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Clindamycin resistance among *Staphylococcus aureus* strains in Israel: implications for empirical treatment of skin and soft tissue infections

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SUMMARY

Objectives: The objectives of this study were to characterize isolates of *Staphylococcus aureus* obtained from skin and soft tissue infections in the community in Israel and to document the sensitivity patterns for commonly used antimicrobial agents.
Methods: The susceptibilities of *S. aureus* isolates from skin and soft tissue infections in the community in Israel were reviewed to determine the appropriate empirical therapy for these infections.
Results: A total of 7221 isolates were collected during the period 2009–2012; 39% were from children (age 0–18 years). In children, *S. aureus* oxacillin resistance dropped from 8.4% to 3.8% ($p = 0.073$). While inducible clindamycin resistance increased slightly from 20% to 25%, there was a prominent increase in constitutive clindamycin resistance from 0.1% to 26.8% ($p = 0.012$). In adults, oxacillin resistance increased from 16% to 23% ($p < 0.001$) and constitutive clindamycin resistance increased notably from 5% to 29% ($p < 0.001$). These findings demonstrate a dramatic increase in clindamycin resistance among *S. aureus* isolates and suggest against the usage of clindamycin as empirical treatment for suspected *S. aureus* infections in Israel.
Conclusions: Beta-lactam anti-staphylococcal agents may be given as empirical treatment for children, but should be considered according to risk factors for adults in Israel.

1. Introduction

During the past two decades, a steep global rise has been seen in infections with community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) in individuals with no known risk factors.[1–3] Unfortunately, clinical and epidemiological characteristics cannot distinguish CA-MRSA infection from methicillin-susceptible *S. aureus* (MSSA) infection.[4]

Although there are no data to determine a specific cut-off prevalence rate of MRSA infection that warrants a change in empirical therapy, a prevalence of >15% has been suggested.[5] As a result, in the USA, the use of clindamycin as an alternative empirical treatment for suspected *S. aureus* infections rose from 21% in 1999 to 63% in 2008.[1] Clindamycin has several advantages—it has both parenteral and oral formulations, with high bio-availability, good skin and soft tissue permeability, it inhibits toxin production, and is relatively cheap.[6] Clindamycin has also been used as an alternative antibiotic for staphylococcal infections in patients with type 1 hypersensitivity to beta-lactam antibiotics. Another optional treatment for staphylococcal infections is trimethoprim–sulfamethoxazole (TMP–SMX), which is also a relatively cheap agent. This anti-staphylococcal bactericidal treatment is also available in both oral and parenteral formulations.

Based on a prevalence of resistance of >15% as a guidance for empirical treatment,[5] it is crucial to examine the local epidemiology in order to optimize the empirical treatment administered in cases of suspected *S. aureus* infection. The objectives of this study were to determine the appropriate empirical treatment for skin and soft tissue infections (SSTIs) through the characterization of isolates of *S. aureus* from SSTIs in the community in Israel and to document their sensitivities to the following antibiotics by age group: oxacillin, clindamycin (constitutive and inducible), and TMP–SMX.

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2. Methods

This retrospective survey was performed in collaboration with the central laboratory of Maccabi Health Care Services, which receives specimens and performs all laboratory tests for all of the Health Maintenance Organization (HMO) patients in the community setting throughout Israel. The computerized database of the central laboratory was reviewed for the characteristics of *S. aureus* isolates obtained from SSTIs during the years 2009–2013. The antibiotic susceptibility patterns of these isolates were documented. Stratification for methicillin resistance among adults was performed according to age groups and long-term care facility (LTCF) residence in the last year of the study. Sensitivity testing was performed using the D-test, as well as with the Vitek automated system.

Comparisons of the distributions of dichotomous and continuous variables were done with the Chi-square test and Student's *t*-test, respectively. *p*-Values of <0.05 were considered significant.

The study was approved by the ethics committees of Wolfson Medical Center and Maccabi Health Services, Israel.

3. Results

Using the computerized data system of Maccabi Health Services, 7221 isolates of *S. aureus* grown in cultures taken from SSTIs between January 2009 and November 2012 were reviewed; 2822 of them (39%) were from children aged 0–18 years. Sensitivity patterns of the isolates to oxacillin and clindamycin are shown in Table 1.

With regard to methicillin resistance, the prevalence of MRSA in 2009 was 8.4% in children aged 0–18 years; the rate declined between 2010 and 2012 to 3.8%, however this change was not statistically significant ($p = 0.073$). In adults aged >19 years, MRSA prevalence increased from 16% in 2009 to 22–23% during 2010–2012. This trend was also not statistically significant ($p = 0.073$).

Further stratification among adults (Table 2) revealed relatively low MRSA rates (7%) in patients aged 18–39 years, but higher rates (18%) among adults 40–69 years of age and in older adults aged ≥70 years (32%). Higher rates of MRSA were detected in LTCF residents in the last two age groups (56% and 73% in adults aged 40–69 years and ≥70 years, respectively).

With regard to the main findings and trends for clindamycin resistance, in children aged 0–18 years the prevalence of inducible clindamycin resistance increased significantly from about 19–20% between 2009 and 2011 to 25% in 2012 ($p = 0.04$). Moreover, the increase in constitutive clindamycin resistance was dramatic: from 0.1–2.2% during 2009–2011 to 26.8% in 2012 ($p < 0.001$). In adults aged >19 years, the prevalence of inducible clindamycin resistance was stable over the years and was about 12–16%. However, the prevalence of constitutive clindamycin resistance showed a similar increase as found in children, from 5% in 2009 to 11–12% during 2010–2011, and rising to 29% in 2012 ($p < 0.001$).

Regarding TMP–SMX susceptibility, more than 96% of isolates in both children and adults were sensitive to TMP–SMX. There were no significant differences between MRSA and MSSA strains in their resistance to both clindamycin and TMP–SMX.

Table 2
MRSA resistance among adults according to age and LTCF residence (2013)

Age (years)		Community		LTCF	
		n	%	*n*	%
18–39	MRSA	15	7	1	6
	MSSA	201	93	17	94
	Total	216		18	
40–69	MRSA	76	18	20	56
	MSSA	350	82	16	44
	Total	426		36	
≥70	MRSA	76	32	61	73
	MSSA	165	68	22	27
	Total	241		83	

LTCF, long-term care facility; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

4. Discussion

Staphylococcus aureus causes a wide range of diseases; it is the main causative agent of SSTIs such as impetigo, cellulitis, and cutaneous abscesses. In addition, it causes invasive infections such as bone and joint infections, pneumonia, sepsis, endocarditis, and meningitis in rare cases.

The emergence of CA-MRSA strains has become a global problem and has been particularly prominent in the USA. A recently published meta-analysis surveyed the CA-MRSA epidemic in the last two decades and demonstrated a resistance rate ranging from 50% to 83% in different geographic areas in the USA.[7] The rate of MRSA in all community-associated *S. aureus* infections in European countries was found to be 59%,[8] while in Asian countries the reported rates range from 2.5% to 39%.[9]

In Israel, reports of MRSA rates have varied depending on the time or methodology: studies on carriage among children have found a prevalence of 0.8–2.6% of *S. aureus* isolates.[10–12] The prevalence was found to be somewhat higher (4.8%) in children hospitalized for *S. aureus* infections.[13] The carriage prevalence among adults in Israel has been found to be higher than in children.[14] There are no recent data on the prevalence of carriage or infection of MRSA in adults in Israel.

The growing expansion of CA-MRSA strains has led to the increased use of alternative anti-staphylococcal drugs, mainly

Table 1
Sensitivity patterns according to years and age groups

Year	Age (years)	*S. aureus* (*n*)	Constitutive clindamycin resistance		Inducible clindamycin resistance		MRSA	
			n	%	*n*	%	*n*	%
2009	0–18	1065	1	0.1	215	20.2	89	8.4
	>19	1532	77	5	245	16	245	16
2010	0–18	577	11	1.8	113	19.7	20	3.5
	>19	857	94	11	103	12	189	22
2011	0–18	627	14	2.2	118	18.9	21	3.4
	>19	1030	124	12	124	12	237	23
2012[a]	0–18	553	148	26.8	136	24.6	21	3.8
	>19	906	263	29	145	16	208	23

MRSA, methicillin-resistant *Staphylococcus aureus*.
[a] 2012: 11 months.

clindamycin. Herigon et al. described the antibiotic treatment of children hospitalized with *S. aureus* infection at 25 centers in the USA over 10 years. They reported an increased incidence of CA-MRSA from 2 to 21 cases per 1000 admissions, with a simultaneous increase in clindamycin use for empirical treatment from 21% in 1999 to 63% in 2008.[1]

There is concern that the increased use of alternative anti-staphylococcal drugs, mainly clindamycin and TMP–SMX, will cause selective pressure leading to the spread of strains that are resistant to these agents. Clindamycin acts by reversible binding to the 50S subunit of the ribosome, leading to the inhibition of protein synthesis. The mechanism of resistance of *S. aureus* to the MLSB antibiotics (macrolide, lincosamide, streptogramin B) is mediated through modification of the target site of these agents. This resistance is encoded by the *erm* gene, usually *erm*(C) or *erm*(A), which encodes the methylation of the 23S rRNA binding site that is shared by these three drug classes.

Phenotypically, resistance can be expressed constitutively (MLSBc phenotype) or only when induced into production following exposure to the antibiotics (MLSBi phenotype; inducible resistance).[15] MLSBc strains are easily recognized as they are resistant to both macrolides and clindamycin, whereas MLSBi strains appear to be resistant to macrolides but susceptible to clindamycin under standard testing conditions. This resistance is detected by placing an erythromycin susceptibility testing disk in proximity to a clindamycin disk; the enhanced expression of resistance among MLSBi strains is expressed by blunting of the clindamycin zone of inhibition on the zone margin closest to the erythromycin disk, resembling the shape of the letter D.[16]

The clinical implications of inducible clindamycin resistance are unclear. Concerns have been raised regarding the use of clindamycin in MLSBi infections, especially those that are deep-seated or with a large bacterial burden, although some patients will respond clinically to clindamycin therapy. While there is evidence that constitutive resistance to clindamycin prevents the inhibition of toxin production and fails to inhibit growth,[17] it is unclear whether inducible clindamycin resistance interferes with the inhibition of staphylococcal toxin production.[15]

This study was performed in collaboration with Maccabi Healthcare Services, the second largest HMO in Israel. Its central laboratory processes all cultures taken from Maccabi Healthcare Services patients in community settings throughout Israel.

The prevalence of MRSA previously found in the pediatric population in Israel was significantly lower than those reported in the USA.[7] The present findings of MRSA prevalence rates of 3–4% out of all *S. aureus* strains isolated from SSTIs among children in the community are in accordance with those of previous studies of the pediatric population in Israel, which have reported MRSA prevalence of 2–5% among *S. aureus* infections leading to hospitalization.[10–12] The prevalence of MRSA carriage among adults in the community setting in Israel was found to be 6.9% in a survey performed in the early 1990s.[14] However, more recent figures are lacking.

The results of this study indicate that due to the low prevalence of MRSA among the pediatric population, anti-staphylococcal beta-lactam antimicrobials are still appropriate as empirical treatment for suspected staphylococcal infections. In contrast, empirical treatment with beta-lactams may not be appropriate for older adults (≥70 years) and LTCF residents with SSTIs in Israel.

In contrast to the relatively low prevalence of MRSA in the community, data regarding clindamycin resistance found in this study are dramatic. For both constitutive and inducible resistance, this study found 50% prevalence among children and 35% among adults. This high rate of resistance suggests against the usage of clindamycin as a single empirical treatment for suspected staphylococcal infection, whether MRSA or MSSA. The resistance to clindamycin, especially among children, was not caused by MRSA strains, since the rate of MRSA in children did not increase during the study period, while clindamycin resistance peaked dramatically.

A study performed in Israel during 2006–2007, reported constitutive resistance to clindamycin among 2% and an acquired resistance among 26% of *S. aureus* isolates from children in tertiary care hospitals. These figures resemble the prevalence rates found during 2009, the first year of the present survey.[18]

Resistance rates to clindamycin among *S. aureus* isolates in the world vary geographically. Abdel Fattah and Darwish reported a considerable prevalence of constitutive resistance of 13% in Egypt.[19] A study conducted in India during 2010 documented a prevalence of constitutive resistance of 9% and inducible resistance of 10% among MSSA strains.[20] A prospective study conducted during 2001–2004 in Texas, USA, found a significant increase in resistance to clindamycin over the 3 years of the study. The prevalence of clindamycin resistance in MSSA and MRSA was found to be 11% and 6%, respectively, mostly constitutive.[2] A study from Israel reported a clindamycin resistance rate of 28% among *S. aureus* isolates recovered from hospitalized children in a tertiary medical center during 2006–2007, the large majority (91%) being inducible resistant strains.[18]

The present data regarding clindamycin resistance suggest against its use alone as the first choice therapy in patients with beta-lactam hypersensitivity. It may be used in children in combination with another anti-staphylococcal agent, such as TMP–SMX, and an alternative approach is a combination of macrolide and TMP–SMX.

Another finding of this study was the relatively low, stable resistance rate for TMP–SMX among both MSSA and MRSA strains, ranging between 2% and 4% during the 5 years of the survey. In contrast to the data regarding clindamycin, this finding indicates that TMP–SMX retains its antimicrobial activity against both MSSA and MRSA and about 97% of these strains are susceptible to this agent. The combination of TMP and SMX has shown high bactericidal activity against many bacteria. Furthermore, the bioavailability of TMP–SMX is relatively high, approximately 85% for both compounds. TMP–SMX is distributed widely throughout the body, although tissue concentrations are generally less than serum concentrations.[21]

Elliott et al. found TMP–SMX to be inferior to anti-staphylococcal beta-lactams and clindamycin for the treatment of SSTIs in a pediatric population.[22] In contrast, it was found to be significantly superior to cephalexin in treating cellulitis.[23] Moreover, a study that compared patients treated with TMP–SMX to those treated with daptomycin or linezolid, showed TMP–SMX therapy not to be inferior to these newer antimicrobials in terms of efficacy and mortality, in addition to being much cheaper.[24] Additionally, the bactericidal activity of TMP–SMX for MRSA was found to be superior to clindamycin, rifampicin, minocycline, and linezolid.[25] However, TMP–SMX has limited activity against group A Streptococcus (GAS), and this should be taken into consideration when this agent is used empirically for SSTIs.

This is the first nationwide survey to examine the incidence of MRSA and sensitivity profiles of *S. aureus* isolates in Israel; however it has several limitations. There could be an upward bias in the resistances rates, since, in the community setting, cultures are often taken when there is no response to empirical treatment. However, it is believed that the high number of isolates included in this survey reduces the likelihood of this type of bias. Furthermore, this bias would not affect the data regarding clindamycin resistance, since in Israel clindamycin is very rarely used as an empirical therapy in the ambulatory setting. Another limitation is the lack of differentiation among geographic regions in the country, although Israel is a geographically small country and it can be assumed that there is no significant variation among these regions.

In conclusion, the high rate of clindamycin resistance is concerning and suggests against the usage of this drug as an empirical treatment for suspected *S. aureus* infections in Israel. The rate of MRSA among the pediatric population in Israel is relatively low compared to reports from other countries and also to the rates in Israeli adults. Currently, anti-staphylococcal beta-lactams can be given as empirical treatment for children, but should be reconsidered in cases of SSTIs in adult patients in Israel, especially in older adults (over 70 years old) and/or in adults residing in LTCFs. The resistance rate to TMP–SMX was found to be relatively low, thus suggesting it as a therapeutic option that can be given empirically, especially when MRSA is suspected.

Conflict of interest: There are no conflicts of interest to declare.

Author contributions: Michal Stein: study design, data collection, data analysis, writing; Jacqueline Komerska: study design, data collection, writing; Miriam Prizade: study design, data collection; Bracha Sheinberg: study design, data collection; Diana Tasher, study design, data collection, data analysis, writing; Eli Somekh: study design, data collection, data analysis, writing.

References

1. Herigon JC, Hersh AL, Gerber JS, Zaoutis TE, Newland JG. Antibiotic management of *Staphylococcus aureus* infections in US children's hospitals, 1999-2008. *Pediatrics* 2010;**125**:e1294–300.
2. Kaplan SL, Hulten KG, Gonzalez BE, Hammerman WA, Lamberth L, Versalovic J, et al. Three-year surveillance of community-acquired *Staphylococcus aureus* infections in children. *Clin Infect Dis* 2005;**40**:1785–91.
3. Miller LG, Quan C, Shay A, Mostafaie K, Bharadwa K, Tan N, et al. A prospective investigation of outcomes after hospital discharge for endemic, community-acquired methicillin-resistant and -susceptible *Staphylococcus aureus* skin infection. *Clin Infect Dis* 2007;**44**:483–92.
4. Miller LG, Perdreau-Remington F, Bayer AS, Diep B, Tan N, Bharadwa K, et al. Clinical and epidemiologic characteristics cannot distinguish community-associated methicillin-resistant *Staphylococcus aureus* infection from methicillin-susceptible *S. aureus* infection: a prospective investigation. *Clin Infect Dis* 2007;**44**:471–82.
5. Boucher H, Miller LG, Razonable RR. Serious infections caused by methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis* 2010;**51**:S183–97.
6. Baker CJ, Frenck RW. Change in management of skin/soft tissue infections needed. AAP news. *Am Acad Pediatrics* 2004;**25**:105–17.
7. Dukic VM, Lauderdale DS, Wilder J, Daum RS, David MZ. Epidemics of community-associated methicillin-resistant *Staphylococcus aureus* in the United States: a meta-analysis. *PLoS One* 2013;**8**:e52722.
8. Rolo J, Miragaia M, Turlej-Rogacka A, Empel J, Bouchami O, Faria NA, et al. High genetic diversity among community-associated *Staphylococcus aureus* in Europe: results from a multicenter study. *PLoS One* 2012;**7**:e34768.
9. Chuang YY, Huang YC. Molecular epidemiology of community-associated meticillin-resistant *Staphylococcus aureus* in Asia. *Lancet Infect Dis* 2013;**13**:698–708.
10. Adler A, Givon-Lavi N, Moses AE, Block C, Dagan R. Carriage of community-associated methicillin-resistant *Staphylococcus aureus* in a cohort of infants in southern Israel: risk factors and molecular features. *J Clin Microbiol* 2010;**48**:531–8.
11. Schlesinger Y, Yahalom S, Raveh D, Yinnon AM, Segel R, Erlichman M, et al. Methicillin-resistant *Staphylococcus aureus* nasal colonization in children in Jerusalem: community vs. chronic care institutions. *Isr Med Assoc J* 2003;**5**:847–51.
12. Regev-Yochay G, Carmeli Y, Raz M, Pinco E, Etienne J, Leavitt A, et al. Prevalence and genetic relatedness of community-acquired methicillin-resistant *Staphylococcus aureus* in Israel. *Eur J Clin Microbiol Infect Dis* 2006;**25**:719–22.
13. Glikman D. [Community-associated methicillin-resistant *Staphylococcus aureus* infections among children in the western Galilee region: the beginning of an epidemic?] *Harefuah* 2009;**148**:761–5. 793, 794.
14. Dan M, Moses Y, Poch F, Asherov J, Gutman R. Carriage of methicillin-resistant *Staphylococcus aureus* by non-hospitalized subjects in Israel. *Infection* 1992;**20**:332–5.
15. Lewis JS, Jorgensen JH. Inducible clindamycin resistance in staphylococci: should clinicians and microbiologists be concerned? *Clin Infect Dis* 2005;**40**:280–5.
16. Fiebelkorn KR, Crawford SA, McElmeel ML, Jorgensen JH. Practical disk diffusion method for detection of inducible clindamycin resistance in *Staphylococcus aureus* and coagulase-negative staphylococci. *J Clin Microbiol* 2003;**41**:4740–4.
17. Coyle EA, Lewis RL, Prince RA. Influence of clindamycin on the release of *Staphylococcus aureus* ca-hemolysin from methicillin resistant *S. aureus*: could MIC make a difference [abstract 182]. *Crit Care Med* 2003;**31**:A48.
18. Shouval DS, Samra Z, Shalit I, Livni G, Bilavsky E, Bilvasky E, et al. Inducible clindamycin resistance among methicillin-sensitive *Staphylococcus aureus* infections in pediatric patients. *Isr Med Assoc J* 2011;**13**:605–8.
19. Abdel Fattah NS, Darwish YW. Antibiogram testing of pediatric skin infections in the era of methicillin-resistant *Staphylococcus aureus*: an Egyptian university hospital-based study. *Int J Dermatol* 2012;**51**:1441–7.
20. Prabhu K, Rao S, Rao V. Inducible clindamycin resistance in *Staphylococcus aureus* isolated from clinical samples. *J Lab Physicians* 2011;**3**:25–7.
21. Brown GR. Cotrimoxazole—optimal dosing in the critically ill. *Ann Intensive Care* 2014;**28**:13.
22. Elliott DJ, Zaoutis TE, Troxel AB, Loh A, Keren R. Empiric antimicrobial therapy for pediatric skin and soft-tissue infections in the era of methicillin-resistant *Staphylococcus aureus*. *Pediatrics* 2009;**123**:e959–66.
23. Khawcharoenporn T, Tice A. Empiric outpatient therapy with trimethoprim–sulfamethoxazole, cephalexin, or clindamycin for cellulitis. *Am J Med* 2010;**123**:942–50.
24. Campbell ML, Marchaim D, Pogue JM, Sunkara B, Bheemreddy S, Bathina P, et al. Treatment of methicillin-resistant *Staphylococcus aureus* infections with a minimal inhibitory concentration of 2 μg/ml to vancomycin: old (trimethoprim/sulfamethoxazole) versus new (daptomycin or linezolid) agents. *Ann Pharmacother* 2012;**46**:1587–97.
25. Kaka AS, Rueda AM, Shelburne SA, Hulten K, Hamill RJ, Musher DM. Bactericidal activity of orally available agents against methicillin-resistant *Staphylococcus aureus*. *J Antimicrob Chemother* 2006;**58**:680–3.