



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.

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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

Table 2

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

Age (years)		Community		LTCF	
		<i>n</i>	%	<i>n</i>	%
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*.

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.

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)	<i>S. aureus</i> (<i>n</i>)	Constitutive clindamycin resistance		Inducible clindamycin resistance		MRSA	
			<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
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.

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