

Demographic Profile and Drug Resistance Pattern in Methicillin Sensitive *Staphylococcus aureus* in Rural and Urban Tertiary Care Centers

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To compare rural and urban setups of Methicillin Sensitive *Staphylococcus aureus* (MSSA) with socio-economic and behavioral factors and their susceptibility patterns to various antimicrobial agents. A total no. of 13774, 5263 (38.21%) from rural and 8511 (61.79%) from urban pus samples were analysed. Samples with confirmed *Staphylococcus aureus* were subsequently tested for methicillin sensitivity and cefoxitin disc antibiotic susceptibility pattern was determined. The data was analysed statistically. Isolated rate of Methicillin sensitive *Staphylococci aureus* (MSSA) 288 (5.47%), (5.24%).ratio of sex was 1:0.77, 1: 0.78 in rural and urban setup. Isolated rate of Methicillin sensitive *Staphylococci aureus* (MSSA) 288 (5.47%), (5.24%).ratio of sex was 1:0.77, 1: 0.78 in rural and urban setup. Ratio of isolation of MSSA in rural and urban group in various socio economic classes were :Upper I(1.4:1),Upper middle II (1:3.7),Lower middle III(1:2.2),Upper lower IV(1.01:1) and Lower V(1.4:1).Average drug resistance percentage (more than 50%) of MSSA in various socio-economic groups from rural setup was for penicillin 91.77%, erythromycin 77.13%, azithromycin 69.07%, ciprofloxacin 74.63%, gatifloxacin 82.34%, cefuroxime 54.95% and cefoperazone 90.89%. Average drug resistance percentage (more than 50%) of MSSA in various socioeconomic groups from urban setup was penicillin 88.77%, erythromycin 69.57%, ciprofloxacin 55.73%, gatifloxacin 68.16%, cefuroxime 57.04% and cefoperazone 79.24%. In both the groups cloxacillin, azithromycin, amikacin, gentamicin, tetracycline, cephalixin, linezolid, vancomycin and piperacillin+tazo can be used. Average drug resistance to penicillins, erythromycin, ciprofloxacin, gatifloxacin and cefoperazone was more in rural areas when compared to urban areas in all the socioeconomic groups requiring the need for regular surveillance of MSSA infection in rural areas.

Key words: Antimicrobial susceptibility, Demographic parameters, Methicillin Sensitive *Staphylococcus aureus* (MSSA), Rural, Urban.

Drug resistance is common in isolates from healthy persons and from patients with community-acquired infections in developing countries like India, where the need for antibiotics

is driven by the high incidence of infectious disease¹.The selection and spread of Multi-resistant organisms in developing countries, which can often be traced to complex socio-economic and behavioral factors, contribute to the escalating problem of antibiotic resistance worldwide². In developing countries, include the irrational use of antibiotics by health professionals, unskilled

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practitioners, laypersons, poor drug quality, unhygienic conditions and inadequate surveillance accounting for the spread of resistant bacteria. Nevertheless, misuse of antibiotics is one of the reasons for the increasing rates of resistance, especially in rural areas².

Staphylococcus aureus is one of common prevalent and clinically significant pathogen, causing a wide variety of infections ranging from simple to life-threatening diseases³. Multi-drug resistant strains of Methicillin resistant *Staphylococcus aureus* (MRSA) well documented worldwide. In our present study we wanted to know drug resistance of Methicillin sensitive *staphylococcus aureus* (MSSA) which is related to socioeconomic and behavioral factors in rural and urban areas and their factors.

MATERIALS AND METHODS

It is a prospective cross sectional study for a period of 1 year 9 months years from August 2013 to April 2015 at tertiary care center of Srikakulam district (rural area) and Visakhapatnam district (urban area). An open ended questionnaire was prepared which collected information on education, occupation, income, history of intake alcohol, smoking habits and history of diseases^{5,6} (i.e. score of Kuppuswamy's scale of 2014-15 Education levels: Professors or honors(7), Graduate or post graduate(6), Intermediate or post high school diploma(5), High school certificate(4), Middle school certificate(3), Primary school certificate(2), Illiterate(1), Occupation levels: Profession(10), Semi-Profession(6), Clerical or Shop-owner(5), Skilled worker(4), Semi-skilled worker(3), Unskilled worker(2), Unemployed(1), income range: d"1802(1), 1803–5386(2), 5387–8988(3), 8989–13494(4), 13495–17999(5), 18000–36016(10), e"36017(12), the sum of total come under socioeconomic class: upper(I), upper middle(II), lower middle(III), lower(V respectively). A total of 13774 pus samples were analyzed, 5263 pus samples were from rural set up and 8511 from urban setups. All the samples were aseptically handled and processed.

Gram's Staining was done for all the samples and the likely organisms were determined. Then the pus samples were inoculated onto Blood agar, Mac Conkey agar & selective media

(Mannitol salt agar) obtained from Hi-Media Laboratories Pvt. Ltd, Mumbai and incubated at 37°C for 24 hours. The suspected colonies of *Staphylococci* were taken and Gram's Staining was done, all the Gram-positive cocci in clusters were further confirmed using a battery of standard biochemical reactions including the production of bound and free coagulase enzymes using slide and tube coagulase tests based on standard methods. All the confirmed *Staphylococcus aureus* strains were subsequently tested for Methicillin resistance based on recommendations of Clinical Laboratory Standard Institute (CLSI). Cefoxitin disc (30µg)⁴ obtained from Hi-Media Laboratories Pvt. Ltd Mumbai was used to isolate MSSA. The isolates were considered Methicillin sensitive *Staphylococcus aureus* (MSSA) if the zone of inhibition was > than 22mm.

Further, the antibiotic susceptibility pattern of Methicillin sensitive *Staphylococcus aureus* strains was determined on the day of their isolation by disc diffusion method on Muller-Hinton agar using the criteria of standard zone sizes of inhibition to define sensitivity or resistance to different antimicrobials⁷. The panel of antibiotics used was penicillin, cloxacillin, erythromycin, azithromycin, amikacin, gentamicin, ciprofloxacin, gatifloxacin, tetracycline, cephalixin, cefuroxime, cefoperazone, piperacillin+tazobactam, linezolid and vancomycin. *Staphylococcus aureus* ATCC-25923 was used as control strain for the standardization of antibiotic susceptibility.

Statistical analysis

Z test and Chi square test was conducted to know the variability in sensitivity patterns to various antibiotics in MSSA in both rural and urban setups.

RESULTS

Isolation of MSSA from rural and urban tertiary care centers

A total number of pus samples analyzed were 13774, 5263 (38.21%) from rural and 8511 (61.79%) from urban setups. Isolates of MSSA in the rural setup were 288 (5.47%) and urban were 446 (5.24%) [Table-1]

Sex and Age distribution of MSSA in rural and urban setup

Ratio of sex was 1:0.77, 1: 0.78, Isolation

rate of MSSA was more in males in both rural and urban setup (i.e. 56.25% and 56.05) [Table-2]. Isolation rate of MSSA in rural children and urban adults with a predominance of MSSA in urban children and rural adults. Isolation rate of MSSA in d"30 years (36.46), (33.63), 31 years to 50 years were (37.15%), (37.67%). e" 51 years (26.39%), (28.70%) in rural and urban area respectively. [Table 2-3].

Isolation of MSSA in relevance with Socioeconomic and Behavioral Factors in rural and urban areas

MSSA isolated in professors, graduates, postgraduates and illiterates were less in both the groups. Isolation of MSSA was more in subjects from the urban area with educational status of Intermediate (P valve < 0.01) and high school

certificate. In urban areas the isolation of MSSA was more than rural in clerical, skilled worker, semiskilled and unskilled worker. In unemployed, MSSA isolation was more in rural areas. MSSA isolation was more in rural subjects with income of ? 1802 and MSSA isolation was more in the urban group with the income of 13495-17999. Ratio of isolation of MSSA in rural and urban group in various socio economic classes were Upper I(1.4:1), Upper middle II (1:3.7), Lower middle III(1:2.2), Upper lower IV(1.01:1) and Lower V(1.4:1) [Table-4, 5, 6 and 7].

Isolation of MSSA in relevance with Behavioral Factors in rural and urban areas

History of alcoholism in males was 104 (36.11%) and females 32 (11.11%). Smoking was

Table 1. Number of MSSA isolates in rural and urban setup

	MSSA	Percentage
Rural area(5263)	288	5.47
Urban area(8511)	446	5.24
Total	734	

Table 2. Sex distribution of MSSA in rural and urban setup

	Rural MSSA (%)	Urban MSSA (%)	P value
Male	162 (56.25)	250 (56.05)	<0.001
Female	126 (43.75)	196 (43.95)	
Total	288	446	

Table 3. Age distribution of MSSA isolates in rural and urban setup

	Total	Rural MSSA (%)	Urban MSSA (%)	P value
Children	152	69 (23.96)	83 (18.61)	<0.001
Adults	582	219 (76.04)	363 (81.39)	
Total	288	446		
		Adults		
	Total	Rural MSSA (%)	Urban MSSA (%)	P value
≤30 years	255	105 (36.46)	150 (33.63)	<0.001
31 to 50 years	275	107 (37.15)	168 (37.67)	
≥ 51 years	204	76 (26.39)	128 (28.70)	

Table 4. Education status of MSSA isolates in rural and urban area

Sr. No.	Education	Score	No. And Percentage Of Rural subjects	No. And Percentage Of Urban subjects	p value
1	Professors or honors	7	11 (3.82)	9 (2.02)	>0.05
2	Graduate or post graduate	6	19 (6.60)	27 (6.05)	>0.05
3	Intermediate or post high school dip.	5	34 (11.81)	124 (27.80)	<0.01
4	High school certificate	4	73 (25.35)	148 (33.18)	>0.05
5	Middle school certificate	3	85 (29.51)	68 (15.25)	<0.05
6	Primary school certificate	2	47 (16.32)	49 (10.99)	>0.05
7	Illiterate	1	19 (6.60)	21 (4.71)	>0.05

observed in 110 (38.19%) males and females 49 (17.01%). History of other diseases associated was seen in 234 (81.25%) males and females 242 (84.03%) in rural areas. Alcoholism in males was 156 (34.98%) females 63 (14.12%), smoking in males 143 (32.06%) females 40 (8.97%) history of other diseases in males 321 (71.97%) and females 335 (75.11%) in urban areas respectively. [Table 8]

Average drug resistance percentage in various socioeconomic groups in MSSA from Rural setup

we have identified upper (I) upper middle (II) lower middle (III) upper lower (IV) lower (V) classes i.e. penicillin 91.77, cloxacillin 41.27, erythromycin 77.13, azithromycin 69.07, Amikacin 31.32, gentamicin 44.57, ciprofloxacin 74.63, gatifloxacin 82.34, tetracycline 9.43, cephalixin

46.32, cefuroxime 54.95, cefoperazone 90.89, Linezolid 0.37, vancomycin 13.63 and piperacillin+tazo 45.09 (Table 10).

Multi drug resistance in MSSA and socioeconomic status in below and above 50% drug resistance in rural setup

upper (I) 8 drugs, 7 drugs, upper middle (II) 8 drugs, 7 drugs lower middle (III) 8 drugs and 7 drugs upper lower (IV) 8 drugs, 7 drugs, lower (V) 7 drugs and 8 drugs resistance in below and above 50% drug resistance respectively [Table 9].

Average drug resistance percentage in various socioeconomic groups in MSSA from Urban setup

we have identified upper (I) upper middle (II) lower middle (III) upper lower (IV) lower (V) classes i.e. penicillin 88.77, cloxacillin 40.16,

Table 5. Occupation of MSSA isolates in rural and urban area

Sr. No.	Education	Score	No. And Percentage Of Rural subjects	No. And Percentage Of Urban subjects	p value
1	Profession	10	13 (4.51)	11 (2.47)	>0.05
2	Semi-Profession	6	31 (10.76)	26 (5.83)	>0.05
3	Clerical or Shop-owner	5	21 (7.29)	53 (11.88)	>0.05
4	Skilled worker	4	65 (22.57)	164 (36.77)	<0.05
5	Semi-skilled worker	3	74 (25.69)	96 (21.52)	>0.05
6	Unskilled worker	2	15 (5.21)	34 (7.62)	>0.05
7	Unemployed	1	69 (23.96)	62 (13.90)	>0.05

Table 6. Income of MSSA isolates in rural and urban area

Sr. No.	Family Income ^{5,6} (2014-15)	Score	No. And Percentage Of Rural subjects	No. And Percentage Of Urban subjects	p value
1	≤1802	1	72 (25.00)	36 (8.07)	<0.01
2	1803-5386	2	43 (14.93)	33 (7.40)	>0.05
3	5387-8988	3	58 (20.14)	59 (13.23)	>0.05
4	8989-13494	4	87 (30.21)	87 (19.51)	>0.05
5	13495-17999	6	14 (4.86)	162 (36.32)	<0.001
6	18000-36016	10	11 (3.82)	51 (11.43)	<0.05
7	≥36017	12	3 (1.04)	18 (4.04)	>0.05

Table 7. socio-economical class of MSSA isolates in rural and urban area

Sum score of education, occupation and income	Socioeconomic Class	No. And Percentage Of Rural subjects	No. And Percentage Of Urban subjects	p value
26-29	Upper (I)	13 (4.51)	9 (2.02)	>0.05
16-25	Upper Middle (II)	23 (7.99)	86 (19.28)	<0.05
11-15	Lower Middle (III)	91 (31.60)	198 (44.39)	>0.05
5-10	Upper Lower (IV)	139 (48.26)	137 (30.72)	<0.01
< 5	Lower (V)	22 (7.64)	16 (3.59)	>0.05
Total	288 (100)	446 (100)		

erythromycin 69.57, azithromycin 45.32, Amikacin 35.12, gentamicin 37.01, ciprofloxacin 55.73, gatifloxacin 68.16, tetracycline 20.61, cephalexin 44.27, cefuroxime 57.04, cefoperazone 79.24, Linezolid 1.31, vancomycin 24.82 and piperacillin+tazo 43.69 [Table 10].

Multi drug resistance in MSSA and socioeconomic status in below and above 50% drug resistance in urban setup

upper (I) 9 drugs, 6 drugs, upper middle (II) 9 drugs, 6 drugs lower middle (III) 9 drugs and 6 drugs upper lower (IV) 9 drugs, 6 drugs, lower (V) 8 drugs and 7 drugs resistance in below and above 50% drug resistance respectively [Table 9].

DISCUSSION

The relationship between antibiotic use and the emergence and spread of resistance is complex^{8,9}. In many developing countries, well-trained health personnel are scarce and cannot serve the entire population, especially in rural areas¹⁰. The irregular drug supply, availability of drugs from unofficial sources, and financial constraints also affect antibiotic choices^{11, 12, 13}. Education has not been successfully implemented in many rural areas comparative with urban areas¹⁴. People are encouraged to buy from unofficial distributors because drugs often are not available

in government hospitals¹⁵. Drug vendors usually have little or no knowledge of the required dosage regimen, indications, or contraindications^{15, 16, 17}. The proportion of patients who self-medicate is probably higher, because patients are often reluctant to admit having taken antibiotics before visiting a hospital in rural areas¹⁸. Residents of rural areas had no sanitary facilities for sewage disposal, Pipe-borne water, often scarce¹⁹.

In most developing countries, antibiotics can be purchased without prescription, even when the practice is not legal². Apparently healthy people in developing countries carry potentially pathogenic, antibiotic-resistant organisms asymptomatically²⁰.

Moreover, surveillance should be conducted regularly and continuously because resistance rates can vary in one region of a country over time²¹. "The usage of antibiotics and other drugs in animal agriculture poses a significant risk to human health due to the selection of cross-resistance in bacteria to antibiotics used in mankind". It results in "increased severity of infections" and "increased frequency of treatment failures"²². Animal agriculture, poultry and dairy farming are major industries in India. A large number of people working in these farms are in close contact with livestock. The use of antibiotics in animal agriculture was not strictly regulated by law in India²³.

Table 8. Behavioral factors of MSSA isolates in rural and urban setup.

Behavioral factors	Rural setup		Urban setup		Chi square test
	Males	Females	Males	Females	
Alcohol	104 (36.11%)	32 (11.11%)	156 (34.98%)	63 (14.12%)	<0.05
Smoking	110 (38.19%)	49 (17.01%)	143 (32.06%)	40 (8.97%)	>0.05
Any Clinical findings / Disease History	234 (81.25%)	242 (84.03%)	321 (71.97%)	335 (75.11%)	<0.05

Table 9. Multi drug resistance of below and above 50% in MSSA isolates among Socioeconomic status of rural and urban areas

Socioeconomic group	Rural	Urban	Rural	Urban
	Below 50%		Above 50%	
Upper (I)	8 drugs	9 drugs	7 drugs	6 drugs
Upper Middle (II)	8 drugs	9 drugs	7 drugs	6 drugs
Lower Middle (III)	8 drugs	9 drugs	7 drugs	6 drugs
Upper Lower (IV)	8 drugs	9 drugs	7 drugs	6 drugs
Lower (V)	7 drugs	8 drugs	8 drugs	7 drugs

Table 10. Drug resistance rate in percentage in various socioeconomic groups in MSSA isolates from Rural and Urban setup

Name of the Drug	Upper (I)		Upper Middle (II)		Lower Middle (III)		Upper Lower (IV)		p value
	Rural	Urban	Rural	Urban	Rural	Urban	Rural	Urban	
Penicillin (P)	92.31	88.89	91.3	89.53	92.32	88.89	90.85	87.5	>0.05
Cloxacillin (COX)	38.46	39.53	43.45	44.44	41.74	39.9	40.97	37.5	>0.05
Erythromycin (E)	76.92	66.67	78.26	70.93	76.94	70.71	77.24	68.75	>0.05
Azithromycin (AZM)	69.23	45.9	69.62	46.51	69.25	44.44	68.2	43.75	<0.001
Amikacin (AK)	23.08	35.04	21.79	34.88	21.96	34.85	68.2	37.5	<0.001
Gentamicin (G)	46.15	37.5	43.45	38.37	43.96	37.88	45.43	33.33	>0.05
Ciprofloxacin (CIP)	76.92	55.81	73.88	55.56	74.72	55.56	72.79	56.25	<0.05
Gatifloxacin (GAT)	84.62	68.61	82.64	68.6	81.3	68.18	81.82	68.75	<0.05
Tetracycline (TE)	7.69	20.71	8.64	20.93	10.98	22.22	9.03	18.75	<0.05
Cephalexin (CN)	46.15	43.75	47.83	44.19	46.14	44.44	45.43	44.44	>0.05
Cefuroxime (CXM)	53.85	55.56	56.7	58.14	54.94	57.58	54.59	56.25	>0.05
Cefoperazone (CPZ)	92.31	78.83	91.28	79.07	90.1	79.29	90.85	81.25	<0.05
Linezolid (LZ)	0	0	0	2.33	1.11	2.02	0	0	>0.05
Vancomycin (VA)	15.38	25	13.02	25.58	13.2	25.76	13.61	22.22	>0.05
Piperacillin with tazobactam (PIT)	46.15	43.8	43.45	43.02	45.07	43.43	45.43	43.75	>0.05

In general, these studies have found that education is more strongly associated with disease than is income and occupation²⁴. Strict regulations on the use of antibiotics in human medicine as well as in animal food production are required to control the emergence of drug resistant clones²³. In urban areas handful of microbiology laboratories available² half knowledge and over confidence in self medication has been responsible for emergence of drug resistance strains in urban area.

In the present study, a total of 13774 pus samples were analyzed, 5263 pus samples were from rural setup and 8511 from urban setups. MSSA were 288(5.47%), 446(5.24%) in both setups. There is a significant difference in isolation of MSSA between the male and female population in both the setups ($p < 0.001$). MSSA isolation were higher among adults in rural and urban population 219(76.04%), 363 (81.39%) when compared to rural and urban children 69(23.96%), 83(18.61%) There is a significant difference between age groups d" 30 years, 31-50 years and e" 51 years ($p < 0.001$) in rural and urban areas.

MSSA isolated in professors, graduates, postgraduates and illiterates were less in both the groups. Isolation of MSSA was more in subjects from the urban area with educational status of Intermediate (P value < 0.01) and high school certificate. In urban areas, the isolation of MSSA was more than rural in clerical, skilled worker, semiskilled and unskilled worker. In unemployed, MSSA isolation was more in rural areas. MSSA isolation was more in rural subjects with income of d" 1802 and MSSA isolation was more in the urban group with the income of 13495-17999. The Ratio of isolation of MSSA in rural and urban group in various socio-economic classes were: Upper I (1.4:1), Upper middle II (1:3.7), Lower middle III (1:2.2), Upper lower IV (1.01:1) and Lower V (1.4:1). The relationship of MSSA isolation and socioeconomic factors in both the setups was similar in Upper I and Lower V. In all the socioeconomic groups isolation of MSSA were more in the urban area indicating better awareness, availability of facilities to isolate MSSA before antibiotic usage.

There is no significant difference between rural and urban upper (I) class in drug resistance to penicillin, cloxacillin, erythromycin, amikacin, gentamicin, cephalixin, cefuroxime, piperacillin +

tazobactam, linezolid and vancomycin ($p > 0.05$) There is a significant difference to azithromycin($p < 0.001$), ciprofloxacin, gatifloxacin, tetracycline, cefoperazone($p < 0.01$).

There is no significant difference between rural and urban upper middle (II) and lower middle (III) classes in drug resistance to penicillin, cloxacillin, erythromycin, gentamicin, cephalixin, cefuroxime, piperacillin + tazobactam and linezolid ($p > 0.05$) There is a significant difference to azithromycin ($p < 0.001$), ciprofloxacin ($p < 0.01$), amikacin, gatifloxacin, tetracycline, vancomycin and cefoperazone ($p < 0.05$).

There is no significant difference between rural and urban upper lower (IV) classes in drug resistance to penicillin, cloxacillin, erythromycin, amikacin, gentamicin, tetracycline, cephalixin, cefuroxime, piperacillin + tazobactam and linezolid ($p > 0.05$) There is a significant difference to azithromycin ($p < 0.001$), ciprofloxacin ($p < 0.01$), gatifloxacin, vancomycin and cefoperazone ($p < 0.05$).

There is no significant difference between rural and urban lower (V) classes in drug resistance to penicillin, cloxacillin, erythromycin, gentamicin, cephalixin, cefuroxime, piperacillin + tazobactam, vancomycin and linezolid ($p > 0.05$) There is a significant difference to amikacin, azithromycin ($p < 0.001$), tetracycline, ciprofloxacin, gatifloxacin and cefoperazone ($p < 0.05$).

There is no significant difference between rural and urban areas of average drug resistance among upper (I) upper middle (II) lower middle (III) upper lower (IV) lower (V) classes to penicillin, cloxacillin, erythromycin, Amikacin, gentamicin, cephalixin, cefuroxime and piperacillin+ tazobactam ($p > 0.05$). There is a significant difference to azithromycin ($p < 0.001$), ciprofloxacin ($p < 0.01$), gatifloxacin, tetracycline, cefoperazone, linezolid, and vancomycin ($p < 0.05$).

In both the groups cloxacillin, azithromycin, amikacin, gentamicin, tetracycline cephalixin, Linezolid, vancomycin and piperacillin+tazo can be used.

In the present study in all the socioeconomic groups isolation of MSSA was more in the urban area indicating better awareness, availability of facilities to isolate MSSA before antibiotic usage. Average drug resistance to penicillin, erythromycin, ciprofloxacin, gatifloxacin

and cefoperazone was more in rural areas when compared to urban areas in all the socioeconomic groups. The regular surveillance of MSSA infection in rural areas is very much necessary to select an appropriate antibiotic, to know the changing trends of antibiotic susceptibility pattern, for developing hospital antibiotic policy and for limiting the use of powerful antibiotics

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