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The Possible Squander of a Useful Antistaphylococcal Agent: Emerging Fusidic Acid Resistance in Methicillin Resistant *Staphylococcus aureus* Isolates in North Western Nigeria

Kumurya A. S.*

Department of Medical Laboratory Science, Faculty of Allied Health Sciences, Bayero University, Kano, Nigeria

Abstract

Fusidic acid has a high degree of activity against *Staphylococcus aureus*, including methicillin resistant *Staphylococcus aureus* (MRSA). Overall, among the 423 MRSA isolates collected from consecutive patients (8 hospitals; 6 states in North-western Nigeria), the mean rate of fusidic acid resistance was 4.9%. Fusidic acid monotherapy, especially topical preparations, has been strongly associated with the emergence of fusidic acid resistance among both methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-susceptible S. aureus (MSSA). Key resistance determinants include mutations in the fus A gene, which encodes elongation factor G, and plasmid-mediated resistance (i.e., acquisition of resistance gene fus B). Clonal outbreaks of fusidic acid–resistant *S. aureus* have been noted in some part of the world, such that the efficacy of fusidic acid is threatened. Fusidic acid in combination with other agents, such as rifampicin, has proven effective for difficult-to-treat MRSA infections and provides a convenient oral alternative to oxazolidinones. Ensuring that systemic fusidic acid is always used in combination and that the use of topical fusidic acid is either abolished or restricted will be crucial if we are to prevent the loss of this potentiallyuseful agent.Given current trends regarding the spread and clinical impact of hospital- and community-acquired MRSA infection, it would seem to be judicious to maintain all possible treatment options, including the potential use of fusidic acid. The information gained from the epidemiology of fusidic acid resistant isolates can help the hospitals infection control teams understand the epidemiology of these organisms in their institutions.

Keywords

Fusidic Acid, *Staphylococcus aureus*, MRSA, Monotherapy, Resistance

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1. Introduction

The development of resistance during treatment with fusidic acid when this antibiotic is used alone is being reported increasingly (Ravenscroft *et al.,* 2000*;* Chang *et al.,* 2000). Fusidic acid has a high degree of activity against *Staphylococcus aureus*, including methicillin resistant *Staphylococcus aureus*(MRSA). Resistance to fusidic acid can be produced by growing *Staphylococcus aureus* with increasing concentration of this antibiotic (O'Brien *et al.,* 1998). Fusidic acid is derived from the fungus *Fusidium coccineum* and was developed by Leo Laboratories in Copenhagen, with the most active derivative, the sodium salt (sodium fusidate), released for clinical use in the early 1960s (Kucers *et al.,*1997). Since that time, acid has been widely used throughout Europe and Australia, particularly for the treatment of staphylococcal infection. For reasons that are unclear, US Food and Drug Administration licensure for fusidic acid has never been sought; thus, the drugis not currently available in the United States, despite the fact that it

* Corresponding author
E-mail address: askumurya.med@buk.edu.ng

provides a potentially useful option (usually in combinationwith rifampicin) for the treatment of infection with multidrug-resistant staphylococci, including methicillin-resistant *Staphylococcus aureus* (MRSA). Although resistance to fusidic acid was recognized as a potential problem soon after its release, clinically significant rates of resistance, in association with the widespread and often inappropriate use of topical fusidic acid (monotherapy) ointment/cream for chronic skin conditions, have emerged mainly over the past few years (Dobie and Gray, 2004).In the present review, while describing the in vitro and clinical efficacy of fusidic acid, we primarily focus on the factors leading to the emergence of resistance, the mechanisms of this resistance,and the strategies that may be applied to prevent the loss of this potentially useful antistaphylococcal agent.

2. Mode of Action of Fusidic Acid

A vital stage in bacterial protein biosynthesis is the elongation phase, in which the nascent polypeptide grows as the ribosome moves along the mRNA in a stepwise fashion. Two elongation factors, EF-Tu and EF-G, are intimately involved in this process, with EF-G particularly associated with the translocation step in which the mRNA is advanced along the ribosome by 1 codon to allow the next round of polypeptide elongation to begin (Hansson *et al.,* 2005). Fusidic acid blocks bacterial protein synthesis by binding to EF-G on the ribosome, thereby preventing release of the EFG– guanosinediphosphate complex and effectively stalling bacterial protein synthesis by inhibiting the next stage in translation (Tanaka*et al*., 1968; Bodley *et al.,* 1969; Hansson *et al*., 2005). The action of fusidic acid is mainly bacteriostatic but, at high concentrations, may be bactericidal. The gene encoding EF-G is *fusA,* which is chromosomally located.

2.1. In Vitro Activity of Fusidic Acid

Fusidic acid is primarily active in vitro against various strains of staphylococci, including methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), heterogeneous and nonheterogeneous vancomycin-intermediate *S. aureus* (hVISA and VISA), and most coagulase-negative staphylococci (Kucers*et al.,*1997; Howden *et al*., 2003). Corynebacteria and gram-positive anaerobes, such as clostridia (*Clostridia tetani, Clostridia perfringens,* and *Clostridia difficile*) and *Peptococcus* and *Peptrostreptococcus* species, are susceptible, whereas fusidic acid has only limited activity against streptococci and enterococci. Mostgram-negative bacteria are resistant, except for *Neisseria* and *Moraxella* species, *Legionella pneumophila,* and some strains of the *Bacteroides fragilis* group. Interestingly, the drug has good in vitro and clinical activity against *Mycobacterium leprae,* and some *Mycobacterium tuberculosis* strains are borderline susceptible. Fusidic acid also has some in vitro activity against *Coxiella burnetii* (Kucers*et al.,* 1997; Collignon and Turnidge, 1999).

2.2. In Vitro Fusidic Acid Breakpoints for *S. Aureus*

Even though there are no defined breakpoints for fusidic acid in Clinical and Laboratory Standards Institute(CLSI), susceptibility is generally defined as an MIC of _0.25 or _0.5 mg/L and resistance as an MIC of_2 mg/L (Collignon and Turnidge, 1999; Turnidge, 1999) or MIC of Isolates were considered to be resistant to fusidic acid if the MIC was ›25 mumg/L (Toma and Barriault, 1995) or By CLSI disc susceptibility methods (Collignon and Turnidge, 1999)., fusidic acid susceptibility (for a 2.5-mg disc) is defined by azone of _22 mm, whereas intermediate and resistant zones are18–21 mm and _17 mm, respectively (Coutant *et al.,* 1996; Skov *et al*., 2001) In vitro studies assessing the interaction between fusidic acid and other antimicrobial agents have produced variable results with *S. aureus*. Fusidic acid plus beta-lactams have demonstrated antagonism, indifference, and synergy, depending on the study; fusidic acid plus fluoroquinolones results in antagonism; and fusidic acid in combination with glycopeptides results in indifference, whereas, for rifampicin, indifference has been reported unless time-kill methods are used, in which case synergy has been observed (Collignon and Turnidge, 1999). The clinical relevance of these in vitro observations is unclear, although combination therapy with beta-lactams or rifampicin appears to be associated with lower rates of fusidic acid resistance.

2.3. Clinical Use of Fusidic Acid

Fusidic acid is obtainable in intravenous, oral, and topical (skin and ophthalmic) preparations and, when given systemically, is widely distributed throughout the body, including areas such as bone, joint fluid, prostate, and large abscesses. CSF penetrationthrough noninflamed meninges is poor, but reasonableconcentrations in cerebral abscesses have been reported. Oral\ fusidic acid is the most popular preparation (usually 500mg for every 8–12 h), achieving serum concentrations similar to those obtained through intravenous administration (Kucers *et al.,* 1997).Fusidic acid is mainly used to treat staphylococcal infections, for which it is usually combined with another antistaphylococcal agent to minimize the emergence of resistant clones, since naturally occurring fusidic acid–resistant strains occur at a rate of 1 in 106–108 colony-forming units (CFU). It can be particularly

useful in treating infections for which there are few other oral treatment alternatives, such as infections due to fluoroquinolone-resistant MRSA, thereby avoiding the need for agents such as the oxazolidinones. In Australia, for example, the oral combination of rifampicin and fusidic acid is commonly used to treat soft tissue/skin and bone/joint infections due to MRSA, after initial effective control with vancomycin therapy. Data to support the use of fusidic acid for these indications are reasonably substantive and have been reviewed recently (Whitby, 1999a; Whitby, 1999b; Atkins B, Gottlieb, 1999). In other countries, particularly in Europe, fusidic acid is added to either beta-lactams or glycopeptides for the treatment of staphylococcal bacteremia, endocarditis, and osteomyelitis (Whitby, 1999;Whitby, 1999b); however, despite the recommendation of these combination regimens by some antibiotic treatment guidelines, there are only limited published clinical data to support their use in these settings (Whitby, 1999). Table 1 summarizes the indications for which fusidic acid has been clinically effective. A key area in which there has been a notable recent increase in fusidic acid monotherapy is topical ointments and creams for the treatment of acute skin infections, including impetigo and potentially infected atopic dermatitis (usually given in combination with topical glucocorticoids) (Dobie and Gray, 2004). Such topical therapyhas proven effective (Table 1) but has also been associated withsignificant emergence of resistance.

Table 1. Selected clinical studies involving fusidic acid.

Staphylococcal infection (s)	Study details	Outcome(s)	Reference(s)
MRSAinfectionInfection type not defined	FA + Rif (38 patients)	Eradicated, 87%; death, 8%; Rifresistance, 3%	Jensen, 1968
Chronic OM	FA alone or FA + another agent (73patients)	Success rate of 37.5% for FA aloneand 63.9% for combination	Ernst,1969
Cystic fibrosis with MRSA infection	Rif + FA oral for 6 months (7patients)	Reduced iv antibiotic; decreasedMRSA isolation	Garske *et al.,* 1984
Osteomyelitis (OM)Acute OM (mainly due toS. aureus) in children	FA + Ery iv for 2 days then oral for21 days (45 patients)	Over 12-month follow-up, 100%success rate	Learmonth *et al.,*1984a; Learmonth et al., 1984b;
Bone/joint, wound, or respiratoryinfection	FA 500 mg t.i.d. + Rif 600 mg/day(8 patients)	Cured, 100%; recolonized, 25%	Cox *et al*., 1995
LeprosyBorderline lepromatous leprosy	FA 500 mg or 500–750 mg per dayfor 12 weeks (9 patients)	Improvement in multiple clinicalparameters	Franzblau *et al*., 1994
CAPD-related infection (prophylaxis)	Topical FA (intranasal and catheter)vs. oral Ofx vs. no treatment	Equivalent clinical and bacteriological efficacycolonization or peritonitis	Golledge, 1999
Neurosurgical infection (prophylaxis)	FA 500 mg t.i.d. (40 patients) vs.Placebo	Lower infection rate for FA (2.4%vs. 9.1%; *P* ! .05)	Golledge, 1999
Acute bacterial conjunctivitis	1% FA drops (121 patients) vs.0.5% Chl drops (129 patients)	Equivalent	Golledge, 1999
*Staphylococcus aureus*bacteremia	FA + Flc (108 patients) vs. Gm + Flc (86 patients)	No difference in mortality; significant decrease in relapse rate with FA combination	Whitby, 1999
*S. aureus*bacteremia and endocarditis	FA (276 patients) vs. non–FA-containing regimen (322 patients)	Decreased mortality with FAregimen (22% vs. 31%)	Whitby, 1999
Dermatological infectionImpetigo in children (96% ofcases due to *S. aureus*)	RCT, placebo controlled: 2% FA	cream vs. placeboFA much more effective	Koning *et al* 2002
Opthalmic infectionBacterial conjunctivitis	RCT: 1% FA drops b.i.d. for 7 daysvs. 0.3% Tmy drops 4–6 times/day for 7 days	Decreased exit-site colonization with FA; no difference in nasal	Jackson *et al*.,2002
*Clostridium difficile*infection*C. difficile*–associated diarrhea	RCT, double blind: FA 250 mg t.i.d.for 7 days (59 patients) vs. Mtz400 mg t.i.d. for 7 days (55 patients)	Equivalent; no difference in cure orrelapse rate	Wullt and Odenholt, 2004

Key: CAPD, continuous ambulatory peritoneal dialysis; Chl, chloramphenicol; Ery, erythromycin; FA, fusidic acid;Flc, flucloxacillin; Gm, gentamicin; MRSA, methicillin resistant *S. aureus;* Mtz, metronidazole; Ofx, ofloxacin; RCT, randomized controlled trial; Rif, rifampicin; Tmy, tobramycin. lead to different changes in MIC, and 2 *S. aureus* strains with low-level fusidic acid resistance that have nucleotide substitutions in *fusA* have been described (O'Neill *et al.,* 2004).

3. Mechanisms of Fusidic Acid Resistance

The understanding of the mechanisms of resistance to fusidic acid is rather limited and mainly focuses on *S. aureus*. The major resistance mechanisms appear to be related to alterations in EF-G structure, leading to reduced fusidic acid binding, or to acquisition of the fusidic acid resistance gene, *fusB,* which causes resistance by an undetermined mechanism. Plasmid-mediatedacquisition of resistance determinants appears to be common, and a recent European

study of an epidemic clone of fusidic acid–resistant *S. aureus* found that presence of the *fusB* gene was the predominant mechanism of resistance (O'Neill et al., 2004). However, inactivation or sequestering of fusidic acid by enzymes has also been described in bacteria other than *S. aureus* (Turnidge J, Collignon, 1999).

3.1. Fusa Mutations Leading to AlteredEF-G

Mutations in the chromosomally located *fusA* gene that lead to individual amino acid exchanges in EF-G are an important mechanism of fusidic acid resistance, presumably as a result of decreased affinity of the drug for the target (Besier *et al*., 2003). This type of resistance is thought to be harboured naturally in *S. aureus,* occurring at a frequency of 1 in 106–108 CFU and being associated with a shift in fusidic acid MIC to 112 mg/mL (Turnidge J, Collignon, 1999; Dobie and Gray, 2004).

3.2. Fusb Acquisition

The predominant mechanism of fusidic acid resistance in *S. aureus* is acquisition of a plasmid-mediated *fusB* resistance determinant (a 21.9-kb plasmid pUB101) that\ encodes modest levels of fusidic acid resistance, as well as beta-lactamase and cadmium resistance [29], and that was first described soon after fusidic acid was introduced (Evans and Waterworth, 1966). However, in a recent European study of a large outbreak of fusidic acid–resistant *S. aureus* infection, the *fusB* gene in some isolates was found to be located on a chromosome, rather than on a plasmid (O'Neill*et al* 2004). These isolates had fusidic acid MICs of 4 mg/L, in contrast to*S. Aureus* strains that harboured *fusB* on the pUB101 plasmid, which had MICs of 16 mg/L (O'Neill*et al* 2004). The mechanism of *fusB* mediated resistance remains unclear; early studies that suggested that it encoded a fusidic acid permeability barrier (Chopra, 1976) are now contradicted by studies showing no alterations in membrane composition in fusidic acid–resistant *S. aureus* strains (O'Brien *et al.,* 2002)

3.3. Other Mechanisms of Resistance

Recently, 4 non epidemic fusidic acid–resistant *S. aureus* strains with low-level resistance have been identified in Europe that do not harbour either the *fusB* resistance determinant or mutations in the *fusA* gene, thereby suggesting that other mechanisms of resistance may occur in *S. aureus*, as has been described for other species. These include binding and sequestering of fusidic acid by the type 1 chloramphenicol acetyltransferase found in enterobacteriaceae, deacetylation by an esterase produced in *Streptomyces* species (Turnidge, 1999), and efflux by the AcrAB efflux system in *Escherichia coli* (O'Neill, 2002).

4. Epidemiology of Fusidic Acid Resistance

Simultaneous testing of 423 methicillin resistant *Staphylococcus aureus* isolates to fusidic acid susceptibility by the disk susceptibility and serial dilutions (MIC) showed 21 (4.9%) isolates that were found to be resistant to fusidic acid (Table 2). The susceptibility patterns of *S. aureus* isolates in the current study were compared with data from an international multi – centre study in which 21 laboratories in 19 countries (including Nigeria) participated (Zinn *et al.,* 2004).A large, multicenter, worldwide 1996 study of staphylococcal resistance suggested that the rate of fusidic acid resistance among *S. aureus* was highly variable (Zinn *et al.,* 2004). Overall, among the 4065 isolates collected from consecutive patients (20 hospitals;19 countries), the mean rate of fusidic acid resistance was 5%(median, 1%; range, 0%–49%), with the highest rates of resistancereported in Greece (49%), Kuwait (20%), and NewZealand (13%), especially in dermatology (10% in all countries)and intensive care units (8%). Typing studies suggested that in each of these countries, a single clone was primarily responsiblefor the high rates (MRSA in Greece and Kuwait; MSSA in New Zealand). Remarkably, low rates of fusidic acid resistance were observed in all the large US hospitals studied (located in Colorado, California, and New Jersey) (Zinn *et al.,* 2004). In Australia, until 1999, fusidic acid resistance was found in ~5% of MRSA and MSSA strains, although topical fusidic acid was only introduced into the country in the mid-1990s (Nimmo *et al.,* 2003).In 2000–2002 in the United Kingdom, there were increasing reports of clonal spread of fusidic acid–resistant strains of *S. aureus,* including the emergence of a multiply resistant hospital-acquired MRSA strain, UK EMRSA-17 (Aucken, 2002). Similarly, a number of Scandinavian and European countries have reported clonal outbreaks of childhood impetigo due to fusidic acid–resistant MSSA, with low-level resistance apparently related tothe presence of chromosomal *fusB* (O'Neill, 2002; Tveten *et al.,* 2002; Osterlund *et al*., 2002). Fusidic acid resistance has also been described among non–multidrug resistant strains of community-associated MRSA (CA-MRSA), including 1 outbreak among intravenous drug users in Liverpool,United Kingdom (Corkill *et al*., 2004). Similarly, fusidic acid resistance has been a feature of 1 of the common CA-MRSA strains in Australia (WA-MRSA-1), although these account for only a small percentage of total Australian MRSA isolates (Coombs *et al*., 2004).Besides having the advantage of oral administration, fusidic acid penetrates tissues better than glycopeptides. The appearance of resistance to this antibiotic will adversely affect affective oral treatment of MRSA infections. Fusidic acid should be used in combination with other antibiotics such as rifampicin when treating MRSA

infections to prevent emergence of resistance to this antibiotic.

5. Factors Associated with the Emergence of Fusidic Acid Resistance

5.1. In Vitro and Animal Studies

Naturally occurring resistantsubpopulations of *S. aureus* with mutations in the *fusA* gene have been isolated from patients who have never been exposed to fusidic acid (Jensen et *al*., 1964). O'Neill *et al.* found that such chromosomalmutations occurred at a rate of 10^{-7} to 10^{-8} when *S. aureus* strains (MSSA, MRSA, and strains with reduced vancomycin susceptibility) were exposed to fusidic acid concentrations of 10 mg/L (which approximates Cmin levels after standard dosing in humans), but no mutants were detected when acid concentrations of 15 or 30 mg/L (which approximate Cmax levels after standard dosing) were used (O'Neill *et al*., 2004). However, a recent study that included CA-MRSA strains suggested that exposure to fusidic acid alone at 64 times the MIC was still associated with the development of resistance (Munckhof *et al*., 2004).In an animal model of MRSA endocarditis, fusidic acid monotherapy lead to development of resistance in 5 of 12 animals treated and was associated with fusidic acid treatment failure. Development of resistance was particularly associated with high bacterial inocula, and combination therapy with vancomycin appeared to prevent such resistance (Fantin *et al*., 1993).

Table 2. Emergence of fusidic acid (FA) resistance in North-western Nigeria.

	Total (n = 423)			CA-MRSA (n = 187)			HA-MRSA (n = 236)
Antibiotics	No. of isolates that were:		Resistance rate (%)	No. of isolates that were:		Resistance rate (%)	Resistance rate (%)
	S	R		S	R		
Gentamicin	165	22	11.8	210	16	11.0	48 (11.3)
Erythromycin	155	32	17.1	184	52	22.0	84 (19.9)
Ciprofloxacin	183	4	2.1	226	10	4.2	14 (3.3)
Chloramphenicol	196	18	9.6	215	21	8.9	39 (9.2)
Ofloxacin	165	22	11.8	178	58	24.6	80 (18.9)
Rifampicin	176	11	5.9	220	16	6.6	27 (6.4)
Fusidic acid	179	9	4.8	244	12	5.1	21 (4.9)

Key: S, Sensitivity; R, Resistance

5.2. Clinical Studies: Systemic Fusidic Acid Therapy

Numerousclinical studies have reported the emergence of fusidic acid resistance among *S. aureus* strains either during fusidic acid monotherapy or after fusidic acid combination therapy; these studies have been summarized recently (Turnidge *et al.,* 1999). The rate of emergence of fusidic acid resistance in 1850patients who received systemic fusidic acid monotherapy for a range of clinical conditions was ~5.1%, (Turnidge *et al.,* 1999; Chang *et al*., 2000), but most of these patients received short courses (14 days) of fusidic acid. Among the patients with chronic osteomyelitis who received prolonged courses of fusidic acid monotherapy, a high rate(15%) of resistance was noted, whereas, among patients with burns, a very high rate (46%) of fusidic acid resistance emergence was reported despite a short duration of therapy. In comparison, the rate of resistance among 1800 patients who received fusidic acid combination therapy was ~0.8%, despite the fact that many patients had serious staphylococcal infections (bacteremia, acute and chronic osteomyelitis, MRSA infection, and hVISA/VISA infection) that often required prolonged therapy. In many of these studies, fusidic acid was combined with a beta-lactam (penicillin, flucloxacillin/cloxacillin, or methicillin), but other combinations included rifamycins, erythromycin, chloramphenicol, lincomycin, and novobiocin (Turnidge *et al.,* 1999; Howden *et al.,* 2004).

5.3. Clinical Studies: Topical Fusidic Acid Therapy

Topical preparations containing fusidic acid has been increasingly used in some part of the world to treat a range of dermatological problems, particularly skin infections (e.g., impetigo, folliculitis, and traumatic wounds) and atopic dermatitis. In the United Kingdom, the use of topical fusidic acid almost doubled from 1995 to 2001 and currentlyconstitutesabout twothirds of the total usage (Dobie and Gray, 2004). This increase as coincided with increased reports of fusidic acid–resistant *S. aureus* from many centers, particularly among patients receiving long-term topical fusidic acid therapy (Dobie and Gray, 2004). Shah and Mohanraj (2003) reviewed all dermatology patients (age range, 6 months to 75 years) for whom there was a positive *S. aureus* culture during a 4-month period at a district hospital in the United Kingdom, and they found that 62% of patients had used topical fusidic acid during the previous 6 months and that a significantly higher proportion of isolates from dermatology patients were fusidic acid resistant, compared with those from non dermatology patients (51%vs. 9.6%). Patients with atopic

eczemawere most affected, with 78% of isolates being fusidic acid resistant. Among patients infected with fusidic acid–resistant or susceptible *S. aureus* isolates, 96% and 29%, respectively, had used topical fusidic acid therapy in the previous 6months.Similar findings have been noted by Ravenscroft *et al*. (2000) in the United Kingdom and by others in The Netherlands and elsewhere (Brown and Thomas, 2002; Peeters *et al*., 2004).Mason *et al.,*(2003) recently reported a significant (*P*p.01) association between high rates of general practice prescribing of topical fusidic acid and the emergence of fusidic acid resistance among strains of MSSA. Similarly, a retrospective case control study performed by those sameauthors in 2002 suggestedthat exposure to topical fusidic acid during the previous6 months was significantly associated (OR, 2.77; *P*p.027) with subsequent infection with fusidic acid–resistant-methicillin susceptible *S. aureus* (MSSA) (Mason *et al.*, 2003). It is difficult to determine to what extent the widespread dissemination of individual fusidic acid–resistant *S. aureus* clones has contributed to these findings from the United Kingdom. Other non-European studies have noted less dramatic results, but these have been confounded by a number of factors, including the use of topical combination therapy (fusidic acid and gentamicin)rather than monotherapy, and treatment courses of brief duration (Nishijim *et al*., 2003). Nevertheless, whether the high rates of cutaneous colonization and infection with fusidic acid–resistant *S. aureus* are clonal or nonclonal, they appear to impact the rate of resistanceamong invasive *S. aureus* isolates, because the rate of fusidic acid resistance in MSSA bacteremia isolates in the United Kingdom increased from2.0% to 6.4% from 1990 to 2001 (figure1) (Nishijim *et al*., 2003). Livermore *et al.* (2002) also noted that the rates of fusidic acid resistance among MRSA and MSSA strains were roughly equal during this time.

6. Conclusions

The emergence and spread of multi-resistant methicillin resistant *Staphylococcus aureus* (MRSA) strains, especially those resistant to fusidic acid in North-western Nigerian hospitals is of concern. Given current trends regarding the spread and clinical impact of hospital- and community-acquired MRSA infection, it would seem to be wise to maintain all possible treatment options, including the potential use of fusidic acid. Especially because combination therapy with rifampicin can be a useful oral treatment option for less severe MRSA infections, such as those involving the skin or soft tissue, and for chronic osteomyelitis or prosthetic joint infections for which long-term parenteral therapy has been unsuccessful and/or for which surgery is not a practical option (e.g., in the elderly population). Thus, prevention of the emergence of fusidic acid resistance (especially when high numbers of organisms and intrinsic resistance are present) by restricting the use of systemic and topical fusidic acid monotherapy appears to be a worthwhile goal, given its documented association with the emergence of fusidic acid resistance. In particular, the use of topical fusidic acid monotherapy, especially for prolonged periods to treat chronic skin disorders, should be reconsidered, because it appears to be a major driver of resistance and clonal selection. Common sense would suggest that antibiotics used topically should be ones that are not used systemically (Dobie and Gray, 2004). When systemic fusidic acid is used appropriately in combination with other agents (e.g., rifampicin), resistance rates appear to remain low, even in regions where usage has been common for many years. To lose the efficacy of this useful agent because of inappropriate use would be dumb. Increase resistance to fusidic acid will further reduce the already limited treatment options for MRSA infections.

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