COMPARISON OF FUSIDIC ACID SUSCEPTIBILITY OF STAPHYLOCOCCI: A MULTICENTER STUDY

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ABSTRACT

Introduction*: The increasing antibiotic resistance of staphylococci, an important factor among societal and hospital-sourced infection factors, reduces the treatment choices available. Fusidic acid (FA), the use of which has recently come to the agenda again, is thought to form a new alternative treatment for staphylococci infections. The aim of our study is to identify the FA resistance situation at certain centers compared to generally increasing antibiotic resistance, to present epidemiological data on new antibiotherapy methods and to aid in treatment planning.*

Materials and methods*: With this aim we determined and compared the susceptibility of 2018 Staphylococcus aureus and 5242 Coagulase negative Staphylococci strains obtained at 11 centers in different regions of our country against FA, oxacillin, penicillin, trimethoprim-sulfamethoxazole and ciprofloxacin.*

Results*: The Coagulase negative Staphylococci strains were determined to be more resistant to all antibiotics compared to S. aureus strains. When the means of all centers are examined, FA resistance was found in 7.1% of S. aureus strains and 55.1% of Coagulase negative Staphylococci strains. Of all antibiotics for both S. aureus and Coagulase negative Staphylococci strains the antibiotic that strains were most susceptible to was trimethoprim-sulfamethoxazole, while the antibiotic that most were resistant to was penicillin.*

Conclusion*: In light of these findings, with high susceptibility of 92.9% for S. aureus strains to FA, it appears to be a good alternative treatment choice for S. aureus infections. Due to high resistance rates of methicillin-resistant Coagulase negative Staphylococci sourced infections, before treatment it is necessary to perform an antibiotic susceptibility test. We believe that broader scale and more comprehensive studies will provide guidance in planning treatment.*

Keywords*: Thalasemia trait, iron deficiency anemia, differentiating index.*

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Introduction

Staphylococci are among the most important factors in a variety of societal and hospital-sourced infections. Among these infections, it is the most common factor in soft-tissue infections. The increasing resistance to first choice medications limits the treatment choices for these infections.

As a consequence of very frequent use of glycopeptides, increased minimal inhibitory concentration (MIC) values and staphylococci strains with moderate resistance to vancomycin which is the only remaining choice for methicillin-resistant staphylococci infections have been identified. The increasing resistance to glycopeptides is becoming a problem for both Coagulase negative

Staphylococci (CoNS) and Staphylococcus aureus (S. aureus); staphylococci strains with moderate resistance to vancomycin have been isolated. CoNS are more resistant microorganisms to antimicrobial agents than S. aureus. Additionally glycopeptides are only used parenterally and due to greater side effects the search for new antibiotics has come to the agenda[1,2].

Fusidic acid (FA), with a structure similar to steroids, is an antibiotic used to treat methicillin-susceptible and methicillin-resistant staphylococcus infections alone or combined with other antibiotics. The development of cross-resistance to this antibiotic, which has the effect of inhibiting protein biosynthesis in bacteria, is difficult. The good distribution of FA in tissues, ease of use through the oral pathway and low allergic and toxic effects make this antibiotic a good alternative especially for the treatment of resistant staphylococcus infections[3,4]. Knowing the regional resistance of antibiotics will aid in choice of correct and reliable empirical treatment approaches for infections where that antibiotic is indicated[1].

In our country it is noteworthy that no broad database on FA susceptibility has been published in a long time. Our study compares the fusidic acid resistance of staphylococcus strains isolated from eleven hospitals in different regions of Turkey with their penicillin (P), oxacillin (OX), trimethoprim-sulfamethoxazole (TMP-SXT) and ciprofloxacin (CIP) resistance. The aim of our study is to identify the FA resistance situation in certain centers in the situation of generally increasing antibiotic resistance, to present epidemiological data for new antibiotherapy methods and to aid clinicians in treatment planning.

Materials and methods

The study included a total of 7270 staphylococcus strains sent from eleven different centers: Adana Numune Training and Research Hospital (ANTRH), Namık Kemal University Medical Faculty Hospital, Tekirdağ (NKUMFH), Ahi Evran University Training and Research Hospital, Kırşehir (AEUTRH), Necmettin Erbakan University Medical Faculty Hospital, Konya (NEUTRH), Ordu State Hospital (OSH), Ordu University Training and Research Hospital (OUTRH), Osmaniye State Hospital (OSSH), Samsun Gazi State Hospital (SGSH), Katip Çelebi University Medical Faculty Hospital, İzmir (KCUMFH), Karadeniz Technical University Medical Faculty Farabi Hospital, Trabzon (KTUMFFH) and İzzet Baysal Training and Research Hospital, Bolu (IBTRH). In addition to results determining FA resistance, the P, OX, TMP-SXT and CIP results of these strains were retrospectively evaluated. Additionally results were interpreted together and in comparison. The strains included in the study were isolated from a variety of clinical samples sent from different units in each center between 2011-2014. Isolates were described using conventional methods and automated systems in each center. Susceptibility results were interpreted using 2014 EUCAST criteria. Also, quality control for the centers included in the study used *S. aureus* 29213ATCC strains.

Statistical analysis

In addition to results stating FA resistance of clinical samples obtained from hospitals included in the research, the results for P, OX, TMP-SXT and CIP resistance of the strains are given as number and percentage (rate). Additionally, to determine whether the results of these parameters changed depending on the hospital sampled, they were evaluated with the chi-square test. Interpretation of findings accepted a probability of $p<0.05$ as significant and all data analysis was completed using the Statistical Package for the Social Sciences (SPSS) software (Version 15.0; Chicago, IL, USA).

Results

The majority of strains included in the study were isolated from material such as wounds, blood, aspirate, abscess, and catheters sent by internal medicine, orthopedic, surgical and intensive care wards. ANTRH participated in the study with the most samples. The distribution of strains at centers included in the study is given in Table 1.

Without separating species, it appears that 41.8% of staphylococci have resistance to FA. However when species are separated, the *S. aureus* isolates were found to be more susceptible to FA compared to CoNS. In each bacteria group the P resistance was identified to be very close to each other. The resistance rates to other antibiotics are shown in Table 2.

The centers where *S. aureus* is most susceptible were identified as KTUMFFH, OSH and NEUTRH. While the strains most susceptible to FA were isolated at KTÜFFH (2.8%), they were followed by

Centers	Total (n)	S. aureus(n)	CoNS (n)
ANTRH	2589	631	1958
OSH	1124	382	742
KTUMFFH	946	178	768
NEUTRH	650	321	329
OUTRH	539	130	409
NKUMFH	254	53	201
OSSH	299	106	193
AEUTRH	379	131	248
SGSH	268	28	240
KCUMFH	160	32	128
IBTRH	62	36	26
Total	**7270**	**2028**	**5242**

Table 1: Strains and distribution at centers included in the study

n: number of strains; ANTRH: Adana Numune Training and Research Hospital; NKUMFH: Namik Kemal University Medical Faculty Hospital, Tekirdağ; AEUTRH: AhiEvran University Training and Research Hospital, Kırşehir; NEUTRH: NecmettinErbakan University Medical Faculty Hospital, Konya; OSH: Ordu State Hospital; OUTRH: Ordu University Training and Research Hospital; OSSH: Osmaniye State Hospital; SGSH: Samsun Gazi State Hospital; KCUMFH: KatipÇelebi University Medical Faculty Hospital, İzmir; KTUMFFH: Karadeniz Technical University Medical Faculty Farabi Hospital, Trabzon; IBTRH: İzzetBaysal Training and Research Hospital, Bolu

OSH (3.4%) and NEUTRH (4.4%). The antibiotic that S. aureus strains were most susceptible to was TMP-SXT, while the antibiotic that had most resistance was P. P resistance was found to have very close values at nearly all centers (81-94%) (p=0.002). However, there were large variations observed between the centers for OX, TMP-SXT, CIP and FA. In other words the resistance situation changed depending on the hospital that the samples came from (p<0.001). The distribution and susceptibility of S. *aureus strains* according to center are given in Table 3.

Staphylococci	Total n (%)	P n (%)	OX n (%)	SXT n (%)	CIP n (%)	FA n (%)
S. aureus	2028 (27.9)	1796 (88.6)	560 (27.6)	98 (4.8)	347 (17.1)	147 (7.2)
CoNS	5242 (72.1)	4571 (87.2)	3914 (74.7)	1293 (24.7)	2774 (52.9)	2890 (55.1)
Total	**7270**	**6367 (87.6)**	**4474 (61.5)**	**1391 (19.1)**	**3121 (42.9)**	**3037 (41.8)**

Table 2: Resistance rates of SA and CoNS strains obtained from all centers.

n: number of strains, FA: Fusidic acid; P: Penicillin; OX: Oxacillin; SXT: Trimethoprim-sulfamethoxazole; CIP: Ciprofloxacin; S. aureus: Staphylococcus aureus:CoNS:Coagulase-negative staphylococci

The centers where CoNS was most susceptible to FA were identified as IBTRH (15.4%), OUTRH (42.2%) and NKUMFH (42.7%).

The highest rate of resistance was identified as 70.3% at KCUMFH. The antibiotic with most susceptibility among all antibiotics was TMP-SXT (24.7%), while the antibiotic with most resistance was P (87.2%). At KCUMFH the rate obtained for TMP-SXT was 2.3%; the highest susceptibility rate obtained. When the resistance rates to all antibiotics are evaluated, there were differences observed between centers and variations depending on the hospital the sample came from (p<0.001). The resistance rates of CoNS isolated at the centers to FA and other antibiotics are given in Table 4.

When the clinics that the samples came from are investigated, it was observed that most came from the internal medicine clinics (n=2355) and least came from dermatology (n=54). The distribution of clinics that the samples were collected is shown in Table 5.

Discussion

Due to increasing beta-lactam resistance of staphylococci, the use of FA in treatment is very important. In our country there is no study reporting broad data on FA resistance of staphylococci in recent times. Our study obtained regional resistance data and revealed the differences in resistance between *S. aureus* and CoNS species.

Ohadian et al. in a study in 2014 used the disc diffusion method to determine the susceptibility of 40 methicillin-resistant *S. aureus* (MRSA) strains and 25 methicillin-sensitive S. aureus (MSSA) strains isolated from wound infections to a variety of antibiotics and identified the susceptibility of MRSA strains to CIP was 51.28%. All of the MRSA and MSSA strains were susceptible to FA[5].

In our study a total of 2028 *S. aureus* strains were included and the CIP susceptibility was 82.9%, while the FA susceptibility was 92.8%. The high CIP susceptibility observed in our study and difference compared to FA susceptibility may be due to the greater number of strains in our study and the fact that many samples from different centers were included in our study. Additionally, while all samples in the previous study were isolated from wound infections, our samples were obtained from different clinical materials, which is another factor that may cause variation.

Research on *S. aureus* propagation on impetigo patients by Salah et al. compared the FA suscep-

tibility for strains identified from 2005-2011. In 2005 the FA resistance rate was 22.8% while this fell to 5% in 2011 (p=0.078)[6]. In our study the low rate of 7.2% identified to *S. aureus* is the total resistance rate for the years from 2011-2014.

Centers	Total n	P n(%)	OX n(%)	SXT n(%)	CIP n(%)	FA n(%)
ANTRH	631	575 (91.1)	175 (27.7)	21 (3.3)	128 (20.2)	53 (8.4)
OSH	382	334 (87.4)	51 (13.3)	5 (1.3)	25 (6.5)	13 (3.4)
NEUTRH	321	267 (83.1)	123 (38.3)	12 (3.7)	97 (30.2)	14 (4.4)
KTUMFFH	178	164 (92.1)	45 (25.2)	22 (12.3)	3 (1.6)	5 (2.8)
AEUTRH	131	108 (82.4)	9 (6.8)	16 (12.2)	22 (16.7)	29 (22.1)
OUTRH	130	120 (92.3)	50 (38.4)	7 (5.3)	12 (9.2)	8 (6.2)
OSSH	106	100 (94.3)	37 (34.9)	5 (4.7)	22 (20.7)	7 (6.6)
NKUMFH	53	47 (88.6)	23 (43.3)	2 (3.7)	5 (9.4)	11 (20.8)
KCUMFH	32	26 (81.2)	9 (28.1)	0 (0.0)	9 (28.1)	2 (6.2)
SGSH	28	24 (85.7)	18 (64.2)	3 (10.7)	13 (46.4)	3 (10.7)
IBTRH	36	31 (86.1)	20 (55.5)	5 (13.9)	11 (30.5)	2 (5.6)
Total	**2028**	**1765 (87.0)**	**540 (26.6)**	**93 (4.6)**	**336 (16.5)**	**145 (7.1)**
c^2-value		28.3	139.9	62.1	136.5	77.4
p-value		0.002	<0.001	<0.001	<0.001	<0.001

Table 3: Resistance of *S. aureus* species isolated from the centers to FA and other antibiotics.

n: number of strains, FA: Fusidic acid; P: Penicillin; OX: Oxacillin; SXT:Trimethoprim-sulfamethoxazole; CIP: ciprofloxacin; ANTRH: Adana Numune Training and Research Hospital; NKUMFH: Namık Kemal University Medical Faculty Hospital, Tekirdağ; AEUTRH: AhiEvran University Training and Research Hospital, Kırşehir; NEUTRH: NecmettinErbakan University Medical Faculty Hospital, Konya; OSH: Ordu State Hospital; OUTRH: Ordu University Training and Research Hospital; OSSH: Osmaniye State Hospital; SGSH: Samsun Gazi State Hospital; KCUMFH: KatipÇelebi University Medical Faculty Hospital, İzmir; KTUMFFH: Karadeniz Technical University Medical Faculty Farabi Hospital, Trabzon; IBTRH: İzzetBaysalTraining and Research Hospital, Bolu.

A study in Turkey covering 12 hospitals and 397 MRSA strains researched the susceptibility to a variety of antibiotics with the agar dilution method. The susceptibility rates to FA and CIP were 91.9% and 6.8% respectively, with FA appearing to be the antibiotic providing most susceptibility[7]. In our study the FA susceptibility of *S. aureus* strains was identified as 92.8%, providing similar results to this study.

In a study of 381 CoNS strains, Ehsan et al. identified FA resistance of 41.7%[8]. In our study this resistance rate was observed to be higher; identified as 55.1%. A possible reason for this is that our study is multi-center and the resistance rates of the centers are different. For example, at centers included in our study while the FA resistance at OUTRH was 42.2%, at KCUMFH this rate was identified as 70%.

A review study by Deveci et al. in 2011 researched the efficacy of FA for 57 methicillin-sensitive Coagulase negative Staphylococci (MSCoNS), 20 methicillin-resistant Coagulase negative Staphylococci (MRCoNS), 30 MSSA and 7 MRSA strains. The resistance rates for MRCONS, MSCoNS, MSSA and MRSA were identified as 40%, 24%, 13% and 14%, respectively. In this group the MRCoNS strains appear to be the most resistant group. In our study the CoNS strains were identified to be more resistant. From 2000-2010 when different studies on the susceptibility of MSSA and MRSA strains to FA are examined, a study of MSSA strains in 2000 found a resistance rate of 3.2%, while in 2010 a study found this rate was 4%. Studies in the intervening years found varying resistance percentages from 0-4%. When different susceptibility research on MRSA strains are examined for the same years, a resistance pattern varying from 3 to 11.3% is observed. From 2000 to 2005 a variety of research on MSCoNS strains identified resistance rates varying from 0 to 20%. The resistance rates identified in studies of MRCoNS strains from 2000 to 2006 found rates varying from 3 to 39%[9]. As can be understood from these studies, as the years pass even at the same center there are variations observed in resistance rates. In our study four-year data from eleven centers were included. Variation in rates for strains identified in wards and clinical material (wound, blood, abscess, urine, etc.) between the centers, in addition to differences in antibiotic susceptibility methods at the centers, may be significant factors affecting the different results.

Ertem et al. researched the FA resistance of 60 MRSA and 60 MRCoNS strains in a study between 2008-2009 and found rates of 8.3% for MRSA strains and 31.7% for MRCoNS strains. They stated that the FA resistance of MRCoNS isolates in the study was notably high (10). In our study the FA resistance of S. aureus strains of 7.2% was similar to that study. The very high rate of 55.1% obtained for CoNS strains in our study leads to the consideration that it may be related to the time of the study and regional differences. In a study researching the FA resistance of nasal S. aureus carriers, Heijer et al. found FA resistance was below 10%[10]. In our study the resistance rate of 7.2% is a similar result.

Research in Spain, on a total of 8326 societal-sourced MRSA strains isolated between 2004 and 2012, identified FA resistance as 2% with CIP resistance of 3.1%[11].

Centers	n	P n(%)	OX n(%)	SXT n(%)	CIP n(%)	FA n(%)
ANTRH	1958	1873 (95.7)	**n(%)**	450 (23.0)	1129 (57.6)	1339 (68.3)
KTUMFFH	768	532 (69.2)	1634 (83.5)	176 (22.9)	330 (42.9)	377 (49.0)
OSH	742	692(93.2)	453 (58.9)	132(18.3)	415 (55.9)	318(42.8)
OUTRH	409	346 (84.5)	581(78.3)	101 (24.6)	199 (48.6)	173 (42.2)
NEUTRH	329	311 (94.5)	295 (72.1)	92 (27.9)	145 (44.0)	160(48.6)
AEUTRH	248	224 (90.3)	270(82.0)	87 (35.0)	127 (51.2)	132 (53.2)
SGSH	240	214 (89.1)	172 (69.3)	128 (53.3)	131 (54.5)	114 (47.5)
NKUMFH	201	137 (68.1)	130(54.1)	72 (35.8)	90 (44.7)	86 (42.7)
OSSH	193	190 (98.4)	100(49.7)	43 (22.2)	106 (54.9)	97 (50.2)
KCUMFH	128	28 (87.5)	172 (89.1)	3 (2.3)	88 (68.7)	90 (70.3)
IBTRH	26	24 (92.3)	85 (66.4)	9 (34.6)	14 (53.8)	4 (15.4)
Total	**5242**	**4571 (87.2)**	22 (84.6)	**1293 (24.7)**	**2774 (52.9)**	**2890 (55.1)**
c^2-value		969.6	**3914 (74.7)**	195.4	83.3	277.2
p-value		<0.001	<0.001	<0.001	<0.001	<0.001

Table 4: Resistance of CoNS species isolated from the centers to FA and other antibiotics.

n: number of strains, FA: Fusidic acid; P: Penicillin; OX: Oxacillin; SXT:Trimethoprim-sulfamethoxazole; CIP: ciprofloxacin; ANTRH: Adana Numune Training and Research Hospital; NKUMFH: Namık Kemal University Medical Faculty Hospital Tekirdağ; AEUTRH: AhiEvran University Training and Research Hospital, Kırşehir; NEUTRH: NecmettinErbakan University Medical Faculty Hospital, Konya; OSH: Ordu State Hospital; OUTRH: Ordu University Training and Research Hospital; OSSH: Osmaniye State Hospital; SGSH: Samsun Gazi State Hospital; KCUMFH: KatipÇelebi University Medical Faculty Hospital, İzmir; KTUMFFH: Karadeniz Technical University Medical Faculty Farabi Hospital, Trabzon; IBTRH: İzzetBaysalTraining and Research Hospital, Bolu.

Geographical changes and different habits of antibiotic use between countries may be assessed as significant reasons for the difference in these rates. As understood from these studies, through the years even at the same center changes in resistance rates may be observed. In our study, the differences in resistance rates between eleven centers may be evaluated as similar to this study.

Gordon et al. in a study of 490 *S. aureus* strains identified the FA resistance rate as 9%. The same study identified CIP resistance as 14% and TMP-SXT resistance as 2% (12). The FA resistance rates are similar to our study (7.2%). In our study the resistance rates for CIP and TMP-SXT of 16% and 4.6%, respectively, are also similar.

Lim et al. researched the fusidic acid resistance of 21 MRSA strains in Malaysia and found a high resistance rate of 33%[13]. This different rate compared to our study may be due to the inclusion of resistant strains and the low number of strains included in the study.

In research using the MIC method on 51 *S. aureus* strains in the USA in 2013, Sahm et al. found that 49 strains (96%) were susceptible to FA[14]. Champion et al. in a study of 277 MRSA strains isolated from cystic fibrosis patients in 2013 identified FA resistance of 3%.

Clinics	n(%)	ANTRH	OSH	OUTRH	AEUTRH	SGSH	OSSH	NKUMFH	KCUMFH	KTUMFFH	NEUTRH	IBTRH
Infection	500 (6.9)	44	200	55	60	10	17	12	7	39	46	10
Intensive Care	1395 (19.1)	67	192	216	232	100	134	25	79	205	130	15
Surgery	1511 (20.8)	554	274	60	25	48	31	25	14	308	150	22
Internal Medicine	2355 (32.4)	1118	349	164	44	14	50	107	60	276	163	10
Plastic	922 (12.7)	723	40	-	-	41	17	4	-	12	85	-
Orthopedics	243 (3.3)	57	12	8	-	6	35	11	-	88	26	-
Urology	290 (4.0)	26	44	36	18	30	15	61	-	16	39	5
Dermatology	54 (0.7)	-	13		-	19	-	9	-	2	11	-
Total	**7270**	**2589**	**1124**	**539**	**379**	**268**	**299**	**254**	**160**	**946**	**650**	**62**

Table 5: Distribution of clinics where samples were obtained.

ANTRH: Adana Numune Training and Research Hospital; NKUMFH: Namık Kemal University Medical Faculty Hospital Tekirdağ; AEUTRH: AhiEvran University Training and Research Hospital, Kırşehir; NEUTRH: NecmettinErbakan University Medical Faculty Hospital, Konya; OSH: Ordu State Hospital; OUTRH: Ordu University Training and Research Hospital; OSSH: Osmaniye State Hospital; SGSH: Samsun Gazi State Hospital; KCUMFH: KatipÇelebi University Medical Faculty Hospital, İzmir; KTUMFFH: Karadeniz Technical University Medical Faculty Farabi Hospital, Trabzon; IBTRH: İzzetBaysalTraining and Research Hospital, Bolu.

The same study found TMP-SXT resistance of 4%[15]. In our study though similar results were obtained for FA at some centers such as NEUMFH (4%) and OSH (3%), the mean of all eleven centers caused the formation of variations in the mean. We obtained a similar result with the 4.6% resistance rate for TMP-SXT.

In Romania the resistance rates of 188 MRSA strains to a variety of antibiotics was researched and FA and CIP resistance was not identified[16]. It is thought that variations in country-wide health administration policies may have caused this difference in resistance rates.

In conclusion, in light of our findings, with a susceptibility rate of 92.8% to FA of *S. aureus* strains, FA may be a good alternative treatment choice for *S. aureus* infections. Due to high resistance rates of MRCoNS sourced infections, before using treatment an antibiotic susceptibility test should be performed. We believe that broader scale and more comprehensive studies will provide guidance in planning treatment.

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