Community-Associated Methicillin-Resistant *Staphylococcus aureus*: Trends in Case and Isolate Characteristics from Six Years of Prospective Surveillance

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SYNOPSIS

Objectives. In 2000, the Minnesota Department of Health (MDH) implemented active, sentinel site surveillance for community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA). Data from 2000–2005 were analyzed to determine trends in case characteristics, pulsed-field types (PFTs), and antimicrobial susceptibilities including inducible clindamycin resistance (ICR).

Methods. Active sentinel site surveillance was initiated in 2000 at 12 hospital laboratories that served inpatients and outpatients. Patient medical records were reviewed to determine if they met the epidemiologic case criteria for CA-MRSA; isolates were obtained from patients meeting these criteria. The MDH Public Health Laboratory performed pulsed-field gel electrophoresis subtyping and antimicrobial susceptibility testing, including ICR.

Results. The proportion of MRSA cases classified as CA increased from 11% to 33% ($p < 0.01$). The proportion of cases with skin or soft tissue infections also increased compared with other infection types from 75% to 87% ($p < 0.01$). During the surveillance period, USA300 replaced USA400 as the dominant PFT. With the change in dominant PFT, the proportion of isolates susceptible to erythromycin (45% to 13%, $p < 0.01$) and ciprofloxacin (80% to 59%, $p < 0.01$) decreased. The proportion of erythromycin-resistant/clindamycin-susceptible isolates with ICR (93% to 14%, $p < 0.01$) decreased. The proportion of susceptible isolates also changed within the USA300 PFT; the proportion of isolates susceptible to erythromycin (33% vs. 3%) and the proportion susceptible to ciprofloxacin (67% to 62%) decreased significantly.

Conclusion. CA-MRSA increased dramatically from 2000 to 2005. Changes in the predominant PFT have impacted susceptibility profiles of CA-MRSA, including ICR. Continued surveillance is needed to monitor the changing epidemiology of CA-MRSA and to inform clinical decisions.

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Methicillin-resistant *Staphylococcus aureus* (MRSA) was first recognized as a health-care-associated (HA) pathogen shortly after the introduction of methicillin in 1960.^{1–3} Established risk factors for HA-MRSA infection include recent hospitalization or surgery, residence in a long-term-care facility, dialysis, and indwelling percutaneous medical devices and catheters.^{4,5} Over time, HA-MRSA strains became resistant to other antimicrobial classes in addition to beta-lactams.⁶ In 2002, the first cases of vancomycin-resistant *Staphylococcus aureus* (*S. aureus*) were identified in the U.S.^{7,8}

MRSA infections have been increasingly reported among people who lack established HA-MRSA risk factors. These community-associated MRSA (CA-MRSA) infections have been observed throughout the U.S.^{9–14} and worldwide^{15–17} in a variety of settings.^{14,15,18–22} In contrast with HA-MRSA isolates, CA-MRSA isolates are generally susceptible to non-beta-lactam antimicrobials.^{12,13} Studies conducted in Minnesota found that isolates from CA-MRSA infections were more likely to be susceptible to ciprofloxacin, clindamycin, gentamicin, and trimethoprim-sulfamethoxazole than were isolates from HA-MRSA infections.²³

In communities in which CA-MRSA strains have been identified, non-beta-lactam antimicrobials such as clindamycin are increasingly being recommended as empiric antimicrobial therapy in patients with suspected *S. aureus* infections.^{24,25} This practice has resulted in concern about the use of clindamycin, because *S. aureus* strains that are erythromycin-resistant/clindamycin-susceptible (ER-CS)²⁶ may be phenotypically susceptible to clindamycin, but have the genotypical potential for clindamycin resistance when a 14- or 15-membered ring macrolide (e.g., clarithromycin, erythromycin, or azithromycin) inducer is present.^{27,28} In addition, in an *S. aureus* strain with inducible clindamycin resistance (ICR), constitutively resistant mutants may be selected at high inocula.²⁷

The Centers for Disease Control and Prevention has classified MRSA pulsed-field gel electrophoresis (PFGE) patterns into pulsed-field types (PFTs) for comparison.²⁹ CA strains have been found to have different PFTs compared with HA strains.²³ The objective of this analysis was to describe case and isolate characteristics of CA-MRSA for the six-year period of 2000–2005 in Minnesota. Case demographic and clinical characteristics, PFTs, and antimicrobial susceptibility patterns, including ICR, were analyzed to determine trends during this time period.

METHODS

Isolate ascertainment and case definitions

The Minnesota Department of Health (MDH) established a sentinel site surveillance network of 12 hospital laboratories that began prospective surveillance for MRSA in 2000. Characteristics of sentinel laboratories have been described elsewhere;²³ of note, all sentinel laboratories served outpatients and inpatients.

Participating hospital laboratories identified all patients with MRSA isolated from clinical culture results. Cases identified from January 1, 2000, to December 31, 2005, and isolates from January 1, 2000, to June 30, 2005, were included in the analysis. Facility infection control practitioners obtained information about patients and their infections via medical record review. HA-MRSA patients were defined as patients with any of the following: an MRSA infection identified after 48 hours of admission to a hospital; a history of hospitalization, surgery, dialysis, or residence in a long-term-care facility within one year prior to the MRSA culture date; a permanent indwelling catheter or percutaneous medical device present at the time of culture; or a known positive culture for MRSA prior to the study period. Patients who had none of these HA-MRSA risk factors were classified as having CA-MRSA infections.

In 2000–2002, patients classified as having CA-MRSA infections on the basis of medical record review were also interviewed to verify case classification. Misclassification was found to be 13% (73/584) in 2000–2002, and case subjects in years 2003–2005 were not interviewed. Information on all MRSA infection sites was obtained; if patients had more than one MRSA infection, only one was selected for analysis. The hierarchy for choosing the type of infection for patients with multiple sources was: blood, bone, pleural fluid, peritoneal fluid, joint, surgical specimen, postoperative wound, eye, ear, sputum, urine, and skin. Infections in which MRSA was cultured from blood, bone, pleural fluid, peritoneal fluid, or a joint were classified as invasive infections.

Laboratory testing

All CA-MRSA isolates submitted to the MDH Public Health Laboratory (PHL) from January 1, 2000, to June 30, 2005, were confirmed and characterized by antimicrobial susceptibility and PFT. Identification of *S. aureus* was confirmed with a tube coagulase test (Difco Laboratories, Detroit, Michigan), oxacillin resistance was confirmed using an oxacillin agar screen test (Becton Dickinson, Cockeysville, Maryland), and antimicrobial susceptibility testing was performed by broth microdilution panel (PML Microbiologicals,

Wilsonville, Oregon). All testing was performed in accordance with Clinical Laboratory Standards Institute (CLSI) standards.^{30,31} Isolates resistant to erythromycin (minimum inhibitory concentration [MIC] ≥ 8 $\mu\text{g/mL}$) and susceptible to clindamycin (MIC ≤ 0.5 $\mu\text{g/mL}$) were classified as erythromycin resistant-clindamycin susceptible (ER-CS).

ER-CS isolates underwent erythromycin disk induction testing of clindamycin (D-testing) to determine if clindamycin resistance was inducible in the presence of erythromycin.³² Testing for ICR was performed by one of three methods: (1) standard disk diffusion (0.5 McFarland suspension on Mueller-Hinton agar incubated 16 to 18 hours in ambient air) with clindamycin (2 μg) and erythromycin (15 μg) disks placed 12 mm apart, (2) standard disk diffusion with disks placed 15 mm apart, or (3) the purity plate method in which the panel inoculum suspension was streaked for isolation on standard 5% sheep blood agar with disks placed 15 mm apart in the first quadrant of the plate.^{31,33} A D-shaped flattening of the clindamycin zone adjacent to the erythromycin disk indicated ICR.²⁸ Isolates that did not exhibit flattening of the clindamycin zone were considered negative for ICR. Molecular typing of isolates was performed by PFGE of genomic DNA after restriction endonuclease digestion with *Sma*I. PFGE patterns were compared using Bionumerics Software³⁴ and the Dice coefficient. Patterns that had

exact matches of all bands in the range of 70–700 kb were considered indistinguishable. CA-MRSA isolates at least 80% similar to PFT reference strain based on the Dice coefficient were considered to be part of that PFT.²⁹

Statistical methods

Bivariate and trend analysis of data was performed using Epi Info³⁵ statistical software. The Mantel-Haenszel Chi-square test for trend was used to examine trends during the study periods. We determined significance using $\alpha \leq 0.05$.

RESULTS

During the six-year study period, a total of 11,554 MRSA infections were identified. Of these, 20% (2,325) were classified as CA-MRSA. The proportion of MRSA infections classified as CA had an increasing trend over time from 11% in 2000 to 33% in 2005 ($p < 0.01$) (Figure 1). The median age of CA-MRSA case subjects was 27 years, and 30% were nonwhite. The median age and the proportion of nonwhite cases did not change over time (Table 1). Skin and soft tissue infections (SSTIs) accounted for 82% of total infections. The proportion of CA-MRSA cases that were SSTIs increased during the study period from 75% in 2000 to 87% in 2005 ($p < 0.01$). Twenty-nine percent of people with

Figure 1. Percent of methicillin-resistant *Staphylococcus aureus* cases classified as community-associated, 2000–2005^a

^an = total number of community-associated methicillin-resistant *Staphylococcus aureus* cases per year

Table 1. Demographic and clinical characteristics of community-associated methicillin-resistant *Staphylococcus aureus* cases, 2000–2005

Characteristic	2000 (n=131) ^a Percent	2001 (n=161) ^a Percent	2002 (n=213) ^a Percent	2003 (n=314) ^a Percent	2004 (n=495) ^a Percent	2005 (n=1,011) ^a Percent	Chi-square for trend (p-value)
Median age (in years)	23	26	26	28	30	28	NS
Adult (age >18 years)	60	60	65	68	71	68	NS
Median adult age (in years)	41	42	41	41	41	39	NA
Pediatric (age <18 years)	40	40	35	52	29	32	NS
Median pediatric age (in years)	8	7	9	9	8	8	NS
Race							
White ^b	40	26	39	34	42	38	NS
Nonwhite	32	29	28	26	29	31	NA
Unknown	28	45	61	40	29	31	NA
Culture site ^c							
Skin/soft tissue ^d	75	75	73	76	83	87	39.7 (p<0.01)
Invasive ^e	5	6	10	6	5	2	18.0 (p<0.01)
Other ^d	20	19	17	18	12	11	20.4 (p<0.01)
Hospitalized	33	31	31	26	32	26	NS
Intensive care admission	5	<1	1	4	3	1	NS

^an = total number of community-associated methicillin-resistant *Staphylococcus aureus* isolates per year

^bComparison of white compared with nonwhite race

^cIf patients had more than one type of infection, only one was selected. The hierarchy for choosing the type of infection for cases with multiple sources was: blood, bone, pleural fluid, peritoneal fluid, joint, surgical specimen, postoperative wound, eye, ear, sputum, urine, and skin.

^dComparison of infection type represented in the row with all other infection types

^eInvasive community-associated methicillin-resistant *Staphylococcus aureus* infections were classified as those in which the culture site was blood, bone, pleural fluid, peritoneal fluid, or joint.

NS = not significant

NA = not applicable

CA-MRSA were hospitalized and 8% of those hospitalized were admitted into an intensive care unit (ICU); the proportion of cases hospitalized or admitted to an ICU did not change over time.

Isolates were obtained for 71% (1,660/2,325) of CA-MRSA cases with culture dates from January 1, 2000, through June 30, 2005; PFGE subtyping and susceptibility testing were performed by the MDH PHL on 88% (1,465/1,660) of isolates. Forty-three percent had PFGE patterns that were USA300 and 25% were USA400. However, the proportion of isolates classified as USA300 increased significantly during the surveillance period, from 6% in 2000 to 68% in 2005 ($p<0.01$). In contrast, the proportion of isolates classified as USA400 decreased from 63% in 2000 to 11% in 2005 ($p<0.01$) (Figure 2).

There were no significant changes in the proportion of isolates susceptible to clindamycin by broth microdilution, tetracycline, rifampin, or vancomycin (Table 2). The trend in the proportion of isolates susceptible to erythromycin significantly decreased from 45% in 2000 to 13% in 2005 ($p<0.01$), and the proportion of isolates susceptible to ciprofloxacin significantly decreased over time, from 80% in 2000 to 59% in 2005 ($p<0.01$).

The trend in the proportion of isolates susceptible to clindamycin by both broth microdilution and D-test increased significantly from 58% in 2000 to 77% in 2005 ($p<0.01$). This change was due to the decreased proportion of isolates with ICR and is further described in this article. Statistically significant increases in the proportion of isolates susceptible to gentamicin and trimethoprim-sulfamethoxazole were also observed. However, very few isolates were non-susceptible (18 non-susceptible to gentamicin and eight non-susceptible to trimethoprim-sulfamethoxazole) and these results are likely not clinically relevant (Table 2).

As shown in Table 2, from 2000 to 2005, the proportion of ER-CS isolates with ICR decreased significantly from 93% to 14% ($p<0.01$). This trend was influenced by the changes in dominant PFT observed during the study. Ninety-four percent of USA400 isolates had ICR compared with 2% of USA300 isolates. The proportion of isolates with ICR within USA300 and USA400 PFTs did not change during the study period.

The proportion of USA300 isolates susceptible to erythromycin significantly decreased over time. In 2000, 33% of isolates were susceptible compared with 3% in 2005 ($p<0.01$). There was also a significant

Figure 2. Percent of community-associated methicillin-resistant *Staphylococcus aureus* isolates by pulsed-field type and inducible clindamycin resistance by year, 2000–2005

ICR = inducible clindamycin resistance

decreasing trend in the proportion of isolates susceptible to ciprofloxacin within USA300 isolates, from 67% to 62% ($p < 0.01$) (Table 3). Significant trends were also observed for increases in the proportion of

USA400 isolates susceptible to gentamicin, tetracycline, and trimethoprim-sulfamethoxazole and USA300 isolates susceptible to gentamicin, trimethoprim-sulfamethoxazole, and rifampin. However, the number of

Table 2. Antimicrobial susceptibility and inducible clindamycin resistance trends of CA-MRSA isolates, 2000–2005^a

Characteristic	2000 (n=106) ^b Percent	2001 (n=145) ^b Percent	2002 (n=200) ^b Percent	2003 (n=279) ^b Percent	2004 (n=434) ^b Percent	2005 ^a (n=301) ^b Percent	Chi-square for trend (p-value)
Erythromycin	45	43	40	28	22	13	92.8 ($p < 0.01$)
Ciprofloxacin	80	77	78	68	68	59	26.9 ($p < 0.01$)
Clindamycin ^c	83	83	86	8	86	88	NS
Gentamicin	94	97	98	99	99	99	21.9 ($p < 0.01$)
Tetracycline	93	94	91	91	94	92	NS
Rifampin	97	100	99	99	99	100	NS
Trimethoprim-sulfamethoxazole	95	100	99	100	100	99	14.6 ($p < 0.01$)
Vancomycin	100	100	100	100	100	100	NS
ER-CS	30	35	44	56	64	75	118.4 ($p < 0.01$)
ICR ^d	93	82	50	36	16	14	155.9 ($p < 0.01$)
Clindamycin total ^e	58	56	64	64	76	77	38.0 ($p < 0.01$)

^aIsolates with culture dates from January 1, 2000, to June 30, 2005, were characterized.

^bn = total number of CA-MRSA isolates per year

^cSusceptible to clindamycin by broth microdilution only

^dPositive for ICR; two ER-CS isolates were not tested in 2000 and 2001, respectively.

^eSusceptible to clindamycin by broth microdilution and negative for ICR (D-test negative) when applicable

CA-MRSA = community-associated methicillin-resistant *Staphylococcus aureus*

NS = not significant

ER-CS = erythromycin resistant/clindamycin susceptible

ICR = inducible clindamycin resistance

non-susceptible isolates in these groups was very small and likely not clinically relevant.

MRSA is resistant to all antimicrobials in the beta-lactam class. Because SSTIs represent the largest proportion of CA-MRSA infections, we analyzed the proportion of SSTI cases that received a beta-lactam or erythromycin as their only reported initial antibiotic treatment (i.e., receipt of an antibiotic that was not likely to be effective against CA-MRSA). Initial antimicrobial treatment was documented for 50% of SSTI CA-MRSA cases. Reporting of an initial antibiotic decreased over time, from 64% in 2000 to 42% in 2005 (Table 4). Receipt of a beta-lactam or erythromycin only for a CA-MRSA SSTI decreased over time, from 61% of SSTIs treated in 2000 to 41% of SSTIs treated in 2005 ($p < 0.01$).

DISCUSSION

To our knowledge, this study is the first to analyze case characteristics, PFT, and antibiotic susceptibilities of CA-MRSA from a relatively large surveillance

population during an extended time period. Case characteristics and clinical presentations were similar to what has been reported elsewhere.²³ During the study period, the number of MRSA infections reported increased, as did the proportion of MRSA infections classified as CA. We also observed a significant increase in the proportion of CA-MRSA infections that were SSTIs, but no significant changes in case demographic characteristics or infection outcomes. Both mild and invasive infections were observed within USA300 and USA400, and further study may reveal whether there are unique clinical features by U.S. genotype.

A significant shift in PFTs from USA400 to USA300 was observed during the study period and influenced antimicrobial susceptibility and ICR trends. Ongoing research aims to explain why USA300 has become the dominant MRSA strain. As changes in the dominant PFT were observed in Minnesota, the proportion of isolates susceptible to erythromycin and ciprofloxacin decreased. The proportion of isolates demonstrating ICR also decreased. It is concerning that within the USA300 PFT the proportion of isolates susceptible to

Table 3. Susceptibility and inducible clindamycin resistance trends of USA400 and USA300 pulsed-field types of CA-MRSA isolates, 2000–2005^a

Characteristic	2000 Percent	2001 Percent	2002 Percent	2003 Percent	2004 Percent	2005 ^a Percent	Chi-square for trend (p-value)
USA400	n=67 ^b	n=80 ^b	n=83 ^b	n=75 ^b	n=70 ^b	n=33 ^b	
Erythromycin	55	53	51	52	51	61	NS
Ciprofloxacin	93	91	98	99	97	97	4.4 (0.04)
Clindamycin ^c	94	100	98	95	93	91	NS
ER-CS	30	38	48	48	43	30	NS
ICR ^d	100	100	92	100	79	100	NS
Clindamycin total ^e	66	61	54	53	67	91	NS
USA300	n=6 ^b	n=15 ^b	n=54 ^b	n=108 ^b	n=252 ^b	n=252 ^b	
Erythromycin	33	20	30	9	4	3	30.5 (0.01)
Ciprofloxacin	67	100	85	74	69	62	16.4 (<0.01)
Clindamycin ^c	83	87	98	99	96	95	NS
ER-CS	50	67	80	90	88	91	10.5 (<0.01)
ICR ^d	0	13	3	1	2	2	NS
Clindamycin total ^e	83	80	96	98	94	93	NS

^aIsolates with culture dates from January 1, 2000, to June 30, 2005, were characterized.

^bn = total number of CA-MRSA isolates per year

^cSusceptible to clindamycin by broth microdilution only

^dPositive for ICR

^eSusceptible to clindamycin by broth microdilution and negative for ICR (D-test negative) when applicable

CA-MRSA = community-associated methicillin-resistant *Staphylococcus aureus*

NS = not significant

ER-CS = erythromycin resistant-clindamycin susceptible

ICR = inducible clindamycin resistance

Table 4. Initial antibiotic treatment of community-associated methicillin-resistant *Staphylococcus aureus* skin or soft tissue infections, 2000–2005

Characteristic	2000 Percent	2001 Percent	2002 Percent	2003 Percent	2004 Percent	2005 Percent	Chi-square for trend (p-value)
Initial antibiotic treatment reported	64	58	63	46	60	42	18.5 (<0.01)
Treatment with a beta-lactam or erythromycin only ^a	61	57	55	75	59	41	31.8 (<0.01)

^aAll methicillin-resistant *Staphylococcus aureus* (MRSA) isolates are resistant to beta-lactam antibiotics. Due to the high proportion of erythromycin resistance among MRSA isolates, the Minnesota Department of Health does not recommend erythromycin for treatment of skin and soft tissue infections with suspected staphylococcal etiology. Minnesota Department of Health. Community-associated methicillin-resistant *Staphylococcus aureus* in Minnesota. Disease Control Newsletter 2004;32:61-7.

erythromycin and ciprofloxacin decreased, suggesting that as CA-MRSA strains continue to circulate, they may become resistant to additional antimicrobial classes.

Studies have implicated antimicrobial pressure as a contributor to the increasing prevalence of CA-MRSA,^{36,37} and recent antimicrobial use has been associated with CA-MRSA colonization.³⁸ The observed decreases in CA-MRSA susceptibilities to erythromycin and ciprofloxacin may be a reflection of the increasing use of macrolides and quinolones in clinical practice. A recent study found that although beta-lactams are still the most commonly used agents in ambulatory care, the prescribing rates of azithromycin and clarithromycin (macrolides) and quinolones (ciprofloxacin) increased from 1992 to 2000.³⁹ Our findings appear to highlight the continued importance of promoting appropriate antimicrobial use.

As part of surveillance, we collected information regarding initial antibiotic treatment and analyzed the data for subjects with CA-MRSA SSTIs. We found that reporting of an initial antibiotic had decreased over time. We do not know if the decrease in reporting an initial antibiotic is a result of changes in treatment practices, such as increased incision and drainage without antibiotic treatment, or if antibiotics were prescribed but reporting was not as thorough (possibly due to the increased reporting burden). Our data do support that among CA-MRSA cases with an SSTI, empiric treatment with a beta-lactam or erythromycin only decreased. This decrease could be the result of increased awareness of CA-MRSA and treatment recommendations among clinicians during the study period, although there is still much room for improvement.⁴⁰

The increased frequency of CA-MRSA infections, particularly among children, has led to recommendations for empiric use of clindamycin for suspected *S. aureus* infections in pediatric patients when antimicrobial therapy is indicated.^{24,25} However, during a course of clindamycin therapy, constitutive clindamycin-resistant

mutants may be selected, particularly when the bacterial inoculum is high.²⁶ This has been demonstrated both *in vitro* and *in vivo*.^{28,41,42} Because the prevalence of ICR varies by PFT,³² determining the presence of ICR in clinical isolates that are ER-CS (as recommended by CLSI)³³ is important in guiding antimicrobial therapy, particularly in severe infections or those with high inoculum. However, among our USA300 isolates, most macrolide resistance was due to an efflux mechanism and did not confer clindamycin resistance.

It is important to consider and evaluate additional treatment approaches for MRSA skin infection. One study found that non-severe MRSA SSTIs (<5 cm in size) may be successfully treated by incision and drainage alone.⁴³ However, another study found that antimicrobial treatment of skin infections was beneficial.⁴⁴ Thorough studies of clinical outcomes for CA-MRSA infections are needed.

Limitations

The study had several limitations. First, the study found a significant increase in the number and proportion of CA-MRSA infections reported from sentinel sites over time. Part of this increase may be a result of changes in culturing practices, due to increased awareness of CA-MRSA infections by clinicians, increasing the likelihood that cultures were obtained for suspected staphylococcal infections. This change in practice may also have impacted the site of CA-MRSA infections reported. During the study years, considerable efforts were made to encourage clinicians to culture SSTIs rather than treat them empirically. Additionally, one sentinel site embarked on a project in 2004 to culture all SSTIs presenting to their emergency department for one month.⁴⁵ This project may have impacted demographic characteristics and site of infection in 2004. However, trends in both the increase in CA-MRSA and the proportion of MRSA that was classified as CA continued in 2005 after the cessation of the project at the sentinel site.

Another limitation of this study was that it was not population-based and the patient population of the sentinel hospitals may not be representative of the entire state. Because of the volume of CA-MRSA cases in 2005, we chose to characterize isolates from only the first six months of the year, which may not be representative of the later half of the year. In addition, some HA-MRSA patients may have been misclassified as CA-MRSA due to incomplete ascertainment of HA risk factors. In general, HA-MRSA isolates are resistant to multiple antimicrobial classes. If misclassification systematically increased over the years, it could have influenced antimicrobial susceptibility trend results. Finally, numbers within some strata are small; for example, the analysis included only six USA300 isolates in 2000.

CONCLUSION

The high proportion of CA-MRSA isolates resistant to erythromycin and ciprofloxacin is concerning. This trend impacts treatment options for CA-MRSA infections, and decreases in susceptibility to these and other antimicrobial classes should be monitored closely using standard case definitions and methodology. More data on clinical outcomes and prevention and control strategies for CA-MRSA are urgently needed.

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