A REVIEW: Glimpse on the Global Multi-Drug Resistant Bacterium *Acinetobacter baumannii*

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Abstract
The rise of drug-resistant bacterial infections coupled with declining antibiotic efficacy poses a substantial challenge to universal healthcare. *A. baumannii* is one of the most difficult ESKAPE pathogens and mechanisms that have facilitated its rise as a successful pathogen are not well studied. *Acinetobacter baumannii* is an emerging nosocomial pathogen involved in range of infections extending from minor soft-tissue infections to more severe infections such as ventilator-associated pneumonia and bacteraemia. *A. baumannii* has become resistant to most of the commonly used antibiotics and multidrug-resistant isolates are becoming a severe delinquent in the healthcare locations. In the past few years, whole-genome sequences of .200 *A. baumannii* isolates have been generated. Numerous strategies and molecular accouterments had been used for genetic manipulation of diverse Acinetobacter spp. The severe insidious and nosocomial nature of *Acinetobacter baumannii* is mainly aided by its ability to form biofilms.

***Key words*: *Acinetobacter baumannii*, Multi Drug Resistance, Disease, Bacteria.**

1. INTRODUTION

In 2017, the World Health Organization (WHO) ranked carbapenem-resistant *Acinetobacter baumannii* as the peak precedence pathogen within the WHO's first-ever listing of priority antimicrobial-resistant pathogens. It is far anticipated that one million *A. baumannii* infections occur worldwide each year, causing 15,000 deaths. Within the United States, *A. baumannii* is accountable for greater than 10% of nosocomial infections, and reasons a diffusion of diseases such as ventilator-associated pneumonia, bacteremia, skin and soft tissue infections, endocarditis, urinary tract infections and meningitis (1). Regardless of the urgency to develop new antimicrobial tablets, we recognize approximately very little *A. baumannii* contamination biology and virulence mechanisms because only some *A. baumannii* virulence genes and their regulation were functionally studied (2).

Acinetobacter baumannii is accountable for approximately 2–10% of all Gram-negative infections in intensive care units (ICUs) and substantially improved mortality of infected sufferers (3). Ribotyping and amplified fragment length polymorphism genomic fingerprinting processes have identified three international companies of epidemic *A. baumannii* lines: clone I, clone II, and clone III (4). However, the fingerprinting-based techniques can handiest provide very restricted phylogenetic records, and their consequences cannot perceive genetic distinctness inside the same clones and amongst different clones. Hence, entire-genome sequences are required for thorough epidemiological evaluation and antibiotic resistance profiling of *A. baumannii* (1). Therefore, the objective of this review is to provide highlight current studies concerning *A. baumannii*.

2. LITERATURE REVIEW

2.1. *Acinetobacter baumannii* Universal Overview

Since the discovery of penicillin in 1928, antibiotics have been a staple in current medical practices for combating bacterial infections. However, as fundamental as they are to global health, research output relating to new antibiotics or viable alternatives to antibiotics seems to have stagnated recently. With ceaseless trend of evolution of antibiotic resistance in bacteria and emergence of multidrug-resistant (MDR), extensively drug-resistant (XDR) and pan-drug-resistant (PDR) strains, devising new strategies to combat antibiotic resistance are paramount for global health. Among the pathogenic bacteria which have evolved or acquired resistance to antibiotics, a group of pathogens collectively referred to as ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and Enterobacter species) are globally the leading cause of nosocomial infections and therefore, particularly significant in nosocomial milieu (5).

Table 1: Taxonomic classification of *A. baumannii (16)*

Domain	**Bacteria**
Phylum	*Proteobacteria*
Class	*Gammaproteobacteria*
Order	*Halobacteriales*
Family	*Moraxellaceae*
Genus	*Acinetobacter*
Species	*Acinetobacter baumannii*
Full Scientific Name	*Acinetobacter baumannii* Bouvet and Grimont 1986
Strain Designation	*2208, 81*

A. baumannii is one of the ESKAPE pathogens routinely implicated in hospital-acquired infections. Due to its innate resilience against environmental stresses such as desiccation, nutrient starvation, and acquired resistance to a wide array of antibiotics including penicillins and cephalosporins, and last resort antibiotics such as polymyxins and carbapenems, *A. baumannii* has emerged as one of the most successful and challenging pathogens (6-7). *A. baumannii* is frequently implicated in nosocomial infections such as hospital-acquired pneumonia, bacteraemia, septicaemia, urinary tract infections and meningitis (8). According to 2010 WHO fact sheet on Multi-drug resistant *Acinetobacter baumannii* (MDRAB), multi-drug resistant strains of *A. baumannii* were estimated

to be responsible for 2 to 10 % of gram-negative infections acquired in ICU in Europe and the USA (9). Due to lack of an active surveillance strategy, statistics about nosocomially acquired *A. baumannii* and MDRAB infections in India are difficult to estimate. However, there is growing evidence for increase in infection and mortality rates associated with MDRAB all over the world (10).

Acinetobacter baumannii is a strictly aerobic gram-negative coccobacillus found commonly in soil. This bacteria generally has low virulence and does not commonly infect healthy adults with robust immune system. On the other hand, *A. baumannii* infections are relatively common in immunocompromised individuals such as patients suffering from other infections, transplanted organ recipients under immunosuppressant drugs or individuals with congenital or inherited immune disorders (11). *A. baumannii* is known to form biofilms on infected tissues or abiotic surfaces such as pacemakers, implants, stents et cetera. Recent evidence suggests that some strains of *A. baumannii* also exhibit resistance to complement mediated opsonisation in vitro and in vivo further improving its in-vivo survival. Improved in-vivo survival in immunocompromised individuals coupled with resistance to wide array of antibiotics makes *A. baumannii* infections particularly difficult to treat (12). Acinetobacter species are glucose-non-fermentative, non-motile, non-fastidious, catalase-positive, oxidative-negative, aerobic Gram-negative coccobacilli. Due to clusters of carefully associated species, it is tough to distinguish Acinetobacter taxonomy by usage of phenotypic developments and chemotaxonomic techniques (13).

Acinetobacter species, once taken into consideration as opportunistic, low virulence pathogens have now emerged as important nosocomial pathogens because of their increase in antimicrobial resistance. It's far an opportunistic pathogen which specially affects immunocompromised people, particularly the ones who have skilled a prolonged (>ninety day) sanatorium live (14). The resistance is because of numerous mechanisms including production of different forms of beta-lactamases which include oxacillinases. They are responsible for a number of hospital acquired infections. To control the spread of *Acinetobacter baumannii* (*A. baumannii*) inside the medical institution, it's far vital to differentiate the outbreak strain from epidemiologically unrelated Acinetobacter.

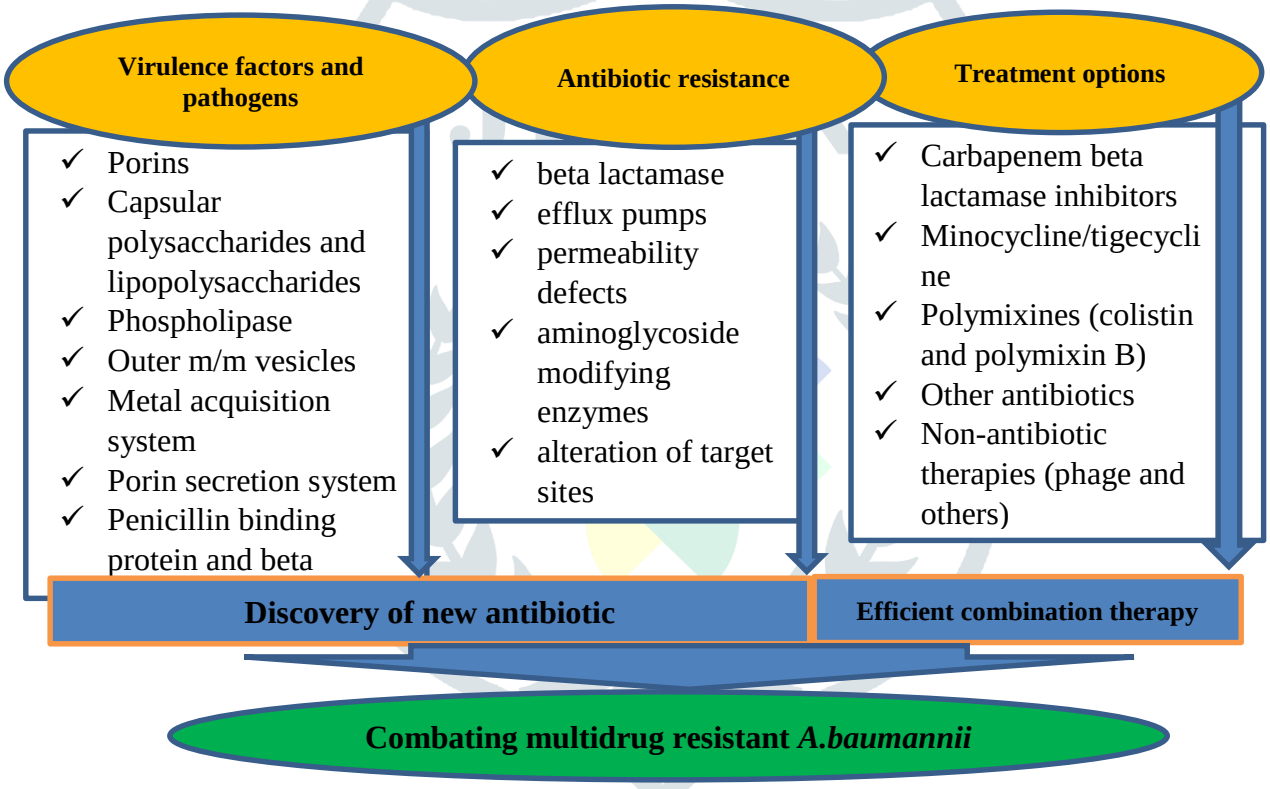

Figure 1: Biology of *Acinetobacter baumannii* (Source: Biology of *Acinetobacter baumannii, (*22)

The RstB/RstA system is a ubiquitous TCS (signal transduction systems) composed of the membrane-associated histidine kinase RstB and its cognate response regulator RstA. In *Escherichia coli* and Salmonella, RstA is under the control of the PhoP/PhoQ TCS, which monitors extracellular Mg2+ levels, and up-regulates the acid-induced *asr*(acid shock RNA) gene and the biofilm regulator *csgD* gene under acidic conditions. Overexpression of RstA in *Salmonella enterica* serovar Typhimurium induced degradation of RpoS and altered biofilm formation (15).

According to Edward Geisinger and Ralph R. Isberg, 2013, recent survey reported that most hospital-acquired *A. baumannii* infections are Multi Drug Resistant (MDR) (17), and strains resistant to all clinically useful antibiotics are emerging. Observations such as these have led the Infectious Diseases Society of America and Food and Drug Administration to designate *A. baumannii* a high priority target for new antibiotic development. Novel approaches to treat *A. baumannii* are urgently needed (18).

A number of *A. baumannii* resistance mechanisms are known, these includes, Presence of the porin channels, efflux mechanisms and the non-static behavior of the bacteria in hot and humid conditions equip the species with extensive antimicrobial resistance(19). It is believed that among the many factors which are responsible for the MDR character of A.baumannii is the presence of rstA gene, though its actual mechanism of action and genetic characterization is not fully disclosed. It was seen in different studies that A.baumannii is resistant to many of the available antibiotics (20, 21). The clear mode of action of antibiotic resistance is not known but many mechanisms were proposed leading to a detail genomic studies for development of curative drugs.

This calls for the comparison of isolates at the subspecies degree that's carried out by epidemiological typing strategies. Phenotypic typing structures based totally on biochemical profiles (biotyping), antibiotic susceptibility patterns, serological reactions (serotyping), phage typing and protein profiles have in most cases been replaced by way of molecular typing systems like ribotyping, Pulsed-field gel electrophoresis (PFGE), Amplified fragment length polymorphisim (AFLP) analysis, Random amplification of polymorphic DNA (RAPD) and many more (23).

A. baumannii is able to gather antibiotic resistance mechanisms which allow this organism to persist in clinic environments and facilitated the global emergence of MDR lines. The fast emergence of multi- and pandrug-resistant lines of Acinetobacter highlights the organism's capacity to quickly acclimatize to selective adjustments in environmental pressures. The three crucial appliances of antimicrobial resistance are (24) enzymatic degradation of antibacterial pills, (25) alteration of bacterial proteins which can be antimicrobial goals, and (26) modifications in membrane permeability to antibiotics. In latest years, it has been targeted as a "crimson alert" human pathogen, arising largely from its enormous antibiotic resistance spectrum (27).

According to Meenu G. *et al*., 2018, stepwise systematic identification and characterization of the potential drug targets of *A. baumannii* American culture strain were conducted, these steps includes Retrieval of essential proteins of *A. baumannii*, Identification of non-human homologous essential proteins in *A. baumannii*, Metabolic pathway analysis, Unique pathway identification i.e. unique metabolic pathways of Acinetobacter were identified through the manual comparison of metabolic pathways of both Acinetobacter and H. sapiens using KEGG Database, Subcellular localization of metabolic proteins (essential non-human homologous protein involved only in unique pathways) of *A. baumannii* to identify the cellular localization of these putative therapeutic targets and Drug target prioritization(28).

On the other note, it has been said that *A. baumannii* will evolve right into a veterinary nosocomial pathogen similar to extended spectrum beta- lactamase (ESBL)-generating Enterobacteriaceae and methicillin-resistant *Staphylococcus aureus* (MRSA) and that the dearth of attention paid to *A. baumannii* in veterinary medication is even more traumatic (29), as reviews suggest a transmission between human beings and animals.

In livestock (cattle, pig), *A. baumannii* has been witnessed as a cause of mastitis, pneumonia, and sepsis. Horses have been reported to develop wound contaminations, septicaemia, and bronchopneumonia as well as neonatal encephalopathy and eye infections. In dogs and cats *A. baumannii* has been isolated from wound, bloodstream and urinary tract infections (30). In another investigative report more than 350 isolates of *A. baumannii* which were resistant to many antibiotics were described by many literatures in different species of animals i.e. cat, cow, horse, chicken geese and insects including moth fly (31).

2.2. Genomic data

The first *A. baumannii* strain to be sequenced was ATCC 17978 (32). Since the 1980s, three main epidemic *A. baumannii* lineages, denoted to as clonal complexes I, II, and III (CC1, CC2, and CC3, respectively), have spread worldwide and are responsible for the majority of hospital outbreaks caused by *A. baumannii* (33). Ninety five complete *A. baumannii* genome sequences and greater than 2,000 draft genomes are available within the GenBank database. Maximum of the genome studies were accomplished with strains belonging to the worldwide clonal lineage (ICL) 1 and 2 (34).

The whole genome sequences of ten *A. baumannii* lines had been defined thus far, these are: 1656-2, AB0057, AB307-0294, ACICU, ATCC 17978, AYE, MDR-TJ, MDR-ZJ06, SDF and TCDC-AB0715. Nine of these are nosocomial isolates, while *A. baumannii* SDF changed into remoted from a human body louse. These genome sequences have confirmed massive divergence due to the acquisition and accretion of numerous cellular genetic factors, particularly those contributing to antimicrobial resistance (35).

2.3. Pathogenesis

The real mechanism of pathogenicity is doubtful but one of a kind genomic and experimental research have identified virulence genes involved in pilus biogenesis, iron uptake and metabolism, quorum sensing and type IV secretion system. Despite the fact that nematode model are used to display the potential virulence genes however novel genes in *A. baumannii* with considerable role in pathogenicity that haven't begun to be assessed in mammalian model (36).

A. baumannii can be transmitted via the area of affected patients or colonizers including linens fomites, curtains, mattress rails, tables, sinks, doors, feeding tubes, or even medical equipment. Contamination of respiratory support, suction gadgets, and devices used for intravascular access could be an important sources of contamination. (37). The respiration tract, blood, pleural fluid, urinary tract, surgical wounds, central nervous system, pores and skin, and eyes are places for contamination or colonization. The pathogen is known to purpose infections including pneumonia, bacteremia, endocarditis, skin and clean tissue infections, urinary tract infections, and meningitis. (38)

These days, research specialize were focused in virulence elements for the genus Acinetobacter. Genomic approaches, together with phenotypic assays and infection models, have contributed in the identification of important virulence factors for *A. baumannii* that play a role in pathogenicity (39). Virulence elements concerned in adhesion and motility (e. g. ompA), biofilms and its regulation (e.g. Bap, Flagelum Csu, PNAG, BfmSR), evasion of the immune system (e. g. pill, LPS), and iron uptake (e. g. acinetobactin) have been studied (40).

2.4. Multi drug resistance profile

Currently, the isolates of *A. baumannii* are resistant to all available antimicrobials have been reported. The hard work of scientific community resulted in discovery of many antibiotics, but their misuse resulted in high degree of resistance. It can be said that pre-antibiotic era has started, where again microbes with greater killing capacity are in abundance. Acinetobacter has been endowed with the genetic setup for rapid development of antimicrobial resistance, and is known as a natural transformant. Scientific literature is full of reports stating it as one of the toughest bacteria (41).

Although a widespread range of studies have been dedicated to optimizing the use of presently available marketers or figuring out any mixture thereof, new chemical entities have now not been developed for the treatment of MDR *A. baumannii* infections since the creation of tigecyclin in 2005. As a consequence, the need for brand new agents to treat infections caused through *A. baumannii* is pressing (42).

Amongst the many ways of mechanism of resistance of selected antibiotics by the *Acinetobacter baumannii* species few are believed to be studied well and compiled. Buddha *et al*., 2013, mentioned in citation that the resistances to β-Lactam in *A. baumannii* are: hydrolysis by betalactames, modifications in PMPs that forestalls their movement, alteration within the shape of outer membrane protein (OMPs) and different protein consisting of penicillin binding proteins (PBPs) and accelerated capacity of Efflux pumps. In *A. baumannii*, there is greater device for resistance to aminoglycosides referred to as amino glycosides modifying enzymes (AMEs). Amendment in the shape of quinolones resistance figuring out areas of gyrA and parC gene is liable for the quinolones resistance. The core mechanism of resistance to liable for colistin, that is a factor for polymixin resistance, lies inside the change of lipopolysaccharide of *A. baumannii* (43).

Clinical use of polymyxin against *A. baumannii* isolates has validated to be extraordinarily a success. Exceptional retroprospective reported up to 87% remedy (44 and 45). Polymyxin had been examined considerably in combination regimes with others marketers to deal with MDRAB. Among those aggregate colistin and carbapenem combination confirmed advanced result that is supported by the work performed by Falagas *et al.,* 2010 (44).

According to Sean Yang, 2013 Susceptibility of *A. baumannii* strains to 18 antimicrobial agents was tested by disc diffusion following the Clinical and Laboratory Standards Institute (CLSI) recommendations, in this study two *A. baumannii* strains were resistant to all tested antibiotics including Ampicillin, Aztreonam, Ceftazidime, Ceftriaxone, Cefuroxime, Chloramphenicol, Ciprofloxacin, Colistin, Gentamicin, Imipenem, Mecillinam, Meropenem, Penicillin, Piperacillin/Tazocin, Sulfonamide, Tigecycline, Tobramycin, and Trimethoprim. (1).

In a study conducted at Reunion Island (46) it was shown that *A. baumannii* strains were present outside the hospital setting with great diversity. Further studies were also recommended to explore more precisely those extra-hospital reservoirs of *A. baumannii* in the Island and the possible ways of dissemination

Little is known about the natural prevalence of Acinetobacter spp. in animals or whether or not animals honestly are a reservoir from which spread to humans occurs. It should be noted that some Acinetobacter spp. are commensal in animals like they'll additionally constitute the normal flora in human, however those Acinetobacter spp. appear to be unrelated and are in distinct in their sequence types and resistance patterns from those found in humans. At the present time *A. baumannii* represents an important veterinary nosocomial pathogen. However, it seems that the majority of *A.baumannii* infections in veterinary medicine are secondary and as a sequela might be fatal or lead to euthanasia in some instances. The recent report on *A. baumannii* infection in farmed mink might be regarded as an exception with reference to the associated fatal pneumonia. In other species relevant to veterinary medicine, fatal pneumonia as a sequela of *A. baumannii* infection appears rare. The emergence of cases of infections in companion animals associated with carbapenem-resistant isolates emphasizes the need for accurate diagnostics (30).

According to J.H. van der Kolk *et al.,* 2018, animal isolates show high genetic diversity and are in general distinct in their sequence types and resistance patterns from those found in humans. However, it cannot be excluded that animals may occasionally play a role as a reservoir of *A. baumannii*. Thus, it is of high significance to implement infection control measures in veterinary hospitals to avoid nosocomial outbreaks with multidrug-resistant *A. baumannii* (47).

2.5. Biofilm Formation

In nature, significant amount of bacteria are prearranged in surface-connected communities, referred to as biofilms. Biofilm producing organisms adhere onto abiotic or biotic surfaces, and are surrounded within extracellular polymeric matrix (phospholipids, proteins, polysaccharides, and nucleic acids) which is produced by the bacteria themselves (7). Within biofilms, bacterial cells are sheltered against different adverse environmental situations such as disinfectants, ultraviolet (UV) light radiation, osmotic changes, pH variability, dehydration, antimicrobial agents, host immune responses and metal toxicity (48).

Among the many suggested virulence determinants in *A. baumannii* microbial functions such as cell communication, surface regulated attachments, and secretion of macromolecules are essential factors for biofilm formation (49). *A. baumannii* expresses several virulence genes which make it a successful pathogen in humans and animals. Some of these factors such as K1 capsular polysaccharides, surface antigen protein 1, iron acquisition systems, outer membrane porins, acinetobactin transporters together with resistance to the majority of antibiotics have made *A. baumannii* an increasingly important pathogen (50). *A. baumannii* harbors repertoires of biofilm-related virulence genes and proteins which contribute to its ability to adhere and form biofilms on biotic and abiotic surfaces (51). The presence of these genes makes *A. baumannii* remain viable in diverse environments and a formidable force against antimicrobials and immune cells.

According to Rahimi S., *et al*., 2018, except the statistical evaluation of the connection among biofilm-forming capacity and antibiotic resistance phenotypes amongst all scientific *A. baumannii* strains using one-way ANOVA test indicated that biofilm formation ability of non-MDR *A. baumannii* isolates changed into significantly higher than that of MDR and XDR ones ($P < 0.001$), suggesting an inverse relationship among biofilm formation ability and the acquisition of MDR/XDR phenotypes. Investigation of the relationship between biofilm-forming capacity and antibiotic resistance phenotypes among *A. baumannii* most important IC types (ICI and ICII) additionally exhibited the sort of massive relationship ($P < 0.0001$). Plainly the relationship among antibiotic resistance phenotypes and biofilm formation capability can be distinctive amongst IC types.

3. CONCLUSION

Globally reported and a major hospital-acquired pathogen Multidrug-resistant *Acinetobacter baumannii*, is a serious health threat and poses great challenge especially to healthcare workers not only in the human but in the animal hospitals. Although there have been many genomic studies on the evolution and antibiotic resistance of this species, the available transcriptome studies on its responses to antibiotics are very limited. *A. baumannii* has developed three basic properties to perfectly adapt to current healthcare settings: (i) widespread resistance to antimicrobial agents; (ii) ability to colonize skin, plastic intravascular devices and mucous membranes and to survive in the hospital environment; and (iii) survival in and on the human host. Circumstantial evidence has recommended that antimicrobial resistance is the principal selective advantage that drives the continuing fast growth of specific rather tricky clonal lineages. Genomic modification studies has to be conducted intensively with regard to the lower rate record of recombinant technology associated researches belonging to *A. baumannii.*

Competing interests

All authors have declared that no competing interests exist.

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REFERENCES

1. Sean Yang-Yi Tan, Song Lin Chua, Yang Liu1, Niels Høiby, Leif Percival Andersen, Michael Givskov, Zhijun Song, and Liang Yang, 2013: Comparative Genomic Analysis of Rapid Evolution of an Extreme-Drug-Resistant *Acinetobacter baumannii* Clone. Oxford university press. Genome Biol. Evol. 5(5):807–818.
2. Carsten Kroger, Keith D. MacKenzie, Ebtihal Y. Alshabib, Morgan W. B. Kirzinger, Danae M. Suchan, Tzu-Chiao Chao, Valentyna Akulova, Aleksandra A. Miranda-Caso Luengo, Vivian A. Monzon, Tyrrell Conway, Sathesh K. Sivasankaran, Jay C. D. Hinton, Karsten Hokamp and Andrew D. S. Cameron., (2018). The primary transcriptome, small RNAs and regulation of antimicrobial resistance in *Acinetobacter baumannii* ATCC 17978. *Oxford University Press Nucleic Acids Research*. Pp1-2
3. Lockhart, S. R., Abramson, M. A., Beekmann, S. E., Gallagher, G., Riedel, S., Diekema, D. J., and Doern, G. V. (2007). Antimicrobial Resistance among Gram-Negative Bacilli Causing Infections in Intensive Care Unit Patients in the United States between 1993 and 2004. Journal of Clinical Microbiology, 45(10), 3352–3359.doi:10.1128/jcm.01284-07.
4. Sean Yang-Yi Tan, Song Lin Chua, Yang Liu1, Niels Høiby, Leif Percival Andersen, Michael Givskov, Zhijun Song, and Liang Yang, 2013: Comparative Genomic Analysis of Rapid Evolution of an Extreme-Drug-Resistant *Acinetobacter baumannii* Clone. Oxford university press. Genome Biol. Evol. 5(5):807–818.
5. S. Santajit, and N. Indrawattana, (2016). Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens (Review Article), *Hindawi Publishing Corporation. Biomed Res. Int.* 2016 (2016) 2475067. doi:10.1155/2016/2475067.
6. C. R. Lee, J.H. Lee, M. Park, K.S. Park, I.K. Bae, Y.B. Kim, C.-J. Cha, B.C. Jeong, and S.H. Lee (2017). Biology of *Acinetobacter baumannii*: Pathogenesis, Antibiotic Resistance Mechanisms, and Prospective Treatment Options, *Front. Cell. Infect. Microbiol.* 7 55. doi:10.3389/fcimb.2017.00055.
7. M. Haeili, M. Kafshdouz, M.M. Feizabadi, Molecular Mechanisms of Colistin Resistance Among Pandrug-Resistant Isolates of *Acinetobacter baumannii* with High Case-Fatality Rate in Intensive Care Unit Patients, Microb. Drug Resist. (2018) mdr.2017.0397. doi:10.1089/mdr.2017.0397.
8. K. Rit, and R. Saha, (2012). Multidrug-resistant acinetobacter infection and their susceptibility patterns in a tertiary care hospital., *Niger. Med. J.* 53.126–8. doi:10.4103/0300-1652.104379.
9. WHO, Multidrug-resistant *Acinetobacter baumannii* (MDRAB) Fact Sheet, (2010). http://www.wpro.who.int/mediacentre/factsheets/fs_20101102/en/ (accessed May 6, 2019).
10. N. Teerawattanapong, P. Panich, D. Kulpokin, S. Na Ranong, K. Kongpakwattana, A. Saksinanon, B.-H. Goh, L.-H. Lee, A. Apisarnthanarak, and N. Chaiyakunapruk, (2018). A Systematic Review of the Burden of Multidrug-Resistant Healthcare-Associated Infections Among Intensive Care Unit Patients in Southeast Asia: The Rise of Multidrug-Resistant *Acinetobacter baumannii*. *Infect.ControlHosp.Epidemiol.*(2018)1–9. doi:10.1017/ice.2018.58.
11. A. Howard, M. O'Donoghue, A. Feeney, R.D. Sleator, *Acinetobacter baumannii* - An Emerging Opportunity Pathogen, Virulence. 3 (2012) 243–250. doi:10.4161/viru.19700.
12. R.E. Nelson, M.L. Schweizer, E.N. Perencevich, S.D. Nelson, K. Khader, H.-Y. Chiang, M.L. Chorazy, A. Blevins, M.A. Ward and M., H. Samore (2016): Costs and Mortality Associated With Multidrug-Resistant Healthcare-Associated Acinetobacter Infections, Infect. Control Hosp. Epidemiol. 37 (2016) 1212–1218. doi:10.1017/ice.2016.145.
13. Lin M. F., Lin Y. Y., Yeh H. W. and Lan C. Y., (2014). Role of the BaeSR two-component system in the regulation of *Acinetobacter baumannii adeAB* genes and its correlation with tigecycline susceptibility. BMC Microbiol. 14:119. 10.1186/1471-2180-14-119
14. Ogasawara H, Hasegawa A, Kanda E, Miki T, Yamamoto K, and Ishihama A., (2007). Genomic SELEX search for target promoters under the control of the PhoQP-RstBA signal relay cascade. J Bacteriol.; 189 (13):4791-9. Epub 2007; 2-5.
15. Yi-C. L., Chung-ke C., Chi-Fon C., Ya-Hsin C., Pei-Ju F., Tsunai Y., Sheng-Chia C., Yi-Ching L., Chwan-Deng H. and Tai-huang H. (2014): Structural dynamics of the two-component response regulator RstA in recognition of promoter DNA element. Nucleic Acids Research, Vol. 42, No. 13 8777–8788 doi: 10.1093/nar/gku572
16. Said K. B., Al-Jarbou A.N., Alrouji M. and Al-Harbi H.O., (2014). Surveillance of antimicrobial resistance among clinical isolates recovered from a tertiary care hospital in Al Qassim, *Saudi Arabia. Int J Health Sci* (Qassim).; 8:3–12.)

17. Sievert D.M., Ricks P., Edwards J.R, Schneider A., and Patel J., (2013). Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemiol 34: 1–14. pmid:23221186
18. Edward Geisinger, and Ralph R. Isberg, (2015). Antibiotic Modulation of Capsular Exopolysaccharide and Virulence in *Acinetobacter baumannii*, PLOS Corporation, California, US, https://doi.org/10.1371/journal.ppat.1004691
19. Bonomo R. A., Szabo D., (2006): Mechanisms of multidrug resistance in Acinetobacter species and *Pseudomonas aeruginosa*. *Clin Infect Dis* 2006; 43(Suppl 2):49–56
20. El-Ageery SM, Abo-Shadi MA, Alghaithy AA, Ahmad MA, Alsharif NH,Alharbi SA. (2012). Epidemiological investigation of nosocomial infection with multidrug-resistant *Acinetobacter baumannii*. *Eur Rev Med Pharmacol Sci.*;16: 1834–9. ,
21. Ning D, De-zhi L, Ji-chao C, Yu-sheng C, Rong G, Ying-hui HU, *et al.*, (2010). Drug resistant genes carried by *Acinetobacter baumannii* isolated from patients with lower respiratory tract infection. Chin Med J; 123:2571–5.
22. Chang-Ro Lee,1, Jung Hun Lee, Moonhee Park, Kwang Seung Park, Kwon Bae,Young Bae Kim, Chang-Jun Cha, Byeong Chul Jeong, and Sang Hee Lee, (2017): Biology of *Acinetobacter baumannii*: Pathogenesis, Antibiotic Resistance Mechanisms, and Prospective Treatment Options. *Front Cell Infect Microbiol*; PMC5346588. 7: 55.
23. Dabet Rynga, Malini Shariff and Monorama Deb (2015): Phenotypic and molecular characterization of clinical isolatesof *Acinetobacter baumannii* isolated from Delhi, India. *Ann Clin Microbiol Antimicrob* 14:40 DOI 10.1186/s12941-015-0101-5,
24. Goyal, M., C. Citu, and N. Singh. (2015): In Silico Identification of Novel Drug Targets In *Acinetobacter baumannii* By Subtractive Genomic Approach. Asian Journal of Pharmaceutical and Clinical Research, Vol. 11, no. 3, Mar. 2018, pp. 230-6, doi:10.22159/ajpcr.2018.v11i3.22105-4.
25. Rice L. B. (2008). Federal funding for the study of antimicrobial resistance in nosocomial pathogens: No ESKAPE. *J Infect Dis*; 197:1079-81.
26. Spellberg B., and Bonomo R. A. (2014): The deadly impact of extreme drug resistance in *Acinetobacter baumannii. Crit Care Med* 2014; 42:1289-91.
27. Cerqueira G. M. and Peleg A. Y. (2011): Insights into *Acinetobacter baumannii* pathogenicity. *IUBMB Life* 2011; 63:1055-60.
28. Meenu Goyal, Citu Citu, and Nidhi Singh (2018). In Silico Identification of Novel Drug Targets in *Acinetobacter baumannii* By Subtractive Genomic Approach. *Asian J. Pharm. Clin. Res.*, Vol 11, Issue 3, 2018, 5-8
29. J.H. (Han) van der Kolk (2015): *Acinetobacter baumannii* as an underestimated pathogen in Vet. Medicine, Veterinary Quarterly, 35:3, 123-124, OI:10.1080/01652176.2015.1066137
30. J.H. van der Kolka, A. Endimianib, C. Graubnera, V. Gerbera, and V. Perretenc (2018): Acinetobacter in veterinary medicine, with an emphasis on *Acinetobacter baumannii*. *ISCIC*. Elsevier. https://doi.org/10.1016/j.jgar.2018.08.011
31. Gamal Wareth, Heinrich Neubauer and Lisa D. Sprague (2018): *Acinetobacter baumannii* – a neglected pathogen in veterinary and environmental health in Germany. Springer. 43:1–6: doi.org/10.1007/s11259-018-9742-0: pp 1-3.
32. Francesco Imperi, Luı´sa C.S. Antunes, Jochen Blom, Laura Villa, Michele Iacono and Paolo Visca (2011): Critical Review-The Genomics of *Acinetobacter baumannii*: Insights into Genome Plasticity, Antimicrobial Resistance and Pathogenicity. *IUBMB Life*, 63(12): 1068–1074. DOI: 10.1002/iub.531.
33. Smith, M. G., Gianoulis, T. A., Pukatzki, S., Mekalanos, J. J., Ornston, L. N., et al. (2007): New insights into *Acinetobacter baumannii* pathogenesis revealed by high-density pyrosequencing and transposon mutagenesis. Gene Devel. 21, 601–614.
34. Snitkin E. S., Zelazny A. M., Montero C. I., Stock F., Mijares L.; Murray P. R., and Segre J. A.(2011): Genome-wide recombination drives diversification of epidemic strains of *Acinetobacter baumannii*. *Proc. Natl. Acad. Sci*. USA 108, 13758–63 (2011)
35. Farrugia D. N, Elbourne L. D. H, Hassan K. A., Eijkelkamp B. A., Tetu S. G, et al. (2013): The Complete Genome and Phenome of a Community-Acquired *Acinetobacter baumannii*. PLoS ONE 8(3): e58628. doi:10.1371/journal.pone.0058628
36. Buddha Bahadur Basnet, Til Bahadur Basnet, Bishnu Joshi, Rajan Kumar Dahal Rajani Malla (2013): Multi Drug Resistant *Acinetobacter baumannii*: A Systematic Review For Microbial And Clinical Study. *IJABPT*. ISSN: 0976-4550.www.ijabpt.com.pp;167-168.
37. Jung J, Park W. (2015): Acinetobacter Species As Model Microorganisms In Environmental Microbiology: Current State And Perspectives. *Appl Microbiol Biotechnol*. 2015; 99(6):2533–2548. [PubMed]
38. Karmostaj A., Najar Peerayeh S. and Hatef Salmanian A. (2013): Emergence of Tigecycline Resistant *Acinetobacter baumannii* From an Intensive Care Unit (ICU) in Tehran. *Jundishapur J Microbiol*. 2013;6(3):215-9. DOI: 10.5812/jjm.4710
39. Antunes, L. C. S., Visca, P. and Towner, K. J. (2014*): Acinetobacter baumannii*: Evolution of a Global Pathogen. Pathogens and Disease ISSN 2049-632X.71, 292–301.
40. Eijkelkamp, B. A., Stroeher, U. H., Hassan, K. A., Paulsen, I. T. and Brown, M. H. (2014): Comparative analysis of surface-exposed virulence factors of *Acinetobacter baumannii*. *BMC Genomics* 15, 1020.
41. Provasi Cardoso J., Cayô R., Girardello R. and Gales A. C. (2016): Diversity of mechanisms conferring resistance to β-lactams among OXA-23–producing *Acinetobacter baumannii* clones. *Diagn Microbiol Infect Dis*. 2016;85(1):90–97
42. Muhammad Asif, Iqbal Ahmad Alvi and Shafiq Ur Rehman (2018): Insight into *Acinetobacter baumannii*: pathogenesis, global resistance, mechanisms of resistance, treatment options, and alternative modalities. *Infection and Drug Resistance*. Dove *press.*76.102.64.113:11.1249–1260
43. Buddha Bahadur Basnet, Til Bahadur Basnet, Bishnu Joshi, Rajan Kumar Dahal Rajani Malla (2013): Multi Drug Resistant *Acinetobacter baumannii*: A Systematic Review For Microbial And Clinical Study. *IJABPT*. ISSN: 0976-4550.www.ijabpt.com.pp;167-168.
44. Falagas M.E., Rafailidis P.I., Ioannidou E., Alexious V.G., Matthaiou D.K., Karageogopoulos D.E., *et al*., (2010): Colistin therapy for microbiologically documented multidrug resistant Gram negative bacterial infections: a retrospective cohort study of 258 patients. *Int J Antimicrob Agents.* 35: 194-199
45. Kallel H, Hergafi L, Bahloul M, Hakim A, Dammak H, Chelly H, et al., (2007): Safety and efficacy of colistin compared with imipenem in the treatment of ventilator -associated pneumonia: a matched case-control study. Intensive Care Med. 33: 1162-1167

46. Xie R., Xiaohua Douglas Z., Qi Z., Bo P. and Jun Z. (2018): Analysis of global prevalence of antibiotic resistance in *Acinetobacter baumannii* infections disclosed a faster increase in OECD countries. Emerging Microbes & Infections. DOI 10.1038/s41426-018-0038-9.
47. J.H. van der Kolka, A. Endimianib, C. Graubnera, V. Gerbera, and V. Perretenc (2018): Acinetobacter in veterinary medicine, with an emphasis on *Acinetobacter baumannii*. *ISCIC*. Elsevier. https://doi.org/10.1016/j.jgar.2018.08.011
48. Beshiru A., Igbinosa I. H. and Igbinosa E. O. (2018): Biofilm formation and potential virulence factors of Salmonella strains isolated from ready-to-eat shrimps. *PLoSONE*13(9):e0204345. https://doi.org/10.1371/journal.pone.0204345
49. Emmanuel C. Eze, Hafizah Y. Chenia and Mohamed E. El Zowalaty (2018): Review: *Acinetobacter baumannii* biofilms: effects of physicochemical factors, virulence, antibiotic resistance determinants, gene regulation, and future antimicrobial treatments. *Dove Press Journal*. Infection and Drug Resistance 2018:11 2277–2299.
50. Harding C. M., Hennon S. W. and Feldman M. F. (2018). Uncovering the mechanisms of *Acinetobacter baumannii* virulence. *Nat Rev Microbiol*. 2018;16(2):91
51. Liu H., Wu Y-Q., Chen L. P. and et al., (2016): Biofilm-related genes: analyses in multi-antibiotic resistant *Acinetobacter baumannii* isolates from mainland China. *Med Sci Monit*. 2016; 22:1801.
52. Rahimi E, Sepehri S, Dehkordi FS, Shaygan S, Momtaz H. (2014): Prevalence of Yersinia species in traditional and commercial dairy products in Isfahan Province, Iran. Jundishapur J Microbiol. 2014; 7(4).