

Human Infections with *Staphylococcus aureus* CC398

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Abstract *Staphylococcus aureus* isolates belonging to clonal cluster 398 (CC398) have emerged over the previous decade as a risk to livestock workers. Though most of the research to date has focused on colonization with these strains, a number of infections have also been documented, ranging from mild skin infections to more serious invasive infections and even death. Here, we review existing reports of human infections with CC398 and discuss their geographic distribution, general characteristics, and implications for future research. We identified 74 publications describing CC398 infections in humans in 19 different countries, suggesting this is an emerging worldwide issue.

Keywords MRSA · *Staphylococcus aureus* · Zoonotic disease · Livestock · Antibiotic resistance · Staph infections

Introduction

Staphylococcus aureus is a leading cause of infectious disease morbidity throughout the world [1]. The bacterium is particularly problematic in hospitals, where it can complicate surgeries and spread nosocomially [2]. Infections often develop in open wounds or medical devices, such as catheters, and can

also cause more serious conditions, including ventilator-associated pneumonia [3] and bacteremia [4].

In the past 20 years, two new groups of methicillin-resistant *S. aureus* (MRSA) have emerged. Previously, MRSA was primarily observed in hospital settings (hospital-acquired MRSA [HA-MRSA]). In the 1990s, novel strains of MRSA found in individuals with no healthcare contact were termed “community-associated MRSA” (CA-MRSA) [5]. These isolates tend to carry an SCC_{mec} cassette smaller than that typically found in HA-MRSA and are resistant to fewer classes of antibiotics. CA-MRSA also tends to carry a putative virulence gene, the Pantón–Valentine leukocidin gene (PVL) [6]. A decade later, a third type of MRSA was identified, typically among individuals working with livestock (livestock-associated MRSA [LA-MRSA]) [7, 8]. LA-MRSA has unique characteristics that distinguish it from HA-MRSA and CA-MRSA. LA-MRSA isolates typically are multilocus sequence type (MLST) 398 (ST398), belonging to clonal cluster 398 (CC398), and are resistant to digestion with the enzyme *Sma*I in pulsed field gel electrophoresis (PFGE) analysis [9]. Multiple reports have shown that they also typically lack common toxin genes frequently carried by human *S. aureus* isolates [10–12].

The majority of publications examining LA-MRSA to date have focused on colonization in both animals (typically, swine, cattle, poultry, and horses) and their human caretakers or veterinarians [13–17]. However, an increasing number of case reports and hospital-based research have identified CC398 as a cause of symptomatic infections. Furthermore, in the past 3 years, CC398 has been split into two distinct lineages: those that are of human origin [18, 19, 20] and those that are truly livestock adapted. Human-origin CC398 isolates tend to be susceptible to tetracycline and methicillin, and carry the *scn* gene. In this review, we discuss reported cases of CC398 clinical infections in humans, as well as the

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implications of the emergence of this strain in livestock and in humans. Reports were collected via review in PubMed, Medline, and Embase, searching for “ST398,” “CC398,” “livestock-associated MRSA,” and “livestock-associated *Staphylococcus aureus*” as of July 2014. Additional publications were also found via reference sections of collected manuscripts. Papers were included if they documented infections due to isolates identified either as ST/CC398 or *spa* types that are typically associated with this clonal complex (including t011, t034, t571, and others, as documented in Table 1). Information on human versus livestock-adapted cases is provided when known.

Geographic Distribution of Cases

To date, the majority of CC398 clinical infections have been reported in Europe, where most research on CC398 has been focused, and many countries have established surveillance programs for *S. aureus* infections (see Table 1). Seventy-four publications were identified. Human infections of any type have been reported in Austria [21–24], Belgium [23, 25, 26], Denmark [23, 27–31], Finland [23, 32], France [33–35, 36, 37–39], Germany [23, 40–44], Greece [45], Italy [46–51], the Netherlands [23, 52–63], Norway [64], Spain [65–71], Sweden [72, 23], Scotland [73], and Switzerland [23]. Outside of Europe, infections have been described in Canada [74], China

Table 1 Summary of CC398-associated infections reported in the literature

CC398-associated <i>spa</i> types	SCC <i>mec</i> types	PVL	Countries	References
t011, t034, t190, t1451	V, NR	Neg	Austria	[21, 22, 24, 100]
t011, t571	V, NR, N/A	Neg	Belgium	[25, 26, 102]
t034, t1250	V	Neg	Canada	[74]
t011, t034, t571, t588, t1250, t1255, t1451, t3625, t4387, ND	III, IV, N/A	Pos and Neg, NR	China	[75–80]
t571	N/A	Neg	Colombia	[81]
t034, t108, t1793	IV, V, NT, NR	Pos and Neg, NR	Denmark	[11, 27–31, 133]
t571, t3625	N/A	NR	Dominican Republic	[82]
t011, t034	IV, V	Pos and Neg	Finland	[32]
t011, t034, t108, t571, t588, t614, t899, t937, t1149, t1184, t1250, t1451, t2155, t2370, t3085, t3642, t4293, t4615, t4896, t5635, t5719, t5881, t6604, t6605, t6606, t6608, t8587, t8592, t8593, t9378, NR	IV, V, N/A, NR	Pos and Neg, NR	France	[33, 34, 37–39, 134]
t011, t034, t108, t567, t571, t899, t1250, t1255, t1451, t1580, t2011, t2330, t2346, t2510, t2576, t2970	IV, V, NR	Neg	Germany	[40–44]
NR	NR	NR	Greece	[45]
t011, t034, t2346, NR	IVa, N/A	Pos and Neg, NR	Hong Kong	[85, 84]
t899, NR	IVa	Neg	Italy	[46–49, 51]
t011, t034, t108, t567, t571, t898, t899, t943, t1254, t1255, t1451, t1939, t2011, t2123, t2383	IV, IVa, V*, NR, N/A	Neg, NR	The Netherlands	[14, 15, 41, 52, 53, 57, 59–63, 99, 101, 103, 135]
t034	V	Pos	Norway	[64]
t034	III	NR	Scotland	[73]
t011, t108, t899, t1197, t1255, t1451	IV, IVa, V	Neg	Spain	[66–71]
t034	NR	Pos	Sweden	[72]
t034, t571, t1451, NR	N/A	Neg	USA	[12, 19, 86–88]
	N/A	Neg	Dominican Republic, Martinique	[83]
t571, t1451, t5635	NR	Pos and Neg	Canada, Dominican Republic, Martinique, the Netherlands, USA	[18]
t011, t034, t108, t567, t571, t588, t753, t898, t899, t1184, t1254, t1255, t1451, t1456, t1457, t2123, t2330, t2383, t2582, t3013	NR	NR	Austria, Belgium, Denmark, Finland, Germany, Italy, the Netherlands, Sweden	[23]

MSSA methicillin-susceptible *Staphylococcus aureus*, N/A not applicable (MSSA), Neg negative, NR not reported, NT nontypeable, ND not determined, Pos positive, PVL Pantone–Valentine leukocidin gene

*Several type III isolates typed using a previous method [136] were subsequently found to be type V [137]

[75–80], Colombia [81], the Dominican Republic [82, 83], Hong Kong [84, 85], Martinique [83], and the USA [12, 18, 19, 86–88].

Though nationwide data are still lacking in many countries, a large study examined data from 24 laboratories in 17 European countries [23]. On the basis of data from 2007, ST398 was detected in 8/15 countries for which typing data were available. Of the 8,262 MRSA isolates typed for this study, 142 (1.7 %) were ST398. The percentages of ST398-associated types were highest in the Netherlands (11.7 %), Belgium (4.7 %), Denmark (1.6 %), and Austria (1.4 %). The proportion of ST398 isolates was found to correlate with the density of pig herds, as well as with cattle density to a lesser extent. These numbers likely underestimate the prevalence of ST398 infections, as only previously identified *spa* types associated with ST398 were included. Additional unidentified types may also exist.

In the Netherlands, a recent dramatic increase in the prevalence of CC398 in recovered MRSA isolates has been observed, changing from 0 % in 2002 to 30 % in 2007 following increased surveillance instituted in 2006 [52, 53, 56, 60]. Interestingly, one publication found two isolates of methicillin-susceptible *S. aureus* (MSSA) ST398 in the Netherlands in a retrospective survey dating back to 1997 [57]. These isolates were identified in a collection of *S. aureus* isolates taken from intensive care unit patients from 14 hospitals in the country. Both ST398 isolates identified were from the southern region of the country, which is an agricultural region. Whether these dramatic increases will occur in other countries where CC398 has been found remains to be seen, particularly as surveillance for these organisms varies widely from country to country.

In China, a large study that examined isolates collected from 1994 to 2008 in a Chinese tertiary hospital determined that the CC398-associated *spa* type t571 was one of the most common MSSA types (18/164; 11 % of all MSSA during the period) [76]. The related *spa* types t034 and t1250 were also present at lower levels, while, overall, CC398 was the most common type of MSSA (31/164; 18.9 % of all isolates). All isolates came from sterile body sites. The high levels of CC398-associated *spa* types observed is interesting, as most MRSA from Chinese pigs has been ST9, not ST398 [89–91], though one recent paper did describe ST398 in Chinese pigs [92]. Thus, most CC398-associated types in China may be of human rather than livestock origin [93].

To date, five reports containing documentation of human symptomatic infections with CC398 have been published in the USA [12, 18, 19, 86, 87]. None have been found to be MRSA, despite confirmation of MRSA CC398 in pigs and pig workers in this country [17, 94–97]. This discrepancy may be due in part to a lack of systematic nationwide surveillance in the USA, particularly in rural areas, where livestock-associated strains are most likely to be found. The isolates

described in all reports originated in urban locations, from the New York metropolitan area [12, 18, 19, 86] and St. Louis, Missouri [87]. In the St. Louis report, one PVL-negative ST398 isolate was identified from a wound/abscess [87], and one blood isolate of ST398 MSSA was identified from the Bronx report [12]. This isolate was PVL negative but did carry the *ser* gene, which encodes an enterotoxin of unknown function.

Additionally, self-reported infections in US swine workers have been documented [98]. Five of 135 participants (3.7 %) reported a history of physician-diagnosed MRSA skin and soft tissue infection (SSTI). The only significant variable found to be a risk factor in the bivariate model for this population was having employees who expressed concern regarding MRSA ($p=0.02$), but in a multivariate model, no risk factors were found to be significant. This publication used retrospective questionnaire data, so it cannot be determined whether all of the reported MRSA infections were indeed culture-positive MRSA, and, if so, whether these infections were due to CC398 or other strains. Another limitation was that the National Pork Board producer database used to recruit participants for the study consisted mainly of smaller owner-operators, while many employees of such individuals were not evaluated directly.

Types of Infections

A spectrum of CC398 infections has been documented, ranging from relatively minor or localized infections (including abscesses [46, 62, 64, 72, 87, 99, 100] and various SSTIs [11, 18, 21, 30, 31, 37, 48, 53, 60, 66, 69, 74, 77, 79, 80, 85, 101]; urinary tract infections [60, 62]; wound infections [21, 26, 32, 40, 59–62, 72, 75, 86, 100, 102]; mastitis [15]; otitis [51, 60]; tonsillitis [31], and conjunctivitis [22]) to more serious or invasive infections (including bacteremia [12, 24, 26, 28, 33, 34, 37, 43, 45, 48, 60, 62, 63, 81, 84, 86]; pneumonia, including necrotizing pneumonia [21, 26, 30, 37, 40, 47, 53, 78]; osteomyelitis [22, 39, 53]; pyomyositis [46]; otomastoiditis [25]; endocarditis [38, 103]; multi-organ failure [27], and postoperative infections [21]). Although most of these cases have been documented in the past 5 years, one MSSA ST398 bacteremia isolate from Denmark dates back to 1992 [28].

Despite the diverse array of infection types, it has been suggested that CC398 isolates may not cause as much disease (relative to colonization) as other human strains, such as USA300 [53, 104]. Supporting this assertion, a targeted study examining invasive *S. aureus* isolates in Europe found that ST398 was responsible for only 0.4 % of those infections, and none were methicillin resistant [105]. Van Cleef et al. also found that in their surveillance, the proportion of ST398 isolates from blood was significantly lower than for other

MRSA types, suggesting a less invasive phenotype [23]. However, some disease manifestations may be enriched for CC398 strains. A French study of osteomyelitis complicating diabetic foot ulcers demonstrated that MSSA CC398 was the dominant clone in these infections, accounting for 38 % of cases of diabetic foot osteomyelitis and appearing in 10 of the 12 clinics monitored [39]. These isolates were found to carry molecular signatures of human, rather than livestock, adaptation.

While many early studies have focused on skin and wound infections, this approach may miss some CC398 infections, as one study has suggested that CC398 was more likely to be associated with respiratory disease rather than skin infections [52]. Another study [60] reported three sputum ST398 isolates but no SSTI among 30 isolates, although there were also 10 wound infections and 4 diabetic foot infections reported. However, these findings were not replicated in a larger study, which found no significant difference between ST398 MRSA and other MRSA types in regard to respiratory infections [23]. Conversely, Lewis et al. reported that all patients who developed symptomatic infections with ST398 were SSTIs, with one later developing sinusitis and another developing multi-organ failure [27].

Respiratory Infections

As noted above, there is conflicting evidence regarding the preponderance of CC398 in respiratory infections versus SSTI. While the prevalence of CC398 as a cause of respiratory infections remains unclear, there have been several case reports documenting ST398 respiratory infections. A 2011 report found ST398-associated pneumonia in a Chinese girl. This isolate was negative for most toxins tested but positive for exfoliative toxin (*eta*) [78]. A Dutch paper noted one case of pneumonia from three identified ST398 infections [53]. Several publications have reported ST398 isolates from bronchial aspirate or lavage specimens [21, 47]. Others have described ST398 pneumonia in individuals associated with pig farming [30] or in those for whom contact with livestock could not be determined [26].

CC398 Fatalities

Despite the reputation of CC398 as a more “mild” type of *S. aureus*, there have been several reported deaths due to CC398 infections. Lozano et al. described a fatal infection in a 79-year-old patient in Spain [68]. The patient was hospitalized, and MRSA was isolated from a thoracic drainage tube and tracheal aspirate, as well as from a nasal swab. The isolates were typed and found to be *spa* type t011 and *SCCmec* type V, both molecular types frequently associated with ST398

strains. Though the patient was treated with intravenous levofloxacin (later changed to linezolid), treatment was unsuccessful, and the patient died following multi-organ failure. The patient lived with his wife and two sons on a pig farm; cultures from swine and one son were found to be identical to the patient’s samples. Both sons worked on the farm, and the patient worked there sporadically, suggesting acquisition from swine, with possible intrafamilial transmission.

Four CC398 deaths have been reported in France in three publications. In the first report, Van der Mee-Marquet et al. analyzed annual surveys of bloodstream infections performed in the central region of France [34]. In 2009, the emergence of cases associated with tetracycline-sensitive, PVL-negative, *spa* type t571 strains was noted. One individual had a history of exposure to animals—a fatal idiopathic community-associated bloodstream infection in an 84-year-old man, who lived on a farm with one pig. The other cases were hospital-acquired bloodstream infections in a 58-year-old man with multiple myeloma, and two cases following surgeries: one an elective digestive tract surgery in a 69-year-old woman, and another after cardiac surgery in a 68-year-old man.

In the second French publication, a previously healthy 14-year-old girl was seen at the emergency room with a flu-like illness, cough, fever, and a 2-day history of severe abdominal pain [35]. She was given intravenous antibiotics (cefotaxime and amikacin), and an exploratory laparotomy was performed. Immediately after surgery, the girl went into acute respiratory distress, and mechanical ventilation was required. *S. aureus* was isolated from bronchoalveolar lavage fluid and a blood culture, and the girl was diagnosed with necrotizing pneumonia. The patient died 6 days after symptom onset, and the origin of the infection was not determined. In this instance, the *spa* type was t571 and the isolate was sensitive to methicillin and tetracycline, similar to the other cases reported in that country [34, 37, 39] and elsewhere [76]. This isolate was also PVL positive. Two additional deaths were reported in a third paper [33], in a 59-year-old male and an 80-year-old male. Both deaths were caused by MSSA t571 strains.

One CC398-associated death has also been reported in China, in a 3-year-old who underwent empyema surgery and had an abscess [75]. The *spa* type of this isolate was not provided, but the isolate was *SCCmec* type IV and resistant to penicillin, erythromycin, and gentamicin, but susceptible to tetracycline. This death was not reported in the original study but was referenced in a later publication [79].

Predisposing Conditions

As is common with clinical infections with *S. aureus*, a number of individuals described in case reports had various predisposing conditions. Previous studies have shown that individuals with immunocompromising conditions (including

diabetes) are at higher risk of infections [106], as are individuals aged 65 years and older [107]. Diabetes was described in a number of publications detailing CC398 infections [25, 39, 47, 49, 59, 60, 70, 81], while individuals of advanced age were noted in others [21, 22, 26, 32, 34, 47, 68, 70, 74, 75]. Additional conditions noted included congenital arteriovenous malformations [49], history of renal transplantation/immunosuppressive drugs [79, 103], obesity [48], young age [22, 30, 52], cancer [34, 45, 68], and skin conditions [99], as well as one case of infection in a 16-year-old girl with muscular atrophy type II, which left her in a wheelchair and on artificial ventilation [61]. A recent graft infection was also noted in Colombia in a woman who had a medical history including diabetes mellitus, hypertension, valvular heart disease, and chronic arterial occlusive disease [81].

Lack of Animal Contact and Human-Origin CC398 Strains

Though most instances of both CC398 colonization and infection have been in individuals who have occupational contact with live animals (particularly swine and cattle), a number of reports have documented CC398 infections in individuals lacking any confirmed animal contact. Many studies for which animal contact is unknown result from an inability to obtain such information, due to the study design (such as the use of retrospective hospital records without any patient follow-up) [19, 26, 33, 37, 74, 86, 87]. In other instances, despite other available information or follow-up interviews with infected patients, still no animal contact was uncovered [32, 45, 47, 49, 60, 72, 99]. In one of the largest studies of CC398 infections, 11/30 patients (36.7 %) had no known contact with livestock [60].

A human reservoir for some t571 CC398 strains has also been suggested [93], eliminating the need for any animal reservoir. There is growing evidence to support this hypothesis. A recent study examining CC398 infections in New York and New Jersey found 13 samples of ST398 and ST291 (a single-locus variant of ST398) from 2004 to 2010; of the ST398 isolates, 6/8 samples were t571. Indeed, in European studies, t571 is uncommon in pigs, accounting for only a single ST398 sample found during sampling of breeding pigs in the European Union [108]. Some t571 and t1451 strains do show unique properties that are not typical of swine-associated lineages [33, 38, 82]. Most are sensitive to methicillin and tetracycline. Van der Mee-Marquet additionally described interesting lineages that appeared to have properties of common ST398 strains, the community-associated strain USA300, and Chinese ST398 isolates, suggesting the potential for horizontal transmission of virulence genes into ST398 lineages [34, 53]. Investigation of an MSSA ST398 t571 infection in a Colombian woman found no evidence of

livestock contact, although she did live in a rural area and had contact with chickens, which may also carry CC398 strains [109, 110]. This isolate, while sensitive to methicillin, was resistant to tetracycline—a hallmark of livestock-associated strains [81].

A genomic analysis of 89 strains further suggests that ST398 does have a “human” lineage. This lineage appears to have originated as MSSA, which was transmitted to farm animals, subsequently acquired resistance to methicillin and tetracycline via agricultural antibiotic use, and is now being transmitted to human caretakers [19]. This evolutionary course is reminiscent of the situation in the poultry population, where an ST5 lineage was introduced into commercial poultry flocks by humans, where it subsequently evolved antibiotic resistance and has been transmitted back to humans on occasion [111]. As previously suggested, t571 *spa* types have been more strongly correlated with human infections (as opposed to animal colonization strains), and the majority of those tested have been MSSA, tetracycline sensitive, and positive for the ϕ Sa3 prophage, suggesting adaptation to humans. In all but one of the animal-origin ST398 isolates tested in this study, ϕ Sa3 was lost. A second paper examining human-origin MSSA ST398 strains and a livestock-origin MRSA ST398 isolate reported similar findings, along with evidence that the apparently human-origin strains also demonstrated increased adherence to human epidermal keratinocytes, compared with LA-MRSA strains, suggesting additional host adaptations [18]. A third paper demonstrated heterogeneity amongst isolates in a variety of responses to *in vitro* assays, suggesting the existence of a hypervirulent lineage within ST398 [112]. However, in this study, all isolates tested were t011 or t034, rather than t571. As such, it is possible for these *spa* types to also show the potential for increased virulence. A recent French paper examining 189 CC398 isolates taken from patients with *S. aureus* infections and from pigs and cattle colonized with *S. aureus* determined that a multiplex PCR targeting the *scn*, *chp*, and *ermT* genes could discriminate animal and human origin CC398 isolates [37], while another recent paper examined the presence of *scn* and *tet(M)* along with a single nucleotide polymorphism (canSNP) assay as a method to distinguish animal and human origin isolates [113].

Conclusions and Future Studies and Unanswered Questions

A decade since the initial recognition of ST398, there still exist a number of unanswered questions regarding the epidemiology and clinical relevance of this strain. CC398 strains have been suggested by several studies to be less transmissible between humans than non-CC398 types in several European studies [114, 115]. One study in the Netherlands quantified this difference, estimating that ST398 was 72 % less

transmissible than other strains in Dutch hospitals [115]. More recently, in the Netherlands, transmissibility of LA-MRSA was found to be 4.4 times lower than that of MRSA not associated with livestock [116]. The duration of carriage of this strain following exposure is also uncertain, with several studies suggesting carriage is quickly lost [95, 117] and others suggesting a longer duration of colonization [118, 119]. These studies have examined livestock-adapted CC398 types for the most part. Studies are still lacking to quantify the transmission potential and carriage duration of human types of CC398 strains. As these strains have no clear reservoir, such studies may be more difficult to carry out epidemiologically. Artificial inoculation studies have also been conducted using livestock-adapted strains, finding that they do successfully compete with other “human” strains of *S. aureus* [120]. Thus, CC398 isolates, even livestock-adapted ones, do seem to have the ability to effectively colonize hosts and cause symptomatic infections.

It should be noted that the only strains discussed in this review are either those identified as CC398 by MLST or CC398-associated types identified by *spa* typing. In the latter case, it is likely that the list of CC398-associated *spa* types is not comprehensive and that additional rare types are likely present in the population, which have not been identified. Furthermore, there are additional MLSTs related to CC398, which are discussed elsewhere [56, 121] and are not thoroughly covered here.

The situation in North America regarding *S. aureus* in livestock appears to be different in substantial ways as compared with that characterized in Europe to date. For example, the diversity of *S. aureus* types found in pigs seems to be higher in North America than in Europe. A number of *spa* types unrelated to CC398 have been found in Canadian and US swine, including t002/ST5 [16, 94, 95, 4], t008/ST8 [123, 124], and t337/ST9 [122]. These types have also been found in raw meat products [125–127] in addition to CC398-associated *spa* types. This diversity enormously complicates any surveillance efforts or attempts to determine a livestock origin versus a human origin of strains that may colonize a number of different species. Additionally, two papers have suggested that proximity to livestock farms or areas where manure is applied may increase the risk of acquiring MRSA colonization or developing an infection [128, 129], suggesting that other environmental factors in addition to direct contact with livestock may play a role in the development of *S. aureus* colonization and infections. And while potential markers for human versus livestock-associated CC398 strains have been suggested [37, 113], these need to be validated on a larger scale, as well as being tested to examine whether these or similar tests can differentiate livestock-associated or human-origin isolates from other sequence types that may be zoonotic. Until such tests are identified and rigorously validated, the

epidemiology of livestock-associated *S. aureus* in North America will remain muddled.

Finally, antibiotic use has been suggested to contribute to the evolution and spread of CC398 within the farming environment. This is due in large part to the findings that most livestock-associated CC398 isolates are resistant to antibiotics commonly used in agriculture, particularly beta lactams, tetracyclines, and macrolides. However, not all CC398 isolates are resistant to these drugs, with human-origin strains being more likely to be methicillin and tetracycline susceptible. Furthermore, resistance to zinc and other metals, which also may be present in animal feeds, could play a role in selection for antibiotic-resistant strains [130–132]. Additional research in this area is needed in order to determine the relative contributions of antibiotics, feed additives, and other practices on the farm and in the community to the evolution and spread of livestock-associated CC398 isolates.

Compliance with Ethics Guidelines

Conflict of Interest Tara C. Smith and Shylo E. Wardyn declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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