Genetically Divert Carbapenemase-resistant *Acinetobacter baumannii*: Better to be Safe than Sorry

Acinetobacter baumannii is a nightmarish organism to be encountered if a patient is admitted to a critical care unit, especially the intensive care unit (ICU), burn, and other units. A part of the ESKAPE group, it needs special mention. Apart from the ability to cause debilitating infections, its becoming a cause for concern due to the increasing incidence of antibiotic resistance.[1] Additionally, organisms are intrinsically resistant to a large number of antibiotics and very few antibiotics available for treatment. The clonal spread of resistance factors contributes to a significant factor in a healthcare setting, making it very challenging to deal with and control.[2]

Carbapenem is almost the last group of reliable and highest group of antibiotics used to deal with multidrug-resistant *A. baumannii.* However, during the last decade, an increase in resistance to these groups has made it very difficult to deal with these infections.[3] In the recently published World Health Organization priority pathogens 2024, carbapenemase-resistant *A. baumannii* (CRAB) has been placed in the critical group along with carbapenem-resistant Enterobacterales and third-generation cephalosporin-resistant Enterobacterales signifying its importance.[4]

Carbapenem resistance in bacteria can be multifactorial and often not possible to characterize in a diagnostic laboratory as it can be multifactorial, and diagnosing all factors can be labor-intensive and time-consuming.[5] Carbapenems are considered antibiotics of choice for treating *A. baumannii* infections; however, in some settings, the prevalence of CRAB can be as high as 40%. This leaves the patient vulnerable, and there is no option but to use higher-reserve drugs.[6]

Development of antimicrobial resistance among any organisms, including bacteria, viruses, fungi, or parasites, can be temporary and/or permanent. It modified the organism structurally as well as genetically. Gram-negative bacteria, including *A. baumannii* have developed β-lactamases production due to various genes. Detection of the genes can give the impression regarding the structural variation of the bacteria. However, in some cases, diagnosing the genes can be very productive as it can positively be decisive in selecting antibiotics. Hence, in recent years, a lot of molecular platforms have opened up that help in diagnosing these genes and have positively impacted patient outcomes.[7]

As per widely used ambler classification, there are four classes (A, B, C, and D) prepared on the base of amino acid sequences. Most commonly, the carbapenem resistance is mediated by Class D carbapenemases such as bla_{oxa-23}, bla_{oxa-40}, $bla_{oxa-58,}$ $bla_{oxa-143,}$ and $bla_{oxa-258}$. It can also be resistant due to the presence of Class B β-lactamases such as *NDM*, *VIM*, *SIM*, and *IMP*.[8]

Apart from mobile genetic elements, *A. baumannii* can get carbapenem resistance by biofilm formation, enzymatic degradation of antibiotics, target site modification, altered membrane permeability, and multidrug efflux pumps.[5,9] *A. baumannii* has at least two intrinsic or naturally acting β-lactamases, an *AmpC* type of cephalosporinases, and a $bla_{oxa-51/69}$. The *AmpC* type only becomes relevant clinically when an insertion sequence *ISAba1* is inserted upstream of $bla_{ampc.}$ This results in resistance to ceftazidime but spares carbapenems.[10] Two groups of enzymes specially can be acquired and can cause carbapenem resistance. Class B (Ambler) carbapenemases also called as metallo-β-lactamases and Class D oxacillinases. Oxacillinases can hydrolyze imipenem (spares meropenem).[8] Various virulence factor-producing drug-resistant genes and their targeting antibiotic agents are summarized in Table 1.[11]

Currently, CRAB is found in hospital environments. ICU and ward-admitted patients have a higher chance of getting an infection from the environment. The isolation of the CRAB is one of the most commonly carbapenemase-resistant Gram-negative bacteria.[10] However, isolation of the CRAB confirms the presence of the bacteria, not the indication of the infection to treat. Clinical presentation of the infection can be supportive to establish it as an infection that needs to be treated. If there is no clinical manifestation, it may be contamination and must be ruled out before treatment initiation. Many a time, removal of the infection source such as a catheter, central line, endotracheal tube, or ventilator-type medical device, becomes effective, and treatment is not required.[12] Colonization of CRAB on invasive medical devices contaminates the specimen during the collection. While treating a case of CRAB, it should be established that the infection is true and not colonization.

Ampicillin–sulbactam is very promising in treatment. Combination therapy should be the norm and should include high-dose ampicillin–sulbactam combined with another active agent such as high-dose tigecycline, polymyxins, or one of the other newer agents (cefiderocol and eravacycline). Polymyxin B and polymyxin E have very good *in vitro* activity with CRAB. Colistin (polymyxin E) has been used in bacteremia, meningitis, and pneumonia. Ideally, it should be used in combination with other active agents for more efficacy and to reduce the rapid development of resistance.[13]

Minocycline, when used in combination with other agents, also has good efficacy against CRAB. Minocycline is

Table 1: Virulence factor producing drug-resistant genes for *Acinetobacter baumannii*[11]

AMR gene family	Specific genes	Drug class
ADC β-lactamase without carbapenemase activity	*ADC−30; ADC−32; ADC−95; ADC−76; ADC−247; ADC−73; ADC−186; ADC−181; ADC−241*	Cephalosporin
ANT (3'')	*APH (3'')-Ib; ANT (3'')-IIc; APH (6)-Id; AAC (3)-IId; APH (3')-Ia; APH (3')-VIa; AAC (6')-Ian; AAC (6')-Ib9*	Aminoglycoside
CARB β-lactamase	*qacE; delta1; qacG*	Disinfecting agents and antiseptics
Fluoroquinolone-resistant parC; fluoroquinolone-resistant gyrA	*AbaQ; aadA; parC; gyrA*	Fluoroquinolone
Intrinsic peptide antibiotic-resistant	*LpsB*	Peptide
MPH	*mphE*	Macrolide
MFS-type efflux pump	*AmvA*	Disinfecting agents and antiseptics Macrolide
	AbaF	Phosphonic acid
	CARB−3	Penam
	catB8; cmlA5	Phenicol
	tet (B); tetR	Tetracycline
Msr-type ABC-F protein	*msrE*	Macrolide Streptogramin
NDM β-lactamase	*NDM−1*	Carbapenem Cephalosporin Cephamycin Penam
OXA β-lactamase	*OXA−23; OXA−66; OXA−58; OXA−64; OXA−104; OXA−68; OXA−65; OXA−106; OXA−144; OXA−259; OXA−371; OXA−422*	Carbapenem Cephalosporin Penam
PER β-lactamase	*PER−7*	Carbapenem Cephalosporin Monobactam Penam
Rifampin ADP-ribosyltransferase (Arr)	*arr−2*	Rifamycin
RND-type efflux pump	*adeF; adeG; adeH; adeL*	Fluoroquinolone Tetracycline
	adeA; adeC; sdeR; adeN	Glycylcycline Tetracycline
	adeI; adeJ; adeK	Carbapenem Cephalosporin Diaminopyrimidine Fluoroquinolone Lincosamide Macrolide Penem Phenicol Rifamycin Tetracycline
SMR-type efflux pump	*abeS*	Aminocoumarin Macrolide
Sulfonamide resistant	*sul1; sul2*	Sulfonamide
TEM β-lactamase	*TEM−1*	Cephalosporin Monobactam Penam

MPH: Macrolide phosphotransferase

a broad-spectrum tetracycline antibiotic that works by attaching to the 30S ribosomal subunit to limit protein synthesis in bacteria. A high dose of tigecycline has shown great efficacy, especially for pulmonary infections. It has a longer half-life and greater tissue absorption into the cerebrospinal fluid and central nervous system than other first-generation tetracycline. Several studies show that microbiologically (*in vitro*), CRAB isolates are still susceptible to minocycline and clinically *(in vivo)* effective in patients.[14]

CRAB, therapy for infections has become very challenging. Careful considerations have to be made while attending to a case of Acinetobacter baumannii. Cefideroco (Siderophore cephalosporin) with sulbactam–durlobactam (β-lactam/β-lactamase inhibitor combination) are recently added as new agents for CRAB and are very promising. Even in increasing situation of CRAB prevalence, Zosurabalpin (which targets LPS transport), and macolacin (a polymyxin) are also very much hopeful. Antibiotic adjuvants and bacteriophages can also be a valid alternative to currently used antibiotics.[14]

Genetic diversity of the genes for CRAB is seen region-wise. Carbapenem-resistant gene detection for the organism helps in suggestive treatment.[11,15-18] Isolation of a similar CRAB strain from different places indicates either the same source of the infection or a similar process of resistant gene development in CRAB. Newer β Lactam/β Lactamases inhibitors like sulbactam–durlobactam, Minocycline, or Polymyxins can be used to treat the CRAB infection. Ruling out contamination and colonization before the initiation of treatment is necessary.

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