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MDR Efflux Pumps: Structure and Regulation

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Abstract:

Multidrug resistance (MDR) represents a major challenge in the treatment of bacterial infections and cancer chemotherapy. A key contributor to MDR is the activity of efflux pumps, which are membrane transport proteins capable of extruding a wide variety of structurally unrelated compounds out of the cell. These efflux systems decrease the intracellular concentration of antimicrobial agents, thereby reducing their efficacy. Based on their structure and energy sources, efflux pumps are classified into several families, including the ATP-binding cassette (ABC), major facilitator superfamily (MFS), resistance-nodulation-division (RND), multidrug and toxic compound extrusion (MATE), and small multidrug resistance (SMR) families. The regulation of efflux pumps involves complex genetic and environmental controls. Global transcriptional regulators, two-component systems, and local repressors or activators tightly modulate efflux pump expression in response to environmental stresses, drug exposure, or metabolic needs. Overexpression of these pumps not only contributes to antibiotic resistance in bacteria but also influences biofilm formation, virulence, and cell survival under stress conditions. Understanding the structural basis and regulatory mechanisms of efflux pumps is crucial for developing inhibitors that can restore drug susceptibility. Efflux pump inhibitors (EPIs), either natural or synthetic, are being investigated as adjuvant therapies to combat MDR pathogens and improve treatment outcomes.

Keywords: Multidrug resistance (MDR); Efflux pumps; ABC transporters; Major facilitator superfamily (MFS); Resistance-nodulation-division (RND); MATE transporters; SMR family; Efflux pump inhibitors (EPIs); Antibiotic resistance regulation.

Introduction:

The structure of the efflux system is comprised of 3 well-defined parts each playing a function in the drug efflux mechanism, including the outer membrane (OM) , the internal membrane (IM) and the fusion protein at the intermediate level (MFP); Each part of the structure of the efflux pumps has a certain factor causing resistance to the antibiotics **(1, 2).**

In reference to further research, it has been proven that there are five different families of efflux pumps present on A. baumannii:

- major facilitation super family (MFS);
- multidrug toxic composite extrusion (MATE) transporters;
- resistance nodulation-division (RND) super family;
- ATP binding cassette (ABC) transporters;
- small multidrug resistance (SMR) family.

Recently other studies have reported a sixth efflux family named PACE (proteobacterial antimicrobial composite efflux) present in the A. baumannii **(3)**.

However, because of inadequate data, we will concentrate much more on the first 5 families **Figure (1)** where a totally understanding of structure and regulation is not complete.

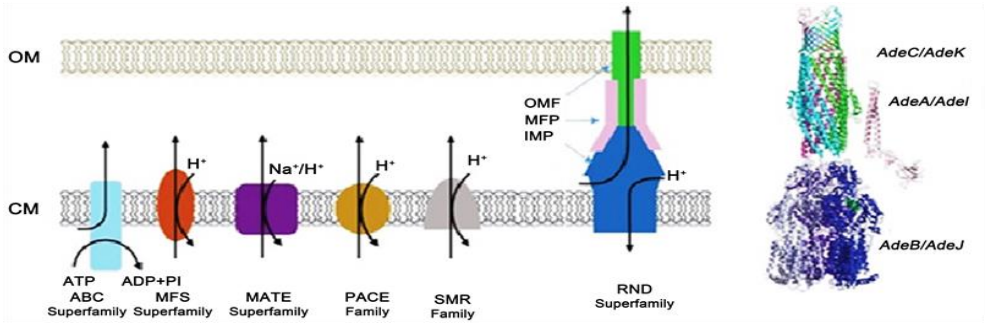

Figure (1): Structure of major families A. baumannii efflux pumps + PACE family a newly superfamily identify (adapted from **(4)**.

1. RND Efflux Pumps

The large family RND efflux is special of the rather complex compared to other family. it is very represented and has a special role in almost all major gram-negative bacteria and developing multiple resistance to antibiotic also call MDR such as A. baumannii, E. coli, and P. aeruginosa **(5)** .

RND efflux on A. baumannii has mainly three gene (adeABC, adeIJK, adeFGH) **Figure (2)** and some special gene (adeDE, adeAA) **(6)** .

a) adeABC

The adeABC operon was newly discovered on the antibacterial agents of fluoroquinolones and aminoglycosides in the efflux system RND and divided into 3 part: adeB on inner membrane efflux transporters, adeA on membrane fusion proteins, and adeC on external membrane proteins **(7)**.

AdeB has the largest representation on A. baumannii strains (80%), adeA and adeC has 42%, and 40% respectively **(8)** . Because of this high proportion of adeB gene compare to the others, its inactivation would dramatically cause sensitization to antimicrobial drugs in the hospital for A. baumannii **(9)**.

The increasing concentration of MIC would be beneficial to important drug classes like aminoglycosides, tetracyclines-tigecycline, β-lactams, fluoroquinolones, macrolides, trimethoprim, and chloramphenicol **(10)** .

Despite the advancement of research, rifampicin, flusidic acid and sometimes colistin remain resistant to isolate A. baumannii. Single last chances of fight against A. baumannii isolates are tigecycline but show a hard resistance to adeABC and also it presents a high resistance efflux. The MIC levels of tigecycline remain a clinical problem **(11).**

Remarkably, about 20% of adeC was found to be involved in tigecycline resistance tests in A. baumannii demonstrating that in the adeABC gene, adeAB can keep walking without adeC . The adeC plays a much more an almost negligible role in RND efflux system.

The two components adeR and adeS are responsible for the regulation of the expression system of adeABC **(12)**.

They are also called protein kinases and are found on both sides of adeABC in different trajectory. AdeRS, plays a determining role in increasing resistance of adeABC. Some result shows that a dysfunction of adeR and or adeS will increase the resistance of tigecyclin, chloramphenicol, minocyline, erythromycine, cefotaxime, tetracycline, fluoroquinolones, and trimethoprim **(13)** ; as well increase the sensitization of amino-glycosides of A. baumannii isolate.

b) adeIJK

The second largest pump of the RND family's adeIJK also comprises of adeI, adeJ, adeK genes which occur on the three parts of the pump efflux structure respectively. AdeIJK was described initially in the years 2008 with the A. baumannii clinical strains fluctuating between 86% and 100% in a presence of the predominant gene adeJ. With various reported a MIC dimness of adeIJK mainly the resistance of A. baumannii to β-lactamines, lincosamides, fluoroquinolones, chloramphenicol, trimethoprime, and fusidic acid has been noticed **(14)**.

The selection of the majority gene adeJ, will lead to an amplification in the sensitivity of chloramphenicol, macrolides, lincosamides, tetracyclines and quinolones and β-lactams **(15)**.

The regulation of adeIJK is less complex than that of adeABC, but at about 750 - 850 kbp of adeIJK operon there is a regulator adeN belonging to the class of tetR **(16)** .

The presence of this regulator adeN and mutation in different media led to an increase the resistance to antimicrobial drugs (ertapenem, aztreonam, tigecycline, meropenem, and minocycline) in A. baumannii **(6)**.

c) adeFGH

Outstanding variation of adeABC and adeIJK, has induced the discovery of adeFGH operon sometime after adeIJK identification. The presence of adeFGH in the genus A. baumannii through exposure to certain antibacterial agents (norfloxacin) **(17)** and is also a true source of multidrug. The genes of the adeFGH operon, the adeG is the most representative of more than 80% of the others **(18)** .

AdeFGH has also become popular in the species of A. baumannii due to its severe resistance to fluoro-quinolones, tetracyclines, tigecycline, chloramphenicol, trimethoprim, sulfamethoxazole and moderate resistance to erythromycin, rifampicin and aminoglycosides, **(17)** and also β-lactams. AdeFGH is regulated by LysR (LTTR), also called adeL. The adeL mutation will conduct to the adeFGH level rise. adeXYZ has also been found in A. baumannii genospecies 3 and has the same structure and positioning of MFP, OM, IM with propositions 80% (adeX), 89% (adeY) and 87% (adeZ) **(19)**.

Previous studies have demonstrated inconsistency between adeDE and adeABC-adeIJK due to the presence of adeABC-adeIJK/inter 1-negative adeS in some isolates for the detection of adeE **(20).**

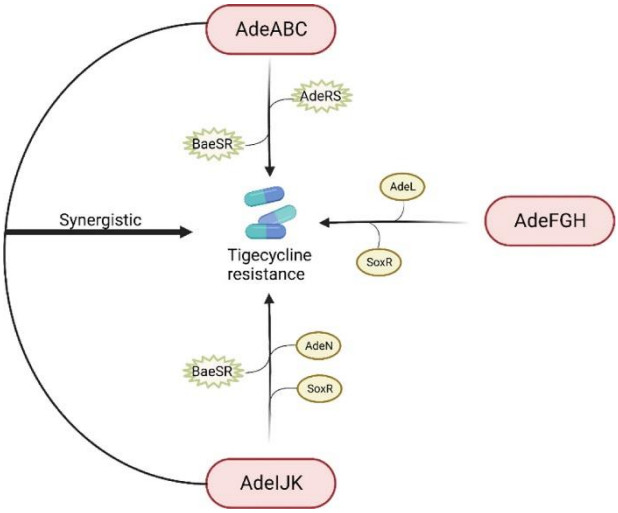

Figure (2): Regulation of tigecycline resistance in Acinetobacter baumannii by AdeABC, AdeFGH and AdeIJK efflux pumps **(6)**.

2. MFS Efflux Pumps

MFS is the subsequent most studied efflux mechanism in species A. baumannii have identified some genes cmlA, tet(A/B), craA, and floR as the most present and appertain to the superfamily MFS **(21)** . Plural research has explained a particularity of resistance caused by tetA and tetB **(17)** .

These two genes are not involved in resistance to tigecycline, yet tetA leads to a tetracycline resistance while tetB induce the resistance to tetracyclin and minocyclin **(22)** .

In A. baumannii isolate resistant to tetracycline, the overexpression rate of tetA is 30% - 45% whereas tetB is 32% - 72% **(23)**. The cmlA gene of MFS is resistant to certain β-lactams, chloramphenicole, fluoroquinolones, tetracycline and

rifampicin. craA is particularly resistant to chloranphenicol, imipenems, quinolones, aminoglycosides, and tetracyclines **(24)** .

The MFS energy source is proton motive force (H^+) facilitating H^+ motive force inhibition to increase the sensitization of antimicrobial drugs **(25)** .

3. MATE Efflux Pumps

The first and most frequent gene of the MATE family present in A. baumannii is the adeM gene. It represents between 63% - 100% in MDR of A. baumannii **(26)**.

AdeM protein contains about 447 amino acids and multiform hydrophobic regions. The antimicrobial drugs resistant due to adeM gene are not related to adeABC and totally known. In certain studies it was noted that adeM is not associated with the resistance of β-lactams, or cephalosporin **(27)** .

But it could have an implication of resistance in that of amino glycosides, trimethoprim, fluoroquinolones, erythrocin, and chloramphenicol. The MATE family is powered by double reservoir of energy PMF (motive force of the proton) and sodium ion gradient Na^+ **(28)**.

4. SMR Efflux Pumps

AdeS gene is the main efflux pump of SMR family present in A. baumannii. This gene adeS belongs to a particular resistance for fluoroquinolones, novobiocin, erythromycin, detergents (benzalkonium chloride), chloramphenicol, and dyes **(29)** .

AdeS is identical at 52% to emrE (E. coli) found in the genome A. baumannii genome. AdeS is composed of about 108 acid amines. Because of its constant need for energy (H^+), the suppression of this energetic source would restore susceptibility to drugs on MDR A. baumannii**(30)**.

5. ABC Efflux Pumps

ATP binding cassette (ABC) of super family efflux pumps are recognized to be censurable for multidrug-resistance due of P-glycoprotein (ABCB1) **(31)**.

ABC proteins are including in the cytoplasm (inner) membrane of germ, and membranes in eukaryotes. In the human body, ABC proteins encodes for 49 proteins, a particular fraction has been distinguished in function and biochemistry terms to others **(32)**.

They have been organized into 7 sub-families established on phylo-genetic examination. P-glycoprotein (ABCB1) contains 170 kDa trans-membrane glycoprotein and practically the most at largely studied transporters that promote cancer cells to develop drug resistance. Unlike the other family of efflux pumps, ABC family is powered by hydrolysis energy sources of ATP (ADP + Pi) which gives cellular resistance to large number of drug molecules **(33)**.

The ABC proteins functionally contain two areas for substrate transport and 2 areas of NBD (nucleotide binding) with ATP hydrolyse in the process.

6. PACE Efflux Pumps

The proteo-bacterial antimicrobial compound efflux family (PACE) is uncommon of the newest families of efflux pumps identified in the latest 15 years **(34)**.

Resistance to antibiotics

1. Resistance to Carbapenems

Carbapenems have the broadest spectrum among all β-lactams and are mainly used as a treatment in infections caused by Gram-negative bacteria **(35)**.

Overexpression of the carbapenem-hydrolyzing oxacillinase (OXA)-51-like-B-lactammase **(36)** and ArmA RNA 16S ribosomal methyltransferase are among the mechanisms that confer resistance to carbapenems among *A. baumannii* strains **(37)**.

Increasing emergence of carbapenem resistance, frequently mediated by production of Ambler's class D β-lactams (OXA) in *A. baumannii* is a major concern **(38)**.

Many of them are found as part of integrons . *A. baumannii* can present intrinsic chromosomal OXA-51-like, and four additional groups of OXA acquired carbapenemases, including OXA-23, 24 (OXA-40-like), -58-like, and -123-like **(39)**. OXA-23 has been associated with greater dissemination and production of carbapenem resistance with clinical consequences **(40)**.

It has been documented that OXA-24 has moderate hydrolytic activity against carbapenems **.**

2. Resistance to Polymyxins

Mechanisms of resistance to polymyxins in *A. baumannii* include (i) drug target alteration by LPS lipid A modification subsequent to mutations in the *pmrCAB* operon and *mcr* genes; (ii) mutations of *lpxA*, *lpxC*, and *lpxD* genes -encoding acyltransferases essential to lipid A biosynthesis and associated with lipid A deficiency; (iii) *lpsB*, *lptD*, and *vacJ* expression associated with permeability defects and osmotic resistance of the outer membrane, subsequently leading to markedly elevated MICs for polymyxins; (iv) insufficient concentration of cofactors constitutional for LPS formation, like biotin, which are essential for susceptibility to polymyxins; and (v) efflux pumps **(41)**.

3. Resistance to Aminoglycosides

Aminoglycoside resistance in *A. baumannii* has been associated with versatile mechanisms, enzymatic modification primarily through N-acetylation, O-nucleotidylation, or O-phosphorylation at different locations of the aminoglycoside molecule are considered the most significant one **(42)**.

However, in the last years other well-studied aminoglycosides resistance mechanism has been identified in *Acinetobacter* genus as antibiotic intracellular accumulation reduction using efflux pumps in synergy with the permeabilization of the outer membrane **(43)**.

4. Resistance to Tetracyclines

Tetracycline antibiotics bind to the 30S ribosomal subunit and thereby inhibit protein synthesis by deterring the start of translation **(44)**.

Resistance to tetracycline antibiotics is attributed to three main mechanisms: (i) efflux dependent on ATP, (ii) inactivation of tetracyclines by enzymes, and (iii) ribosomal protection proteins (RPPs) **(45)**.

5. Resistance to Tigecycline

Tigecycline is a third-generation tetracycline derivative, and the main difference between tetracycline and tigecycline is that ring D of tigecycline is linked to 7-dimethylamido and 9-t-butylglycylamido moieties. The main mechanisms of tigecycline resistance in *A. baumannii* can be divided into five categories:

I. Efflux pumps systems

Overexpression of efflux pumps is a key mechanism responsible for drug resistance in A. baumannii. Efflux pump excretes antimicrobial drugs from cells, which leads to the decrease of drug concentration and drug resistance **(46).**

II. Outer membrane permeability

To prevent the entry of antimicrobial agents into cells, reducing the permeability of the outer membrane is another common mechanism of resistance **(46).**

III. Antibiotic targets of action

Changing the target of antibiotic action is also one of the mechanisms by which bacteria develop resistance.

Bacteria prevent antibiotic binding by altering the target structure, thereby creating resistance **(47).**

IV. Antibiotic-inactivating enzyme

Resistance to antibiotics by degrading and modifying antibiotics to make them inactive is an important resistance mechanism for bacteria **(47).**

V. DNA repair pathway

It has been demonstrated that DNA damage under antibiotic induction can mediate the killing of *A. baumannii* **(48)**, and

recA and recBCD are important pathways for DNA repair.

References:

1. Penwell, W. F., Shapiro, A. B., Giacobbe, R. A., Gu, R. F., Gao, N., Thresher, J., ... & Miller, A. A. (2015). Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in Acinetobacter baumannii. Antimicrobial agents and chemotherapy, 59(3), 1680-1689.
2. Yonehara, R., Yamashita, E., & Nakagawa, A. (2016). Crystal structures of OprN and OprJ, outer membrane factors of multidrug tripartite efflux pumps of P seudomonas aeruginosa.
   Proteins: Structure, Function, and Bioinformatics, 84(6), 759-769.
3. Hassan, K. A., Jackson, S. M., Penesyan, A., Patching, S. G., Tetu, S. G., Eijkelkamp, B. A., ... & Paulsen, I. T. (2013). Transcriptomic and biochemical analyses identify a family of chlorhexidine efflux proteins. Proceedings of the National Academy of Sciences, 110(50), 20254-20259.
4. Chitsaz, M., & Brown, M. H. (2017). The role played by drug efflux pumps in bacterial multidrug resistance. Essays in biochemistry, 61(1), 127-139.
5. Allen, H. K., Donato, J., Wang, H. H., Cloud-Hansen, K. A., Davies, J., & Handelsman, J. (2010). Call of the wild: antibiotic resistance genes in natural environments. Nature reviews microbiology, 8(4), 251-259.
6. Angoti, G., Bandehpour, M., Goudarzi, H., Hajizadeh, M., Zarringhalam Moghaddam, M., & Kouchaki, A. (2016). Detection of efflux pump genes (adeA, adeB, adeC and abeM) in Acinetobacter baumannii isolated from hospitalize patients, North-west of Iran.
   Infection Epidemiology and Microbiology, 2(4), 8-11.
   Journal of clinical outcomes management: JCOM, 17(8), 363.
7. Yoon, E. J., Courvalin, P., & Grillot-Courvalin, C. (2013). RND-type efflux pumps in multidrug-resistant clinical isolates of Acinetobacter baumannii: major role for AdeABC overexpression and AdeRS mutations. Antimicrobial agents and chemotherapy, 57(7), 2989-2995.
8. Zarrilli, R., Pournaras, S., Giannouli, M., & Tsakris, A. (2013). Global evolution of multidrug-resistant Acinetobacter baumannii clonal lineages.
   International journal of antimicrobial agents, 41(1), 11-19.
9. Venter, H., Mowla, R., Ohene-Agyei, T., & Ma, S. (2015). RND-type drug efflux pumps from Gram-negative bacteria: molecular mechanism and inhibition. Frontiers in microbiology, 6, 377.
10. Sugawara, E., & Nikaido, H. (2014). Properties of AdeABC and AdeIJK efflux systems of Acinetobacter baumannii compared with those of the AcrAB-TolC system of Escherichia coli. Antimicrobial agents and chemotherapy, 58(12), 7250-7257.
11. Wright, G. D. (2011). Molecular mechanisms of antibiotic resistance. Chemical communications, 47(14), 4055-4061.
12. Dal, T., Aksu, B., Pagès, J. M., & Over-Hasdemir, U. (2013). Expression of the adeB gene and responsiveness to 1-(1-naphthylmethyl)-piperazine and phenylalanyl-arginyl-β-naphthylamide in clinical isolates of Acinetobacter baumannii. Journal of Antimicrobial Chemotherapy, 68(5), 1200-1202.
13. Chin, C. Y., Gregg, K. A., Napier, B. A., Ernst, R. K., & Weiss, D. S. (2015). A PmrB-regulated deacetylase required for lipid A modification and polymyxin resistance in Acinetobacter baumannii.
   Antimicrobial agents and chemotherapy, 59(12), 7911-7914.
14. Blair, J. M., Webber, M. A., Baylay, A. J., Ogbolu, D. O., & Piddock, L. J. (2015). Molecular mechanisms of antibiotic resistance. Nature reviews microbiology, 13(1), 42-51.
15. Asai, S., Umezawa, K., Iwashita, H., Ohshima, T., Ohashi, M., Sasaki, M., ... & Miyachi, H. (2014). An outbreak of bla OXA-51-like-and bla OXA-66-positive Acinetobacter baumannii ST208 in the emergency intensive care unit.
16. Blair, J. M., Richmond, G. E., & Piddock, L. J. (2014). Multidrug efflux pumps in Gram-negative bacteria and their role in antibiotic resistance.
   Future microbiology, 9(10), 1165-1177.

17. Schindler, B. D., Frempong-Manso, E., DeMarco, C. E., Kosmidis, C., Matta, V., Seo, S. M., & Kaatz, G. W. (2015). Analyses of multidrug efflux pump-like proteins encoded on the Staphylococcus aureus chromosome. Antimicrobial agents and chemotherapy, 59(1), 747-748.
18. Smani, Y., Fàbrega, A., Roca, I., Sánchez-Encinales, V., Vila, J., & Pachón, J. (2014). Role of OmpA in the multidrug resistance phenotype of Acinetobacter baumannii. Antimicrobial agents and chemotherapy, 58(3), 1806-1808.
19. Vargiu, A. V., Pos, K. M., Poole, K., & Nikaido, H. (2016). Bad bugs in the XXIst century: resistance mediated by multi-drug efflux pumps in Gram-negative bacteria. Frontiers in microbiology, 7, 833.
20. Du, D., Wang, Z., James, N. R., Voss, J. E., Klimont, E., Ohene-Agyei, T., ... & Luisi, B. F. (2014). Structure of the AcrAB–TolC multidrug efflux pump. Nature, 509(7501), 512-515.
21. Yan, N. (2013). Structural advances for the major facilitator superfamily (MFS) transporters. Trends in biochemical sciences, 38(3), 151-159.
22. Vilacoba, E., Almuzara, M., Gulone, L., Traglia, G. M., Figueroa, S. A., Sly, G., ... & Ramírez, M. S. (2013). Emergence and spread of plasmid-borne tet (B):: IS CR2 in minocycline-resistant Acinetobacter baumannii isolates. Antimicrobial agents and chemotherapy, 57(1), 651-654.
23. Wallace, L., Daugherty, S. C., Nagaraj, S., Johnson, J. K., Harris, A. D., & Rasko, D. A. (2016). Use of comparative genomics to characterize the diversity of Acinetobacter baumannii surveillance isolates in a health care institution. Antimicrobial agents and chemotherapy, 60(10), 5933-5941.
24. Yan, N. (2015). Structural biology of the major facilitator superfamily transporters. Annual review of biophysics, 44(1), 257-283.
25. Si, H., Zhang, W. J., Chu, S., Wang, X. M., Dai, L., Hua, X., ... & Liu, S. (2015). Novel plasmid-borne multidrug resistance gene cluster including lsa (E) from a linezolid-resistant Enterococcus faecium isolate of swine origin. Antimicrobial agents and chemotherapy, 59(11), 7113-7116.
26. Blanco, P., Hernando-Amado, S., Reales-Calderon, J. A., Corona, F., Lira, F., Alcalde-Rico, M., ... & Martinez, J. L. (2016). Bacterial multidrug efflux pumps: much more than antibiotic resistance determinants. Microorganisms, 4(1), 14.
27. Lin, M. F., Lin, Y. Y., Tu, C. C., & Lan, C. Y. (2017). Distribution of different efflux pump genes in clinical isolates of multidrug-resistant Acinetobacter baumannii and their correlation with antimicrobial resistance. Journal of Microbiology, Immunology and Infection, 50(2), 224-231.
28. Nie, L., Grell, E., Malviya, V. N., Xie, H., Wang, J., & Michel, H. (2016). Identification of the high-affinity substrate-binding site of the multidrug and toxic compound extrusion (MATE) family transporter from Pseudomonas stutzeri. Journal of Biological Chemistry, 291(30), 15503-15514.
29. Zhao, S. Y., Jiang, D. Y., Xu, P. C., Zhang, Y. K., Shi, H. F., Cao, H. L., & Wu, Q. (2015). An investigation of drug-resistant Acinetobacter baumannii infections in a comprehensive hospital of East China. Annals of clinical microbiology and antimicrobials, 14, 1-8.
30. Yang, Y.-S., Lee, Y., Tseng, K.-C., Huang, W.-C., Chuang, M.-F., Kuo, S.-C., Lauderdale, T.-L. Y., & Chen, T.-L. (2016). In vivo and in vitro efficacy of minocycline-based combination therapy for minocycline-resistant Acinetobacter baumannii. Antimicrobial agents and chemotherapy, 60(7), 4047-4054.
31. Temgoua, F. T. D., & Wu, L. (2018). Mechanisms efflux pumps of Acinetobacter baumannii (MDR): increasing resistance to antibiotics. Journal of Biosciences and Medicines, 7(1), 48-70.
32. Lewinson, O., & Livnat-Levanon, N. (2017). Mechanism of action of ABC importers: conservation, divergence, and physiological adaptations. Journal of molecular biology, 429(5), 606-619.
33. López, M., Álvarez-Fraga, L., Gato, E., Blasco, L., Poza, M., Fernández-García, L., ... & Tomás, M. (2016). Genome sequence of a clinical strain of Acinetobacter baumannii belonging to the ST79/PFGE-HUI-1 clone lacking the AdeABC (resistance-nodulation-cell division-type) efflux pump. Genome Announcements, 4(5), 10-1128.
34. Spengler, G., Kincses, A., Gajdács, M., & Amaral, L. (2017). New roads leading to old destinations: efflux pumps as targets to reverse multidrug resistance in bacteria. Molecules, 22(3), 468.

35. Jeon, J. H., Lee, J. H., Lee, J. J., Park, K. S., Karim, A. M., Lee, C. R., ... & Lee, S. H. (2015). Structural basis for carbapenem-hydrolyzing mechanisms of carbapenemases conferring antibiotic resistance. International journal of molecular sciences, 16(5), 9654-9692.
36. Rumbo, C., Gato, E., López, M., Ruiz de Alegría, C., Fernández-Cuenca, F., Martínez-Martínez, L., ... & Tomás, M. (2013). Contribution of efflux pumps, porins, and β-lactamases to multidrug resistance in clinical isolates of Acinetobacter baumannii.
Antimicrobial agents and chemotherapy, 57(11), 5247-5257.
37. Adams-Haduch, J. M., Paterson, D. L., Sidjabat, H. E., Pasculle, A. W., Potoski, B. A., Muto, C. A., ... & Doi, Y. (2008). Genetic basis of multidrug resistance in Acinetobacter baumannii clinical isolates at a tertiary medical center in Pennsylvania. Antimicrobial agents and chemotherapy, 52(11), 3837-3843.
38. Perez, F., Hujer, A. M., Hujer, K. M., Decker, B. K., Rather, P. N., & Bonomo, R. A. (2007). Global challenge of multidrug-resistant Acinetobacter baumannii.
Antimicrobial agents and chemotherapy, 51(10), 3471-3484.
39. Higgins, P. G., Pérez-Llarena, F. J., Zander, E., Fernández, A., Bou, G., & Seifert, H. (2013). OXA-235, a novel class D β-lactamase involved in resistance to carbapenems in Acinetobacter baumannii. Antimicrobial agents and chemotherapy, 57(5), 2121-2126.
40. Mugnier, P. D., Poirel, L., Naas, T., & Nordmann, P. (2010). Worldwide dissemination of the blaOXA-23 Carbapenemase gene of Acinetobacter baumannii1. Emerging infectious diseases, 16(1), 35.
41. Moffatt, J. H., Harper, M., & Boyce, J. D. (2019). Mechanisms of polymyxin resistance. Polymyxin antibiotics: From laboratory bench to bedside, 55-71.
42. Niederman, M. S., & Kollef, M. H. (2015). The road forward in the management of Acinetobacter infections in the ICU. Intensive care medicine, 41, 2207-2209.
43. Neidell, M. J., Cohen, B., Furuya, Y., Hill, J., Jeon, C. Y., Glied, S., & Larson, E. L. (2012). Costs of healthcare- and community-associated infections with antimicrobial-resistant versus antimicrobial-susceptible organisms. Clinical Infectious Diseases, 55(6), 807-815.
44. Chukwudi, C. U. (2016). rRNA binding sites and the molecular mechanism of action of the tetracyclines. Antimicrobial agents and chemotherapy, 60(8), 4433-4441.
45. Warburton, P. J., Amodeo, N., & Roberts, A. P. (2016). Mosaic tetracycline resistance genes encoding ribosomal protection proteins.
Journal of Antimicrobial Chemotherapy, 71(12), 3333-3339.
46. Meyer, C., Lucaβen, K., Gerson, S., Xanthopoulou, K., Wille, T., Seifert, H., & Higgins, P. G. (2022). Contribution of RND-type efflux pumps in reduced susceptibility to biocides in Acinetobacter baumannii. Antibiotics, 11(11), 1635.
47. Sun, C., Yu, Y., & Hua, X. (2023). Resistance mechanisms of tigecycline in Acinetobacter baumannii. Frontiers in Cellular and Infection Microbiology, 13, 1141490.
48. Sampson, T. R., Liu, X., Schroeder, M. R., Kraft, C. S., Burd, E. M., & Weiss, D. S. (2012). Rapid killing of Acinetobacter baumannii by polymyxins is mediated by a hydroxyl radical death pathway. Antimicrobial agents and chemotherapy, 56(11), 5642-5649.