Rapidly disseminating \( \text{bla}_{\text{OXA-232}} \) carrying \textit{Klebsiella pneumoniae} belonging to ST231 in India: multiple and varied mobile genetic elements

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Abstract

\textbf{Background:} Recently, in India, there has been a shift from NDM to OXA48-like carbapenemases. OXA-181 and OXA-232 are the frequently produced variants of OXA48-like carbapenemases. OXA48-like carbapenemases are also known to be carried on transposons such as Tn1999, Tn1999.2 and it is also associated with IS1R carried on Tn1999. In India, there are no previous reports studying the association of mobile genetic elements (MGEs) with OXA48-like carbapenemases. The present study was aimed at determining the genetic backbone of OXA48-like carbapenemases to determine the role of MGEs in its transfer and to investigate the Inc plasmid type carrying \( \text{bla}_{\text{OXA48-like}} \).

\textbf{Results:} A total of 49 carbapenem resistant \textit{K. pneumoniae} which included 25 isolates from South India and 24 isolates from North India, were included in the study. Whole genome sequencing using Ion Torrent PGM was performed to study the isolates. OXA-232 was present in 35 isolates (71%). In 19 isolates (39%), \( \text{bla}_{\text{OXA48-like}} \) was associated with MGEs. Insertion sequences such as ISX4, IS1, IS3, ISKpn1, ISKpn26, ISKpn25, ISSpu2, ISKox1, IS4321R, ISEC36, and ISPa38; and transposons such as TnAs3 and Tn2, were present. Isolates from northern and southern India belonging to same sequence type (ST) had diverse genetic backbone for \( \text{bla}_{\text{OXA48-like}} \). ST14 isolates from north had IS5 and Tn3 families while from south they had IS1, IS5 and IS630 families. ST231 from north had IS5, IS6 and Tn3 families with \( \text{bla}_{\text{OXA-232}} \) while from south, IS1, IS3 and IS5 families were observed; with ISKpn26 being present among isolates from both the regions. \( \text{bla}_{\text{OXA48-like}} \) was predominantly found on ColKP3 plasmid. ST231 was the predominant ST in 22 isolates (45%).

\textbf{Conclusion:} OXA-232 is the predominant variant of OXA48-like carbapenemase with ST231 being the commonest ST of OXA48-like carbapenemase producing \textit{K. pneumoniae} in India. Diverse MGEs have been associated with both \( \text{bla}_{\text{OXA-232}} \) and \( \text{bla}_{\text{OXA-181}} \) which contribute to their spread. The MGEs in the present study are different from those reported earlier. There is no clonal expansion of \( \text{bla}_{\text{OXA48-like}} \) producing \textit{K. pneumoniae} since diverse STs were observed. Monitoring the genetic backbone of OXA48-like carbapenemase is essential to better understand the transmission dynamics of XDR \textit{K. pneumoniae}.

\textbf{Keywords:} \textit{K. pneumoniae}, \( \text{bla}_{\text{OXA-232}} \), ST231, India, Insertion sequences, Transposons

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Background
OXA carbapenemases are oxacillinases which hydrolyse isoxazolylpenicillins. They have been divided into 12 groups based on amino acid sequences. OXA48-like is the commonly seen group among K. pneumoniae. OXA-181 and OXA-232 are the frequently produced variants of OXA48-like carbapenemases. OXA-181 and OXA-232 differ from each other by four amino acids: T104A; N110D; E168Q; S171A [1]. OXA-232 is a five amino acid variant of OXA-48 (T104A; N110D; E168Q; S171A; R214S). OXA-232 varies from OXA-181 by single amino acid (R214S) [1]. OXA-181 and OXA-232 have been reported with NDM-1 especially in India [2, 3]. Turkey, Morocco, Egypt, Libya and India are considered to be endemic for OXA48-like carbapenemases [4].

The blaOXA48-like genes are always carried on plasmids. Initially, IncI plasmids mediated the spread of blaOXA48-like genes. However, they have now been reported among other plasmid types such as IncH, IncA/C, IncX3 and ColKP3 [5–8]. OXA48-like carbapenemases are also known to be carried on transposons such as Tn1999, Tn1999.2 and it is also flanked by IS1R carried on Tn1999 [9, 10]. In India, there are no previous reports studying the association of mobile genetic elements with OXA48-like carbapenemases. Recently, in India, there has been a shift from NDM to OXA48-like carbapenemases [11]. Hence it is important to understand the role of mobile genetic elements (MGEs) in transfer of blaOXA48-like. The present study was aimed at determining the genetic backbone of OXA48-like carbapenemases in order to determine the role of MGEs in its transfer. The study also investigated the Inc plasmid type carrying blaOXA48-like.

Molecular characterisation
DNA was extracted from 18 to 24 h old cultures using Qiasymphony (Qiagen, Hilden, Germany) as per manufacturer’s instructions. Multiplex PCR for determination of carbapenemases such as blaIMP, blaVIM, blaNDM, blaSPM, blaOXA48-like and blaKPC were performed as described previously [2].

The isolates were subjected to whole genome sequencing using Ion Torrent PGM platform with 400 bp chemistry. Raw reads were assembled using Assembler SPAdes v.5.0 software in Torrent suite server version 4.4.3. The genome was annotated using RAST (Rapid Annotation using Subsystems Technology- http://rast.nmpdr.org/), Patric (Pathysystems Resource Integration Centre - https://www.patricbrc.org/) and the National Centre for Biotechnology Information Prokaryotic Genomes Automatic Annotation Pipeline (NCBI PGAP) softwares. The resistance genes were identified using ResFinder version 2.1 (https://cge.cbs.dtu.dk/services/ResFinder/) and Multi-locus Sequence typing (MLST) was determined using database at https://cge.cbs.dtu.dk/services/MLST/ . Plasmids present in the genome were identified by PlasmidFinder version 1.3 available at https://cge.cbs.dtu.dk/services/PlasmidFinder/.

The presence of insertion sequences and other mobile genetic elements adjacent to blaOXA-181 and blaOXA-232 were determined by NCBI annotation and further using ISFinder (https://www-is.biotoul.fr/) to confirm the identity of insertion element.

Whole genome single nucleotide polymorphism (SNP) tree was constructed using CSI Phylogeny at https://cge.cbs.dtu.dk/services/CSIPhylogeny/ . For the phylogenetic tree, metadata was labelled using iTOL software at https://itol.embl.de .

Results
The isolates from CMC, Vellore, were distributed over a span of 6 years: 2013 (n = 3), 2014 (n = 5), 2015 (n = 3), 2016 (n = 5), 2017 (n = 6) and 2018 (n = 3). All the isolates were resistant to aminoglycosides, β-lactams, fluoroquinolones and minocycline. Twenty one isolates were colistin resistant with minimum inhibitory concentrations (MIC) ranging from 4 to 1024 μg/ml. All isolates except Kp21 and Kp22 were susceptible to tigecycline. The accession numbers for genomes, blaOXA48-like variant, year of isolation, plasmid carrying blaOXA48-like and MLST have been mentioned in Table 1. Among the CMC study isolates, 19 carried blaOXA-232 and six carried blaOXA-181. Three isolates co-expressed blaNDM with blaOXA48-like as mentioned in Table 1.

In six isolates from CMC, blaOXA-232 was associated with insertion sequences as depicted on Fig. 1. Figure 1 also shows the genetic backbone among two isolates in which blaOXA232 is not flanked by insertion sequences. The...
| Centre                  | Isolate no. | Accession no/ Bioproject ID | blaOXA-48 variant | Plasmid               | Insertion sequence flanking blaOXA-48 variant | MLST |
|------------------------|-------------|-----------------------------|------------------|-----------------------|-----------------------------------------------|------|
| CMC, Vellore           | Kp1         | MPT0000000000               | OXA-232          | ColKP3                | ISKpn26, IS5 family; IS110 family              | ST231|
|                        | Kp2         | MOXL000000000000            | OXA-232          | ColKP3/ IncFIl        | None                                           | ST231|
|                        | Kp3         | PUXB0000000000              | OXA-181 NDM-5    | unidentified          | None                                           | ST147|
|                        | Kp4         | MEBR0000000000              | OXA-232 NDM-1    | unidentified          | ISKpn26, IS5 family                            | ST14 |
|                        | Kp5         | MDZG0000000000              | OXA-232          | ColKP3                | TnAs3, Tn3 family                              | ST231|
|                        | Kp6         | MOXN0000000000              | OXA-232          | ColKP3                | ISX4, IS1 family; ISRaq1, IS3 family           | ST231|
|                        | Kp7         | MOXM0000000000              | OXA-232          | ColKP3                | None                                           | ST14 |
|                        | Kp8         | MIEJ0000000000              | OXA-232          | ColKP3                | IS1A and IS1F, IS1 family                      | ST14 |
|                        | Kp9         | LZYNO0000000000              | OXA-181          | ColKP3                | None                                           | ST147|
|                        | Kp10        | MCF000000000000              | OXA-232          | ColKP3                | None                                           | ST231|
|                        | Kp11        | MCFP0000000000              | OXA-181          | unidentified          | None                                           | ST43 |
|                        | Kp12        | NTHQ0000000000              | OXA-232          | ColKP3                | None                                           | ST231|
|                        | Kp13        | PJOP0000000000              | OXA-232          | ColKP3                | None                                           | ST16 |
|                        | Kp14        | PKMV0000000000              | OXA-181          | unidentified          | None                                           | ST147|
|                        | Kp15        | PETC0000000000              | OXA-232          | ColKP3                | None                                           | ST231|
|                        | Kp16        | PKLO0000000000              | OXA-232          | ColKP3                | None                                           | ST231|
|                        | Kp17        | PKOK0000000000              | OXA-232          | unidentified          | ISKpn26, IS5 family; ISSpu2, IS630 family      | ST14 |
|                        | Kp18        | NSCV0000000000              | OXA-232          | unidentified          | None                                           | ST231|
|                        | Kp19        | NRSU0000000000              | OXA-232          | ColKP3                | None                                           | ST231|
|                        | Kp20        | PKOM0000000000              | OXA-181          | IncA/C2               | None                                           | ST231|
|                        | Kp21        | PPSX0000000000              | OXA-232          | ColKP3                | None                                           | ST395|
|                        | Kp22        | PPXT0000000000              | OXA-232          | unidentified          | ISKpn1, IS3 family; IS4321R, IS110 family      | ST570|
|                        | Kp23        | PUIG0000000000              | OXA-181          | unidentified          | None                                           | ST14 |
|                        | Kp24        | PYSM0000000000              | OXA-232          | unidentified          | None                                           | ST231|
|                        | Kp25        | PUF0000000000              | OXA-232 NDM-5    | ColKP3                | None                                           | ST147|
| AIIMS Trauma Centre     | Kp26        | PWAFO0000000000              | OXA-181          | unidentified          | ISKox1, partial, IS66 family                   | ST43 |
| New Delhi               | Kp27        | PWAD0000000000              | OXA-181          | unidentified          | ISKox1, partial, IS66 family                   | ST43 |
|                        | Kp28        | MNPB0000000000              | OXA-232          | ColKP3                | ISPz38, Tn3 family; IS4321R, IS110 family      | ST11 |
|                        | Kp29        | MNPC0000000000              | OXA-232          | ColKP3                | ISKpn25, ISL3 family                           | ST11 |
|                        | Kp30        | MNPG0000000000              | OXA-232          | ColKP3                | ISPz38, Tn3 family                             | ST11 |
|                        | Kp31        | MNPH0000000000              | OXA-232          | unidentified          | ISKpn26, IS5 family                            | ST14 |
|                        | Kp32        | PRJNA494951                | OXA-232          | unidentified          | TnAs3, Tn3 family                              | ST14 |
|                        | Kp33        | PRJNA494951                | OXA-232          | ColKP3                | Tn2, Tn3 family                                | ST2040|
|                        | Kp34        | MNPA0000000000              | OXA-232          | unidentified          | IS26, IS6 family; IS903, IS5 family; ISPa38, Tn3 family | ST231|
|                        | Kp35        | PYUL0000000000              | OXA-181          | unidentified          | ISKox1, IS66 family; ISEc36 IS3 family; ISKpn42 IS110 family | ST43 |
|                        | Kp36        | PRJNA494951                | OXA-181          | unidentified          | ISKpn1, IS3 family                             | ST43 |
|                        | Kp37        | PRJNA494951                | OXA-181          | unidentified          | ISKpn1 partial, IS3 family                     | ST11 |
|                        | Kp38        | PRJNA494951                | OXA-232          | unidentified          | ISKpn1 partial, IS3 family                     | ST11 |
|                        | Kp39        | PWAH0000000000              | OXA-232          | unidentified          | None                                           | ST101|
|                        | Kp40        | PWAE0000000000              | OXA-232          | ColKP3                | None                                           | ST231|
genetic backbone is diverse among the isolates as shown in Fig. 1 even among isolates belonging to same sequence type. Isolates belonging to ST14 had insertions from IS1, IS5 and IS630 families while those of ST231 had insertions belonging to IS5, IS1, IS3 and Tn3 families (Table 1).

Seven sequence types were observed among the South Indian isolates which include ST231 (n = 12), ST14 (n = 5), ST147 (n = 4), ST16 (n = 1), ST43 (n = 1), ST395 (n = 1) and ST570 (n = 1). ST231 has been isolated throughout the study period. ST231 and ST43 belong to the same clonal complex (CC), CC43. ST231 is a triple locus variant of ST43 varying in pgI, phoE and tonB genes with 11SNPs.

The isolates from AIIMS, New Delhi, were obtained during 2016 and 2017. The isolates belonged to diverse sequence types including ST231 (n = 7), ST11 (n = 5), ST43 (n = 4), ST14 (n = 2), ST15 (n = 3), ST16 (n = 1), ST101 (n = 1), and ST2040 (n = 1). CC11 including ST11, ST14, ST15 and ST2040, was predominant in north India. ST231 is predominantly present in both the study centres. Among the 24 isolates from AIIMS, eight

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Table 1 Details of study isolates including accession numbers (Continued)

| Centre | Isolate no. | Accession no/ Bioproject ID | bla\textsubscript{OXA-48} variant | Plasmid | Insertion sequence flanking \( \text{bla}_{\text{OXA-48}} \) variant | MLST |
|--------|-------------|-----------------------------|-----------------|--------|---------------------------------|------|
|        |             |                             |                 |        |                                 |      |
| Kp41   | PRJNA494951 | OXA-232                     | CoI KP3         | None   |                                 | ST231|
| Kp42   | PRJNA494951 | OXA-181                     | CoI KP3         | None   |                                 | ST16 |
| Kp43   | PRJNA494951 | OXA-181                     | IncA/C2         | None   |                                 | ST231|
| Kp44   | PRJNA494951 | OXA-232                     | CoI KP3         | None   |                                 | ST15 |
| Kp45   | PRJNA494951 | OXA-232                     | CoI KP3         | None   |                                 | ST15 |
| Kp46   | PRJNA494951 | OXA-181                     | CoI KP3         | None   |                                 | ST15 |
| Kp47   | PRJNA494951 | OXA-232                     | CoI KP3         | None   |                                 | ST231|
| Kp48   | PRJNA494951 | OXA-232                     | CoI KP3         | None   |                                 | ST231|
| Kp49   | PRJNA494951 | OXA-232                     | CoI KP3         | None   |                                 | ST231|

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Fig. 1 Mobile genetic elements flanking \( \text{bla}_{\text{OXA-48}} \) in K. pneumoniae from CMC, Vellore. a and b: \( \text{bla}_{\text{OXA-48}} \) without insertion sequences in Kp2 and Kp10 respectively. c to h: \( \text{bla}_{\text{OXA-48}} \) associated with insertion sequences and transposon in Kp1, Kp4, Kp5, Kp6, Kp17, KP22 respectively.
Fig. 2 Genetic environment of blaOXA-48-like among *K. pneumoniae* from AIIMS, New Delhi, India

Kp27
**bla**OXA-48-like
IP6, Tr1 family partial
IP6, Tr1 family partial
IP6, Tr1 family partial

Kp28
Mobilization protein
Replicase
blaOXA-48-like
RDNase
Invertase
IP6, Tr1 family partial
IS1416
IS1510

Kp29
Mobilization protein
Replicase
blaOXA-48-like
RDNase
Invertase
IP6, Tr1 family partial
IS1416
IS1510

Kp30
Mobilization protein
Replicase
blaOXA-48-like
RDNase
Invertase
IP6, Tr1 family partial
IS1416
IS1510

Kp31
Translation elongation factor
Invertase
blaOXA-48-like
IP6, Tr1 family partial
IS1416
IS1510

Kp32
Replicase
blaOXA-48-like
General secretion pathway protein B
General secretion pathway protein D
General secretion pathway protein F

Kp33
Replicase
blaOXA-48-like
TolC, Tr3 family partial
TolC, Tr3 family partial

Kp34
Replicase
blaOXA-48-like
General secretion pathway protein F
General secretion pathway protein D
General secretion pathway protein B

Kp35
Replicase
blaOXA-48-like
TolC, Tr3 family partial
TolC, Tr3 family partial

Kp36
Replicase
blaOXA-48-like
NSA polymerase

Kp37
Replicase
RDNase
IP6, Tr1 family partial
IS1416
IS1510

Kp38
Replicase
RDNase
IP6, Tr1 family partial
IS1416
IS1510

Kp39
Replicase
RDNase
IP6, Tr1 family partial
IS1416
IS1510

Fig. 2 Genetic environment of blaOXA-48-like among *K. pneumoniae* from AIIMS, New Delhi, India Kp27, Kp28, Kp29, Kp30, Kp31, Kp32, Kp33, Kp34, Kp35, Kp36, Kp37, Kp38, Kp39
were OXA-181 producers and 16 were OXA-232 producers. The genetic backbone among these isolates from New Delhi seems to be very diverse despite the clonality. Genetic backbone of isolates with \( \text{bla}_{\text{OXA48-like}} \) associated with mobile genetic elements is shown in Fig. 2.

As seen from Table 1, isolates from northern and southern India belonging to same clone had diverse genetic backbone for \( \text{bla}_{\text{OXA48-like}} \). Isolates from North belonging to ST14 had MGEs from IS5 and Tn3 families while from South they had MGEs from IS1, IS5 and IS630 families. A single isolate of ST231 from north had MGEs from IS5, IS6 and Tn3 families with \( \text{bla}_{\text{OXA-232}} \) while from south, IS1, IS3 and IS5 families were observed. This shows that there is no clonal expansion of OXA48-like producers in India.

Diverse mobile genetic elements have been associated with both \( \text{bla}_{\text{OXA-232}} \) and \( \text{bla}_{\text{OXA-181}} \) belonging to \( \text{bla}_{\text{OXA48-like}} \). This includes: a) insertion sequences such as ISX4, IS1, IS3, IS\textit{Kpn}1, IS\textit{Kpn}26, IS\textit{Kpn}25, ISSpu2, IS\textit{Kox}1, IS4321R, ISEc36, and ISP\textit{Pa}38; b) transposons such as Tn\textit{As3} and Tn2, belonging to Tn3 family. IS\textit{Kpn}26 has been seen among isolates from Vellore and New Delhi. This indicates the role of diverse MGEs in transmission of OXA48-like carbapenemases in India.

Figure 3 shows the phylogenetic tree of OXA48-like carbapenemase producing \( K. \) pneumoniae. MLST, variant of OXA48-like carbapenemase and centre from where the isolates were obtained are shown in Fig. 3. Mobile genetic elements associated with OXA48-like has also been indicated.

**Discussion**

The commonest variants of \( \text{bla}_{\text{OXA48-like}} \) reported among \( K. \) pneumoniae are \( \text{bla}_{\text{OXA-181}} \) and \( \text{bla}_{\text{OXA-232}} \). In the present study, significantly, 80% of the isolates were \( \text{bla}_{\text{OXA-232}} \) producers. In 14 of the study isolates, \( \text{bla}_{\text{OXA-232}} \) was associated with mobile genetic elements such as insertion sequences (IS) and transposons. Interestingly, among the isolates with IS, the regions flanking \( \text{bla}_{\text{OXA-232}} \) were diverse. No two isolates had the same genetic environment even among the isolates in which \( \text{bla}_{\text{OXA-232}} \) was not flanked by IS. IS\textit{Kpn}26 was found with \( \text{bla}_{\text{OXA-232}} \) in four isolates.

Tn\textit{1999} and its isoforms have been frequently described carrying \( \text{bla}_{\text{OXA-232}} \) along with IS1R [9, 10, 13]. ISE\textit{cp}1 was reported among isolates from France and Brunei belonging to ST14 and ST231 [14, 15]. However, in the present study these mobile genetic elements were
OXA-232 is the predominant variant of OXA-48-like carbapenemase with ST231 being the commonest ST of OXA-48-like carbapenemase producing *K. pneumoniae* in India. Diverse MGEs have been associated with both bla~OXA-232~ and bla~OXA-181~ which contribute to their spread. The MGEs in the present study are different from those reported earlier. There is no clonal expansion of bla~OXA-48-like~ producing *K. pneumoniae* since diverse STs were observed. Among isolates belonging to same ST, diverse MGEs were observed associated with bla~OXA-48-like~. Monitoring the genetic backbone of OXA-48-like carbapenemase is essential to better understand the transmission dynamics of XDR *K. pneumoniae*.

**Abbreviations**

ATCC: American Type Culture Collection; CC: Clonal Complex; CLSI: Clinical and Laboratory Standards Institute; Inc.: Incompatibility; IS: Insertion sequence; MGE: Mobile Genetic Elements; MLST: Multi-locus sequence typing; NCBI: National Centre for Biotechnology Information; NDM: New Delhi metallo-β-lactamase; OXA: Oxacillinase; Patric: Pathosystems Resource Integration Centre; PCR: Polymerase Chain Reaction; PGAAP: Prokaryotic Genomes Automatic Annotation Pipeline; RAST: Rapid Annotation using Subsystems Technology; SNP: Single Nucleotide Polymorphism; ST: Sequence Type; Tr: Transposon; XDR: Extensively Drug Resistant

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**Authors’ contributions**

CS: Laboratory methods, data analysis and manuscript correction. PM: Study design, provided isolates for characterisation, manuscript correction. MV: Laboratory methods. AK: Data analysis and manuscript writing. SA: Study design, manuscript correction. SK: Laboratory methods. BV: Study design, manuscript correction. All authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and analysed during the current study are available from the corresponding author on reasonable request. The whole genome sequences are deposited in GenBank with accession numbers provided in Table 1 of the manuscript.

**Ethics approval and consent to participate**

This is a retrospective study in which the isolates are used without the patient identifier. Hence ethical approval and patient consent were not required.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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absent and significantly different from global isolates. Also, IncL/M type of plasmids are frequently found carrying bla~OXA-48-like~ gene [16]. However, in the present study, none of the isolates harboured IncL/M plasmid. In contrast, in most of the isolates bla~OXA-48-like~ gene was present on ColKP3 plasmid and on IncA/C2 in one of the isolates. IncA/C harbouring bla~OXA-48-like~ gene has been previously reported [7]. A recent study in the US reported bla~OXA-232~ in all the study isolates to be present on ColKP3 plasmid [17].

In two of the study isolates, along with bla~OXA-48-like~, bla~NDM-5~ was also present. bla~NDM-5~ was flanked by ISABA125 which is frequently associated with bla~NDM~ [18, 19]. Both these isolates were of ST147 isolated during 2013 and 2018. bla~OXA-181~ and bla~NDM-5~ has been previously reported in USA and South Korea [17, 20].

Similar to the present study, coexistence of bla~OXA-181~ and bla~NDM-5~ have been reported among *E. coli* and *K. pneumoniae* [20, 21].

Totally, 11 sequence types were observed in the present study. These were diverse and the two major clonal complexes were CC11 and CC43. ST14 and ST147 have been frequently reported among OXA-48-like producing *K. pneumoniae* in various regions such as North America and Germany [22, 23]. ST14 and ST147 have been described as international high risk clones associated with extensively drug resistant (XDR) *K. pneumoniae* [24]. ST395 has also been reported among European and African OXA48-like producing *K. pneumoniae* [15].
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