

Community-acquired methicillin-resistant *Staphylococcus aureus*: a global problem

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ABSTRACT

Infections by Community acquired *Staphylococcus aureus* (CA-MRSA) have drawn attention worldwide, including Brazil. **Objective:** to describe the epidemiology of CA-MRSA cases in Brazil order to understand its occurrence, risk factors and forms of management in the country compared with the worldwide situation. **Method:** literature review and for articles selection considering the databases: Scopus, Science Direct, Isi Web of Knowledge, PubMed and BVS. **Results:** ten national articles describing 21 cases of CA-MRSA were identified, mostly in children, adolescents and adults with skin and soft tissue infection progressing to severe infections related to Oceania Southwest Pacific Clone (OSPC) leading to hospitalization. **Conclusión:** although CA-MRSA is considered a global important microorganism we found a lack of published data about its epidemiology in Brazil, which hinder the design of the reality of the country against CA-MRSA. **Key words:** Community Acquired Infections; Drug Resistance, Bacterial; Infection Control; Methicillin Resistant *Staphylococcus Aureus*.

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INTRODUCTION

Staphylococcus aureus is a Gram-positive bacteria, present in various parts of the human body such as: nasal passages, throat, intestines and skin, it may cause infection when there is skin barrier disruption⁽¹⁾. The nasal epithelium stands out as the place with the highest colonization, whose prevalence reaches on average 40% in the adult population. As part of the human microbiota, this bacteria is not a risk, and may be carried for a long period without harming the health of individuals⁽²⁾.

However, under immunosuppression the presence of *Staphylococcus aureus* may favor the occurrence of infection⁽¹⁾. In general, these microorganisms are associated with skin and soft tissue infections, it may also cause severe and even fatal diseases⁽²⁾.

Staphylococcus aureus is a major agent within the antibiotic resistance approach since the 1960s, emerging immediately after the introduction of penicillin⁽³⁾. This bacteria acquired resistance to oxacillin, analogue to methicillin in the United States, justifying the acronym MRSA (Methicillin-resistant *Staphylococcus aureus*) used to identify them.

MRSA infections were predominantly considered a hospital problem until the 1980s, when the first cases of strains from Community origin or CA-MRSA (Community-Acquired) were registered. Since then, MRSA strains showing genetic and phenotypic characteristics different from hospital strains, HA-MRSA (Healthcare-Acquired), have been identified in the community causing infections in healthy people, not exposed to the usual risk factors, resulting in an epidemiology change of these microorganisms⁽³⁾.

Although the first cases were registered in the 1940s, bacterial resistance is still a very current problem and of such importance that justified its proposal by the World Health Organization as a global challenge by the World Alliance for Patient Safety in 2008⁽⁴⁾.

Resistant microorganisms from community have been recognized as important pathogens whose incidence has grown in many parts of the world. CA-MRSA infections have drawn attention due to its rapid emergence⁽⁵⁾, increase in the prevalence⁽⁶⁾ and the potential to cause serious infections⁽⁷⁾. However, despite the progress, Brazil still does not have a well-established discussion of these microorganisms to provide greater disclosure of the scenario, prevalence and aspects related to prevention. In this sense, the following question emerged, *what is the national situation regarding the occurrence and spread of CA-MRSA?*

Thus, the aim of the study is to describe the epidemiology of cases of CA-MRSA identified in Brazil in order to understand their occurrence, associated risk factors and management in relation to the world situation.

METHODOLOGY

This is an integrative review, which sought to identify studies on the occurrence of CA-MRSA infections in Brazil to describe the epidemiology of these cases comparing to the world literature. We chose this design because it is an

under-discussed topic in Brazil and, above all, due to the need to meet the national situation in order to enable reflections on prevention and control at the rapid emergence of this microorganism in the world.

The selection of studies was conducted through searches in the following databases: Scopus, Science Direct, Isi Web of Knowledge, PUBMED (National Library of Medicine) and Virtual Health Library (VHL) covering LILACS, IBECs, MEDLINE, Cochrane and SciELO. We used the descriptors in Health Sciences (decs.bvs.br) in English and Portuguese languages, respectively as follows: community-acquired infections; drug resistance, bacterial; infection control; methicillin resistant *Staphylococcus aureus* and *infecções comunitárias adquiridas*, *farmacorresistência bacteriana*, *controle de infecções*, *Staphylococcus aureus resistente à meticilina* separately and along with the connector AND.

The search for studies was conducted from 2007, the year when the Guideline for Isolation Precaution⁽⁸⁾ was published changing the nomenclature for hospital infections to Healthcare-associated Infections (HAI). The new definition seems to be more appropriate to current reality, it expands the previous concept warning the possibility of occurrence of these diseases hospital environment.

Inclusion criteria for selection of studies were: original studies, independently of the design used, that addressed the epidemiological profile of the affected individual or group, pathogenesis and/or clinical outcomes, risk factors, prevention, control and treatment recommended in these cases, must be conducted in Brazil, independently of the language of publication or design used.

We excluded studies regarding HAI acquired in the hospital environment which clinical manifestation occurred in the community associated with CA-MRSA and those whose infections were defined as community only in accordance with the phenotypic and microbiological characteristics of strains and not according to the place of origin of the infection.

Initially we identified 482 studies. Of this total, 95 were selected considering the title, six duplications were excluded. After reading the abstracts, 42 were selected, and 21 of these were related to the topic of the study, and only ten of these studies were carried out in Brazil, as previously defined as inclusion criteria.

Data collection was conducted systematically after reading and analysis of studies, previously selected through a questionnaire developed by the authors and the results are presented in Box 1 and 2, descriptively.

RESULTS

Ten studies were identified in Box 1, which met the pre-defined inclusion criteria.

Most study designs were case studies, clinical cases or case series (8/10) and seven studies were published in national journals. All cases have been reported in large urban centers in the southern, southeast and northeast of Brazil except one city from the countryside of Sao Paulo⁽¹⁶⁾. The cases of infection by CA-MRSA described in studies that met the inclusion criteria were compiled and are presented in Box 2.

Box 1 – Characteristics of the studies included in the integrative review of literature (2007-2008), Belo Horizonte, 2014

ID	Study location	Journal	Year	Objective	Study design
(9)	Rio de Janeiro Porto Alegre	Diagn Microbial Infec Dis	2007	To describe the detection of OSPC isolates in Rio de Janeiro and the emergence of other international clone of CA-MRSA in Brazil.	multicentric study
(10)	Rio de Janeiro	Braz J Infect Dis	2008	To describe the first case of endocarditis caused by CA-MRSA in Brazil.	Case study
(11)	Porto Alegre	Rev Soc Bras Med Trop	2009	To report a case of sepsis in children, complicated by secondary pneumonia to soft tissue injuries by CA-MRSA in southern Brazil.	Case study
(11)	Rio de Janeiro	Braz J Med Biol Res	2009	To describe the first well characterized case of a severe CA-MRSA infection in a child in Rio de Janeiro.	Case report
(12)	São Paulo	Rev Soc Bras Med Trop	2009	To describe a case of necrotizing pneumonia by CA-MRSA, which did not identify the PVL toxin.	Case study
(13)	Porto Alegre	Diagn Microbiol Infect Dis	2009	To review the clinical and epidemiological characteristics of patients with SCCmec IV isolates treated at a hospital in Porto Alegre and evaluate the molecular epidemiology of these isolates.	Clinical case
(14)	Recife	An Bras Dermatol	2012	To evaluate the antimicrobial resistance profile of Staphylococcus aureus obtained from ambulatory patients with infection of skin and soft tissues.	Series of case studies
(15)	Salvador	Braz J Infect Dis	2013	To describe the spectrum of diseases acquired in the community presented by patients infected with Staphylococcus aureus and compare patients infected with MSSA and MRSA.	Retrospective Cohort
(16)	São Paulo	Diagn Microbial Infect Dis	2013	To report a case of MRSA sepsis in a male patient of 16 years, from a small town in countryside of Brazil.	Case study
(17)	Rio Grande do Sul	Rev AMRGS	2013	To describe a clinical case with literature review, in view of the importance of suspicion diagnoses and consequent early use of glycopeptide.	Case study

ID: identification of studies according to number of citation in the references.

Box 2 – Characterization of isolated cases of CA-MRSA in Brazil between 2007 and 2014

Case N°	Age group	Primary infection	Secondary infection	ATB	Length of stay	Condition to discharge	Clone Features	ID
1	7a	Skin abscess	Sepsis/pneumonia/osteomyelitis/Liver and lung abscesses	CLI GEN	50d	Cure	OSPC SCC mecIV Positive PVL	(1)
2	10a	Furunculosis	Septic Shock/pneumonia with pleural empyema/Endocarditis /Osteomyelitis	VAN CLI TEI	66d	Cure	OSPC SCC mecIV Positive PVL	(11)
3	17a	Infection of the upper airways	Bronchopneumonia /	TEI MER	72d	Cure	OSPC SCC mec IV Hemolysin Enterotoxin O	(12)
4	27a	Skin abscess	septic shock	CEF VAN	90d	Cure	SCC mec IV Positive PVL	(10)

Continua

Box 2 (cont.)

Case N°	Age group	Primary infection	Secondary infection	ATB	Length of stay	Condition to discharge	Clone Features	ID
5	3-56a	Skin abscess	ND*	ND*	ND*	ND*	OSPC SCC mecIV Positive PVL Enterotoxin E	(9)
6		Skin abscess						(9)
7		Skin abscess						(9)
8		Epididymis-orchitis						(9)
9		Septic arthritis						(9)
10	21a	Axillary abscess	ND*	CEF	ND*	Cure	OSPC SCC mecIV Positive PVL	(13)
11	46a	Pustules		SXT	35d			(13)
12	50a	Abscess		CFT CLI	ND*			(13)
13	47a	Furuncle	ND*	ND*	0d	ND*	ND*	(14)
14	14d	Pneumonia	ND*	CFL AMI OXC	19d	Cure	ND*	(15)
15	16d	Pneumonia	ND*	PEN AMI	12d	Cure	ND*	(15)
16	3a	Dactylitis	ND*	Não	7d	Cure		(15)
17	05m	Pyoderma	ND*	OXC	15d	Cure		(15)
18	2-20a	ND*	ND*	VAN	ND*	ND*		(15)
19	2-20a	ND*	ND*	VAN	ND*	Death		(15)
20	16a	Abscess	Orchitis/Pneumonia/Severe sepsis.	CFP VAN IMI SUT	42d	Cure	ST5-5 spat311 SCC mecIV Positive PVL Enterotoxin A	(16)
21	38a	Severe pneumonia	ND*	VAN PTZ	Between 14d and 21d	Cure	Positive PVL	(17)

ID: Reference; **ATB:** antibiotic; **AMI:** Amikacin; **CEF:** Cephalexin; **CFL:** Cephalotin; **CFP:** Cefepime; **CFT:** Ceftriaxone; **CIP:** Ciprofloxacin; **CLI:** Clindamycin; **GEN:** Gentamicin; **IMI:** imipenem; **MER:** Meropenem; **OXC:** Oxacillin; **PEN:** Penicillin; **PTZ:** Piperacillin/tazobactam; **SUT:** sulfamethoxazole/trimethoprim; **TEI:** teicoplanin; **VAN:** Vancomycin; **ND*** - No information described in the analyzed study.

The affected patients were sequentially numbered 1-21 identifying the age or age group, primary focus of infection and secondary infections, antibiotics used during treatment, length of hospital stay, conditions to discharge, clone isolated characteristics and study references.

Among the 10 studies included, 21 cases of infection by CA-MRSA were described. Most cases were reported in children, adolescents and adults evidenced by case report in this age group in the analyzed studies and there were no reports on elderly over 60 years.

Mostly, these patients were affected initially by infection of skin and soft tissue region with previous local trauma. Subsequently, they developed serious complications such as sepsis^(1,11-12), endocarditis⁽¹⁰⁾, necrotizing pneumonia⁽¹²⁾, orchitis^(9,16) and osteomyelitis^(1,11). These patients required

a prolonged hospital stay that lasted up to 90 days in one case⁽¹⁰⁾ with an estimated average of about 40 days. Except for one patient who progressed to death⁽¹⁵⁾ all other patients were discharged after cure, however, one of them, after discharge, remained with chest tube and ileostomy⁽¹²⁾ and other splenectomized⁽¹⁰⁾.

As for genotypic characterization of microorganisms in studies that provided identification, CA-MRSA clone, most commonly isolated, was the Oceania Pacific Southwest Clone (OSPC) not reported in only one study⁽¹⁶⁾, the *Staphylococcal cassette Chromosome* (SCC) *mec* type IV in the same way was not isolated in one study⁽¹⁷⁾ and all the studies reported positive strains for the gene which encodes exotoxin Pantone-Valentine Leucocidin (PVL). Also other toxins produced by the strains analyzed in these studies were hemolysin, enterotoxin O⁽¹²⁾, E⁽⁹⁾ and A⁽¹⁶⁾.

DISCUSSION

In order to improve our understanding analysis and discussion, data were grouped according to the following sub-topics: epidemiological profile of individuals/groups affected, pathogenesis, clinical manifestations, and treatment measures as well as possible measures to prevent and control these cases.

Epidemiological profile of individuals/groups affected

Most studies were published in 2009 (4/10) and no publications were found last year (2014). This fact reflects the dynamic nature of the problem of bacterial resistance that progresses rapidly with the isolation of new strains, previously unknown, reflecting the multiple microorganisms that deserve attention in this matter.

Most cases described in Brazil are in children, adolescents and young adults with previous skin lesion which progressed to complications. It is noteworthy that the presence of risk factors for infections was not addressed in these studies.

In international studies, CA-MRSA infections have been recorded since the 1980s. These studies point to the occurrence of these infections primarily in healthy populations, well-defined, living or exposed to conditions of agglomerations, with strict physical contact between them and with little or no contact with health services⁽²⁾ being commonly reported in children⁽¹⁸⁻²⁰⁾ and young adults^(3,21). However, with regard to the description of the epidemiological profile of individuals affected by infection with CA-MRSA in Brazil, due to the reduced number of studies relating to this subject, we still cannot provide a clear profile.

In the world, a higher incidence of these infections has been demonstrated in Aborigines in Australia⁽²¹⁾ and male homosexuals in the United States⁽²²⁾ when compared to the general population. In Denmark, a study conducted between 1999 and 2006 identified 35.6% and 3% of CA-MRSA infections were, respectively, in foreign individuals and patients with a recent history of travel to areas of high endemicity (United States, Thailand, Philippines and Mediterranean countries)⁽⁶⁾. And yet, athletes were also found to be individuals more likely to acquire and spread CA-MRSA because of the frequency of contact between them, sharing items and frequent skin lesions⁽²³⁾.

Regarding the possible factors related to cases of infection/colonization by CA-MRSA international studies described their association with frequent physical contact, breaking of skin integrity, sharing items⁽²³⁾, poor housing and hygiene conditions, previous antibiotic use^(21,24) illicit drug use, multiple sexual partners⁽²²⁾, nasal colonization with CA-MRSA, people without higher education, previous MRSA skin infection, previous contact with health workers⁽²⁴⁾ and contact with individuals from high endemicity areas⁽⁶⁾.

The incidence of these infections as well as colonization cases vary geographically⁽⁷⁾ and over time. In San Francisco, the annual incidence of infections by USA 300, common CA-MRSA strain in the US was estimated at 275 cases/100,000 inhabitants⁽²²⁾. In Denmark the incidence of CA-MRSA infections increased from 0.21 to 2.81/100,000 inhabitants between

1999 and 2006 with the last year exceeded the incidence rate of infection by HA-MRSA strains⁽⁶⁾. It is noteworthy that, in this country, MRSA infections were systematically reported to the Statens Serum Institut (SSI) by physicians and general practitioners for characterization purposes since 1986. These data, however, reinforces the importance of reporting the cases in the country in order to favor the adoption of early measures considering that the prevalence of this microorganism in the country is not known.

Pathogenesis

In Brazil, CA-MRSA strains, especially the clone OSPC, have been associated with cases of community-acquired infections. However, CA-MRSA infections in the country are not limited to the community setting also been identified in HAI related to the USA 300 and USA 400 clones in Rio de Janeiro and Porto Alegre^(9,25) and these are also important internationally identified clones^(3,7,24).

CA-MRSA infections occur in tissue invasion and subsequent inflammation, however, it is very important in the expression of virulence factors and production of toxins. Therefore, these infections can be associated with clinical manifestations even more severe than those observed in infections caused by strains of HA-MRSA⁽²⁶⁾.

CA-MRSA strains can produce up to 18 different toxins from those found in hospital strains including PVL, staphylococcal enterotoxin B, γ hemolysin⁽¹⁸⁾ and arginine catabolic mobile element (ACME)⁽¹⁹⁾. In cases associated with the occurrence of infections in Brazil, all the isolates were positive for the gene which encodes exotoxin PVL while some presented the ability to produce hemolysin and the enterotoxins O⁽¹²⁾, E⁽⁹⁾ and A⁽¹⁶⁾.

The PVL constitutes one of the most common virulence factors among strains of CA-MRSA and relates to the lysis of neutrophils and subsequent damage to the underlying tissues⁽¹⁹⁾. Encoded by the genes LukF and LukS⁽¹⁾ the PVL is present in most CA-MRSA strains and its prevalence varies geographically⁽¹⁰⁾. It has been identified in strains involved in cases of serious infections⁽¹⁾ especially lung and skin⁽¹⁹⁾. Although significant associations between necrotizing pneumonia and CA-MRSA PVL positive strains have been shown⁽¹⁸⁾, this association was not observed by Geng et al (2010). Thus, the controversial of whether such toxin constitutes the main virulence factor in these strains remains.

CA-MRSA is also characterized by possessing genetic islands known as SCCmec type IV and to a lesser degree, type V^(1-2,5,19) or new variant⁽²⁾. SCCmec contains the mec A gene⁽¹⁹⁾, involved in the production of penicillin binding protein (PB-P2a), responsible for resistance to β -lactam antibiotics⁽²⁾.

The SCCmec type IV, found on all the strains identified in the national studies evaluated, it is one of the smallest known chromosomal cassettes⁽¹⁻²⁾ losing resistance genes and introducing susceptibility to various classes of non- β -lactam⁽¹²⁾. Its small size facilitates its intense horizontal transfer between strains⁽²⁶⁾ which may have contributed to the origin of these microorganisms through the acquisition of SCCmec by strains of multi-susceptible *Staphylococcus aureus* (MSSA) with subsequent dissemination of these clones on the environment⁽⁵⁾. This theory

is supported by the study of Tong et al (2009) which showed similar behavior between strains of CA-MRSA and MSSA.

In USA 300 strains it was observed that the genes encoding the SCCmec type IV are physically linked to the encoding type I toxin ACME, which has been observed in experimental animal models such a reduction of the pathogenic strains after deletion of this element⁽²⁷⁾.

The type of genetic element associated with methicillin resistance to toxins produced are important to identify CA-MRSA strains from molecular methods such as MLST (*Multi-locus Sequence Typing*) and PFEG (*Pulsed-field Electrophoresis Gel*)⁽⁷⁾ allowing the classification of strains in different clones as: Pacific clone - ST59, OSPC - ST30, *European clone* - ST80, USA 300- ST8 Pandemic clone, Midwest clone (ST1). However, the classification of these strains is still a challenge in addressing these microorganisms since none of these known criteria are unique to CA-MRSA strains⁽²⁾.

Clinical implications

In Brazil, severe cases of CA-MRSA infections such as infective endocarditis⁽¹⁰⁾, sepsis^(1,11,16) and necrotizing pneumonia⁽¹²⁾ were registered in the south, southeast and northeast of the country. In general, these patients were admitted to the emergency service or hospitalization for extended periods or died.

In hospitalized children in Taiwan the infectious conditions related to CA-MRSA included similarly to those complications in Brazil such as sepsis, necrotizing pneumonia, osteomyelitis/arthritis with or without septic pulmonary embolism, pyomyositis and necrotizing fasciitis, which 29% of them developed shock or serious illness and remained on average 18 days in intensive care unit⁽¹⁸⁾. In addition, 36.4% of children with primary pneumonia showed necrotizing pneumonia associated with empyema. Episodes of acute hemorrhage syndrome necrotizing pneumonia has largely been associated with CA-MRSA strains affecting children⁽²⁰⁾ generally after flu condition⁽⁷⁾.

Tables of necrotizing fasciitis is characterized by pain, swelling, erythema and subsequent appearance of local bulous lesions and should be considered when there is soft tissue infection associated with systemic signs of toxicity⁽¹⁹⁾.

Treatment measures

In therapeutic approach, the selection of antimicrobial should be performed according to the site of infection and the pattern of the micro-organism sensitivity. CA-MRSA strains are typically sensitive to various antibiotics showing resistance to β -lactam additionally to one or two other drugs⁽²²⁾, different to the HA-MRSA strains, resistant to multiple antibiotics⁽³⁾.

In Brazil, most antimicrobials used to treat infections by CA-MRSA in hospitals were vancomycin and clindamycin. Other international studies reported that sulfamethoxazole/trimethoprim and clindamycin have been widely used in the treatment of CA-MRSA infections in outpatients as vancomycin has been the main drug of choice in hospital treatment⁽²⁸⁾, sepsis, pulmonary disease or multifocal⁽¹⁹⁾ and infection of the nervous system and/or in the presence of endocarditis^(11,29). In skin and soft tissue infections to early incision and drainage

with wide resection of necrotic tissues proved critical to the success of treatment^(19,29). Patients undergoing drainage associated with antibiotic therapy showed a failure rate of 25% compared to 60% failure in patients who received only drainage⁽²⁸⁾.

Besides these, fluoroquinolones, linezolid, minocycline, teicoplanin, tigecycline and daptomycin constitute therapeutic options for the treatment of CA-MRSA infections^(3,29).

However, an increase in resistance to β -lactam antibiotics have not been observed worldwide in recent years. In China, children with pneumonia caused by CA-MRSA, resistance profiles were identified for vancomycin 100%, three or more drugs 73%, four and over 65.4% or five or more 55.8%⁽²⁸⁾. Important to highlight the high clindamycin and erythromycin index resistance rate seen in this study were associated by researchers to great use of these drugs in the country by this age group. A study performed in Denmark found that approximately 50% of the evaluated CA-MRSA strains were multidrug-resistant, i.e. resistant's to oxacillin and/or kanamycin (53.6%), fusidic acid (44.4%), tetracycline (43.8%), streptomycin (37.1%), erythromycin (27%), clindamycin (18.8%), fluoroquinolones (18%), rifampicin (2%) and glycopeptides (0,5%)⁽⁶⁾.

Measures to prevent and control

Although not the subject of investigation of this study, we highlight the fact that preventive measures were not addressed in any of the national studies analyzed considering that they are extremely important aspects to discuss the occurrence of CA-MRSA.

On the other hand, the measures of prevention of CA-MRSA infections registered in the international literature were multiple and highlighted by studies as a way to halt the spread. Preventing and controlling the spread of CA-MRSA covers the general recommendations applicable to infection control and surveillance to multiresistant microorganisms, standardization of protocols and rational use of antibiotics, educational measures for health professionals, precaution applications of contact and hygiene of hands, cohort for infected or colonized patients and decolonization when there is indication, investment in more sensitive analytical methods, fast and easy to use for the detection of patients infected or colonized^(5,26) as well as curative maintenance on lesions until they heal⁽³⁰⁾.

In the community, strategies like enhance environmental and personal hygiene measures, especially hand, besides the use of dressing over the lesion at home, should be encouraged^(19,24,30). For people in situations of agglomerations or confinement is recommended to frequent washing clothes and towels avoiding sharing of these items in addition to the use of liquid soap, as CA-MRSA can be transmitted through bar soap⁽²⁴⁾. Regarding decolonization although a practice adopted in health institutions, there are no formal recommendations for their use in household contacts of patients with CA-MRSA infection^(7,25).

CONCLUSION

In Brazil, despite the progressive registration of the spread of bacterial resistance in hospitals environment, we were

identified only ten studies describing infections associated with CA-MRSA. So, even though this is considered a microorganism that is a national problem, the lack of published data on its occurrence, risk factors and management, hinder the estimation of its prevalence and implementation of control measures, management and prevention aimed mainly in its community origin.

The cases reported in Brazil occurred generally in children, adolescents and adults, with initial skin and soft tissue infection progressing to severe infections related to clone OSPC,

requiring hospitalization and use of antibiotics for prolonged periods.

The registry of few studies in the national context still raises a concern related to the professional training, lack of resources, technology and access to clinical laboratories to enable the identification of CA-MRSA which has serious implications for a reliable and fast diagnosis. These factors together hinder the identification, approach and implementation of measures which can impact directly on the knowledge of the true prevalence of CA-MRSA.

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