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Review Article

Overview of β-Lactam-Resistance Genes in Pandemic Multidrug-Resistant *Acinetobacter baumannii*: A Troublesome Pathogen in the Indian Intensive Care Unit

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ABSTRACT

Objectives: *Acinetobacter baumannii* is responsible for many infections in admitted patients, especially in the intensive care unit (ICU). Several risk factors may lead to an enhanced risk of *A. baumannii* colonization and infections. β-lactam antibiotics are frequently administered to treat Gram-positive and Gram-negative bacterial infections due to their minimum side effects, but the acquisition of β-lactamase genes has been the most challenging and troublesome situation and an imminent threat to the world as it increases mortality, medical expenses, and hospital stays. Hence, the present systematic review focused on the screening of β-lactam resistance genes that have been identified in the *A. baumannii* isolates' genome and the nosocomial infections they cause in the Indian ICU.

Material and Methods: This review has been done according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline 2020. After screening, 317 genomes were included in this systematic review. We downloaded data from the bv-brc.org website on an Excel spreadsheet for statistical analysis. We presented categorical data in percentages (%) and in the form of a graph and pie chart.

Results: Among the 317 isolates, pneumonia was caused by 189 strains (59.62%), bacteremia was caused by 109 strains (34.38%), respiratory infection by 12 isolates (3.79%), sepsis by 5 isolates (1.58%), and wound infection by 2 isolates (0.63%), which indicated that *A. baumannii* strains are highly involved in pneumonia followed by bacteremia. We did comparative genome analysis and found 26 β-lactamase genes; among them, the *ADC2* gene was found to be in higher frequency (312) and was identified in 98.42% of *A. baumannii* isolates, followed by the *OXA23* gene (303), which was found in 95.58% of isolates. The *NDM-1* gene was identified in 181 (57.09%) isolates. *OXA66* was found in 156 (49.21%) isolates. Our findings show a higher frequency of the *ADC2* gene, followed by the *OXA23* gene, in all these nosocomial infections. We have found that *NDM-1, ADC2, OXA23,* and *OXA-66* genes coexisted in higher frequency in the *A. baumannii* isolates (137; 43.21%), followed by *OXA23, OXA-66,* and *ADC2* (52; 16.40%).

Conclusion: *A. baumannii* is a notorious pandemic pathogen, designated as a "priority of concern" by the World Health Organization. Our study indicates a high prevalence of the *ADC2* gene, which gives resistance against the cephalosporin group and co-existence of β-lactamase genes (*ADC2, OXA23, OXA66*, and *NDM-1*) in various *A. baumannii* isolates' genomes. This is a worrisome situation. Global molecular surveillance and the "One Health Concept" are crucial, as are research studies on plant extracts' *in vitro* and *in vivo* efficacy against *A. baumannii.* Combating multidrug-resistant *A. baumannii* requires a multifaceted approach that involves infection control measures, antimicrobial stewardship, surveillance, education, research, and collaboration. Implementing these strategies and staying vigilant in the face of this resilient pathogen is essential to minimize its impact on health-care systems and public health.

Keywords: Acinetobacter, Antibiotic resistance, Beta-lactamase, Nosocomial infection

INTRODUCTION

Acinetobacter baumannii is a Gram-negative, catalase-positive, and oxidase-negative non-fermenting coccobacillus, and it belongs to the *Moraxellaceae* family. It is responsible for many infections in the admitted patients, especially in the intensive care unit (ICU). The infections caused by this notorious pathogen are "Hospital-acquired and ventilator-associated pneumonia, urinary tract infections, bacteremia, skin and soft-tissue infections, and meningitis."[1-6] Its incidence in ICUs worldwide is up to 31%, and coinfection with SARS-CoV2 has been reported between 1 and 12.5%.[7-9]

Several risk factors may lead to an enhanced risk of *A. baumannii* colonization and infection. These include coexistent morbidities, prematurity in newborns, old age, major trauma, immunosuppressed conditions, major surgery, mechanical ventilation, presence of indwelling devices, extended hospital stay, and prior exposure to broad-spectrum antibiotics, for example, β-lactam antibiotics (Ampicillin, carbapenems, third-generation cephalosporins, and β-lactam + β-lactamase inhibitors), fluoroquinolones, aminoglycosides, etc. While attempting to overcome resistance, new broad-spectrum antimicrobials have fewer therapeutic alternatives.[10,11]

A. baumannii can develop antibiotic resistance through various mechanisms, including changing the antibiotic's target area, managing how antibiotics penetrate its cell membrane, and enzyme-driven alterations of the antibiotics, making them ineffective. Beyond these typically genetically driven factors, *A. baumannii* can enhance its resistance using methods associated with its ability to cause disease. These include modifications in its outer cell protective layers, the uniqueness of the enzymes it produces, quorum sensing, and biofilms. It can achieve specific movement called twitching motility using hair-like structures (type IV pili) and has systems to obtain essential micronutrients. Furthermore, it employs specialized protein delivery methods and type II and VI secretion systems.[12,13]

While attempting to overcome resistance, new broad-spectrum antimicrobials have fewer therapeutic alternatives. Due to their limited side effects, β-lactam antibiotics are frequently administered to treat Gram-positive and Gram-negative bacterial infections. The β-lactam antibiotics exert their antibacterial activity by impeding the formation of the bacterial cell wall and have an enormously beneficial effect on managing life-threatening bacterial infections. However, they can be broken down by *A. baumannii through several methods*, including drug efflux pumps, drug target alterations, reduced membrane permeability, and the production of hydrolyzing enzymes. The acquisition of β-lactamase genes has been the most challenging and troublesome situation and an imminent threat to the world as it increases mortality, medical expenses, and hospital stays.[14]

Hence, the present systematic review focused on the screening of β-lactam resistance genes that have been identified in the genomes of *A. baumannii* isolates' genome and nosocomial infections they cause in the Indian ICU.

MATERIAL AND METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline 2020 for this systematic review.[15] We have used the Bacterial and Viral Bioinformatic Resource Center (bv-brc.org) website for analysis of β-lactam resistance genes in *A. baumannii* isolates' genome that have been collected and submitted from various parts of India. Their accession numbers are available on NCBI.[16] All the isolates are divided according to nosocomial infections they cause(bacteremia, pneumonia, other respiratory infections, sepsis, and wound infection) for genotypic analysis. For statistical analysis, we collected data on a Microsoft Excel spread-sheet. We presented categorical data in percentages (%) and in the form of graphs and pie charts.

RESULTS

Following the PRISMA guidelines 2020, we identified 14,474 genomes on the bv-brc.org website. By applying filters for "India," "only human host," "complete genome," and "good quality," we ultimately selected 317 *A. baumannii* isolates' genomes for our β-lactam resistance gene analysis [Figure 1].

Genome sequencing was done using various platforms, such as Illumina HiSec, Ion torrent, PacBio, and Oxford Nanopore MiniIon, and various assembly methods were used in these Bio projects such as SPAdes v. 5, SPAdes 3.14.1, Canu v.v 1.6, Canu v.v 1.7, UniCycler v.0.4.6, and UniCycler v.0.4.8. Typing was done through multilocus sequence typing. Data were then downloaded from bv-brc.org onto an Excel spreadsheet for further analysis. The mean coding sequence was 3900. The average genome size was found to be 3,995,080 bp. The maximum genome size was found in *A. baumannii* SP 1917, which harbors the *AmpC* gene and is involved in pneumonia whereas *A. baumannii* strain SP25 had a minimum genome size of 3,620,806 bp. *A. baumannii* strain VB958 contained the maximum number of transfer RNA (tRNA) (76) whereas the minimum number (25) of tRNA was found in *A. baumannii* BA22708. The average G + C% content of all *A. baumannii* isolates was 38.54%.

Descriptive statistics analysis

We divided the total 317 *A. baumannii* isolates into five groups according to the infections they caused, which were bacteremia, pneumonia, other respiratory infections, sepsis, and wound infection. Among 317 isolates, pneumonia was

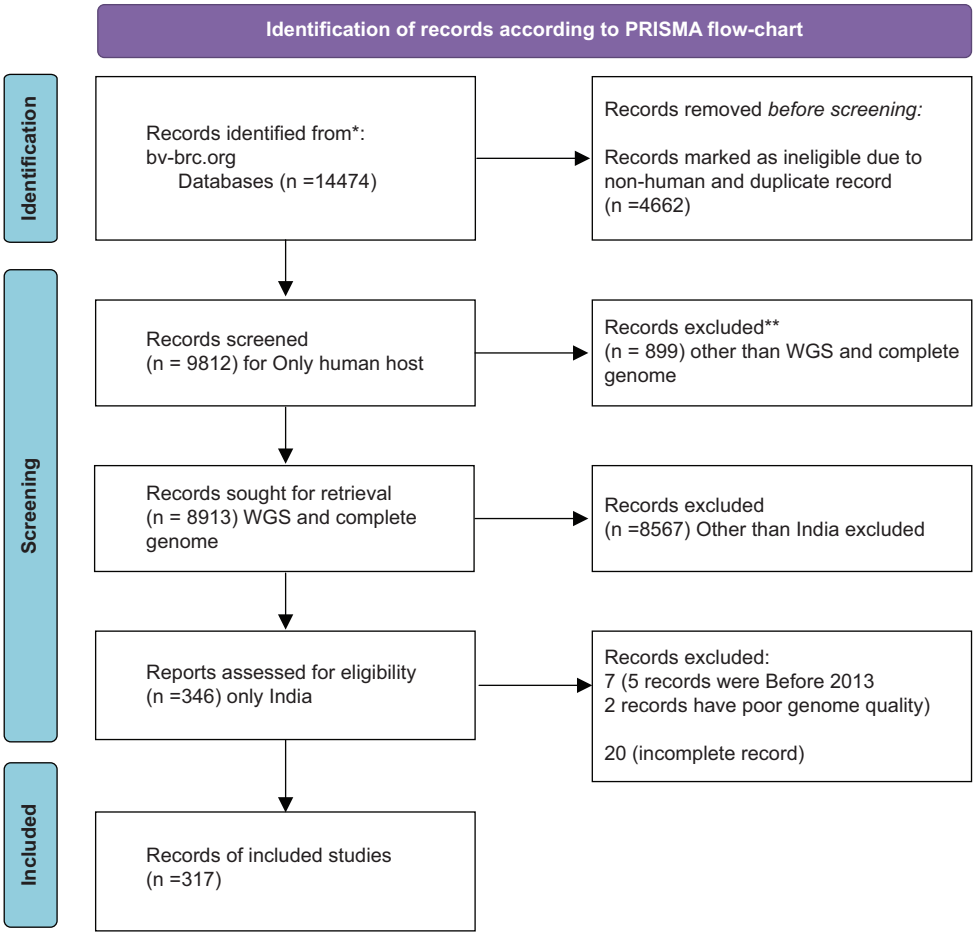

Figure 1: Identification of records according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow-chart 2020.

caused by 189 strains (59.62%), bacteremia by 109 strains (34.38%), respiratory infection by 12 isolates (3.79%), sepsis by 5 isolates (1.58%), and wound infection by 2 isolates (0.63%). This indicated that *A. baumannii* strains are highly involved in pneumonia, followed by bacteremia [Table 1 and Figure 2].

Effect of β-lactam resistance genes in host's health

We identified a total of 26 β-lactam resistance genes in the various *A. baumannii* isolates' genomes, which are given in Tables 2 and 3, Figure 3. Mostly, these genes are found to be involved in pneumonia (mean score 24.19 ± 53.83 standard deviation [SD]) followed by bacteremia (mean score 15.57 ± 32.17 SD).

Among 26 β-lactamase genes, the *ADC2* gene was found to be more frequent (312) and was identified in 98.42% of *A. baumannii* isolates, followed by *OXA23* gene (303), which was found in 95.58% isolates. *NDM-1* gene was identified in 181 (57.09%) isolates. *OXA66* was found in 156 (49.21%) isolates.

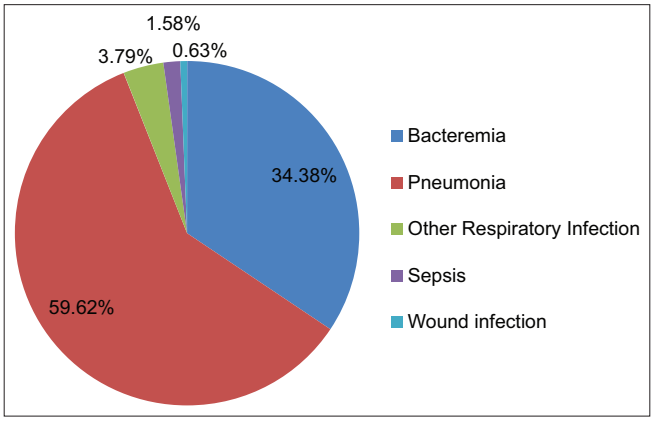

Figure 2: Graphical representation of host health and *Acinetobacter baumannii* isolates (%).

We did a comparative genome analysis and found that among all the other β-lactam resistance genes, the *ADC2* gene, followed by the *OXA23* gene, was highly involved in pneumonia, followed by bacteremia among other infections. Our findings show a higher frequency of the *ADC2* gene,

Table 1: Host health and *A. baumannii* isolates' proportion identified in comparative genome analysis.

Variable	Level	Total no. of isolates	Count	Proportion	*P*-value
Host health	Bacteremia	317	109	0.34	<0.001
	Pneumonia	317	189	**0.596**	<0.001
	Other respiratory infection	317	12	0.038	<0.001
	Sepsis	317	5	0.016	<0.001
	Wound infection	317	2	0.006	<0.001

n=317 *Acinetobacter baumannii* isolates, Confidence level 95%, Bold value indicates higher value of Proportion

Table 2: Coexistence of β-lactamase genes found by comparative genome analysis in various *Acinetobacter baumannii isolates*.

Gene group	Total no. of isolates
OXA23, OXA144, NDM1, ADC2	2
OXA208, ADC2	1
OXA23, OXA104, ADC2	3
OXA23, OXA104, PER7, ADC2	4
OXA23, OXA104, PER7, NDM1, ADC2	11
OXA23, OXA144, PER7, CARB3, ADC2	1
OXA23, OXA180, OXAADC2	1
OXA23, OXA27, OXA49, NDM1, ADC2	1
OXA23, OXA27, OXA68, PER7	1
OXA23, OXA371, ADC2	1
OXA23, OXA371, NDM1, ADC2	3
OXA23, OXA49, OXA66, NDM1, ADC2	1
OXA23, OXA49, OXA64, ADC2, PER7	1
OXA23, OXA49, OXA66, ADC2	1
OXA23, OXA58, OXA68, PER7, ADC2	1
OXA23, OXA64, ADC2	4
OXA23, OXA64, PER7, ADC2	8
OXA23, OXA66, OXA98, NDM1, ADC2	2
OXA23, OXA66, ADC2	52
OXA23, OXA66, ADC2, PER7	16
OXA23, OXA66, ADC2, TEM1	25
OXA23, OXA66, NDM1, ADC2	137
OXA23, OXA66, NDM1, TEM1	1
OXA23, OXA68, OXA420, ADC2, CARB1, PER7	1
OXA23, OXA68, ADC2	1
OXA23, OXA68, NDM1, ADC2	4
OXA23, OXA68, PER7, ADC2	3
OXA23, OXA69, NDM1, ADC2	13
OXA23, OXA70, ADC2	1
OXA23, OXA98, ADC2, NDM1	2
OXA33, ADC2	1
OXA33, AmpC	1
OXA371, NDM1, ADC2	1
OXA58, OXA64, CARB1, NDM1, ADC2	2
OXA67, ADC2	2
OXA68, OXA23, NDM1, ADC2	1
OXA68, PER7, ADC2	2
OXA98, ADC2	2
AmpC	1
PER1, AmpC	1

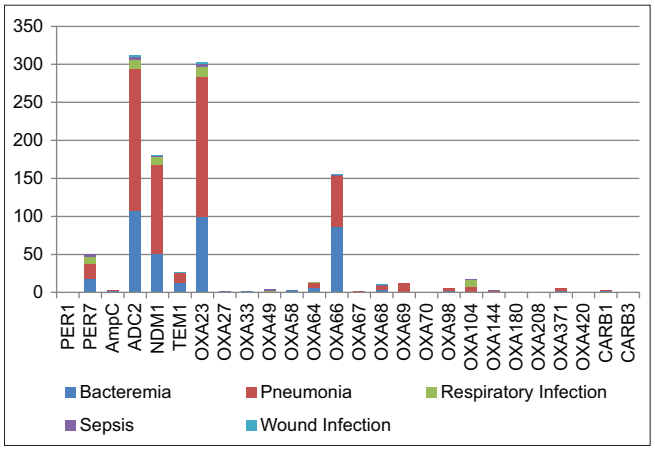

Figure 3: β-lactam resistant genes that have been identified in various *Acinetobacter baumannii* isolates' genome.

followed by the *OXA23* gene, in all nosocomial infections. We found that *NDM-1, ADC2, OXA23,* and *OXA-66* genes coexisted in higher frequency in the *A. baumannii* isolates (137; 43.21%), followed by *OXA23, OXA-66,* and *ADC2* gene (52; 16.40%).

In 95 (69.34%) out of 137 *A. baumannii* isolates, the *OXA23, OXA-66, NDM-1,* and *ADC2* genes are jointly involved in pneumonia, and in 41 isolates (30%), they are found to be associated with bacteremia, and only one isolate caused other respiratory infection. In 31 (59.61%) out of 52 *A. baumannii* strains, *OXA23, OXA-66,* and *ADC2* coexisting genes were involved in pneumonia, and 21 strains (40.38%) caused bacteremia.

DISCUSSION

A. baumannii, a notorious pathogen known for causing most hospital-acquired infections, is becoming more menacing. Known for its unmatchable virulence and pathogenicity, it has become a consistent and prominent concern for intensivists and infectious diseases specialists.[17,18] *A. baumannii* has acquired the capability to cause untreatable infections gradually through various mechanisms such as efflux pumps, reduction or inactivation of expression of porins, modification in expression or synthesis of new penicillin-

Table 3: Frequency of β-lactam resistance genes in various diseases.

Genes	Bacteremia	Pneumonia	Other respiratory infection	Sepsis	Wound infection	Total
ADC2	107	187	12	4	2	312
NDM-1	51	117	10	2	1	181
TEM-1	13	12			1	26
AmpC	2	1				3
PER1	1					1
PER7	18	19	10	3		50
CARB1	2	1				3
CARB3				1		1
OXA23	100	184	12	5	2	303
OXA27				2		2
OXA33	2					2
OXA49	1		1	2		4
OXA58	3					3
OXA64	6	7	1			14
OXA66	87	66	1	1	1	156
OXA67		2				2
OXA68	3	6		1	1	11
OXA69	1	11				12
OXA70	1					1
OXA98	2	4				6
OXA104	1	7	9	1		18
OXA144	1	1		1		3
OXA180			1			1
OXA208		1				1
OXA371	2	3				5
OXA420	1					1

binding proteins and presence of β-lactamases.[11,14,19] Among these, the presence of β-lactamases is the most prominent and p seriously threatens mankind. Based on sequence homology, β-lactamases are grouped into molecular classes A, B, C, and D.[20,21] All four classes of β-lactamases have been identified in *A. baumannii*.[20]

Class A beta-lactamases are classified as serine beta-lactamases due to the presence of Serine in the enzyme's active site. The most prevalent Class A beta-lactamases are *TEM* and *SHV*. Our study found *TEM-1* in 26 isolates, with 13 involved in bacteremia, 12 in pneumonia, and 1 in wound infection. *A. baumannii* often possesses plasmids that encode extended-spectrum beta-lactamases, along with resistance to other antimicrobials (e.g., narrow-spectrum cephalosporin), including aminoglycosides and fluoroquinolones. Shali *et al*., in 2022, found that all *A. baumannii* isolates collected from burn patients exhibited *TEM-1*, giving resistance against penicillin and cephalosporin classes.[22]

Class B Metallo β-lactamases differ from other classes by being Metallo-lactamases as opposed to other classes, which are serine β-lactamases. As a result, these enzymes require metallic ions to act, namely Zn^{2+}. They are further divided into B1, B2, and B3, depending on the number of Zn^{2+} ions being utilized. The most notorious enzyme in this class is *NDM-1* (New Delhi *Metallo* β lactamases, first isolated from a urine sample in *New Delhi*).

In our comparative genome analysis, we identified the *NDM-1* gene in 181(57.09%) isolates, whereas Sharma *et al*., 2023 found that out of 317 isolates, 189 (59.62%) were harboring the *NDM-1* gene.[23] The strains producing other variants, such as *NDM-2, NDM-5, NDM-6,* or *NDM-42*, have been sporadically reported.[24-28]

Various other enzymes, such as *NDM* (over 24 subtypes), *IMP, GMP,* and *VIM*, have been identified in this class. The action of Tn125 likely facilitates the acquisition of the NDM-1 gene. The presence of integron 1 is the main driving force behind bacteria acquiring this enzyme, which also confers the property of other antibiotic resistance, namely, aminoglycosides. Since integron 1 is located over plasmids, which are easily transferred horizontally, widespread dissemination is their hallmark. This has been seen in other bacteria as well. Even with the chelation of heavy metal ions, NDM does not lose its potency as it is anchored to the outer membrane protein, which prevents its destabilization. *blaNDM-1* is typically linked to several genetic determinants that indicate resistance to a wide range of antibiotics, leaving only last-resort antibiotics – which are usually employed in combination therapies – as a viable treatment option.[29]

Class C β-lactamases comprise mainly *Acinetobacter* derived cephalosporinases (ADCs), which are intrinsic to this bacterium. The presence of *ISAba1* causes overexpression of *AmpC*, which belongs to the same family of Class C β-lactamases.[30] They usually confer resistance to β-lactam inhibitors but are inhibited by cloxacillin or boronic acid. Rao *et al.* (2020) found out the *ADC* gene in all *A. baumannii* isolates, whereas in our systematic review, we identified the *ADC2* gene in 98.42% of isolates.[31] No further research work has been done on the *ADC2* gene in India, yet according to our comparative analysis, it has been found in almost all *A. baumannii* isolates.

Class D β-lactamases, also called oxacillinases (OXAs) as they hydrolyze oxacillin better than benzylpenicillin, are usually plasmid-mediated. Since the 1980s, more than 400 types of OXAs have been identified, such as *OXA-23, OXA-24/40, OXA-58, OXA-143,* and *OXA-235*.[32] The *bla* gene, almost in all its subtypes, is preceded by an IS element, ISAba1 or ISAba4, which leads to its overexpression, hence is the prime reason for its dissemination throughout the globe.

We have depicted in our previous article that OXA23 *(*314; 92.62%) followed by OXA66 *(*241; 71.09%) has a higher frequency in *A. baumannii* isolates,[10] and more research work is required on this c*lass* D enzymes due to its weak hydrolysis activity. Researchers neglected this class and only focused their work on other virulent carbapenemase. In our present study, we identified the *OXA23* gene in 95.58% isolates' genome. Kumar *et al.* (2019)found a high prevalence of *OXA23* genes (97.7%) in *A. baumannii* isolates.[28]

CONCLUSION

A. baumannii is a notorious pandemic pathogen designated as a "priority of concern" by the World Health Organization. Our study indicates a high prevalence of the *ADC2* gene, which gives resistance against the cephalosporin group and co-existence of β-lactamase genes (*ADC2, OXA23, OXA66*, and *NDM-1*) in various *A. baumannii* isolates' genomes, which is a problematic situation. Global molecular surveillance and the "One Health Concept" are crucial, as is research on plant extracts *in vitro* and *in vivo* efficacy against *A. baumannii.* Combating multidrug-resistant *A. baumannii* requires a multifaceted approach that involves infection control measures, antimicrobial stewardship, surveillance, education, research, and collaboration. Implementing these strategies and staying vigilant in the face of this resilient pathogen is essential to minimize its impact on healthcare systems and public health.

Author contribution

All the authors contributed equally.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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