available antibiotics are increasing. The popular drug of choice for the treatment of *Acinetobacter* infections in the Kingdom, carbapenem, is decreasing in susceptibility over the past few years approaching 90% resistant rate is some hospitals. This left polymyxin as the last resort antibiotic in the Kingdom, in which the emergence of resistance has been reported. This review is also documented higher resistant rate in two holyland hospitals, Makkah and Madinah probably due to mixture of pathogens during hajj or umrah. There is a need for a more comprehensive program based on molecular epidemiological characterization to confirm this hypothesis. In addition to that, effective antibiotic stewardship programs should be promoted for optimal use of the antibiotics to prevent resistant isolates from emerged. Lastly, newer agents and other treatment options such as bacteriophage therapy need to be developed for the treatment of patients in the future.

Conflict of Interest: Nil

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