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Topical mupirocin-steroid for wound care in an era of rising antibiotic resistance

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ABSTRACT

Wound infections are characterized by antibiotic-resistant bacteria, a growing issue. When these microbes infect a wound, it's treated aggressively. A few therapeutic antibiotics make this therapy problematic. Mupirocin and other newly discovered methods show promise as bacterial wound-killing agents. This study includes three topical mupirocin-steroid therapies that were tested for their ability to treat antibiotic-resistant clinical isolates. Wounds may be treated using mupirocin-based liquid, cream, and dressing coating. The reduction in viable bacterial population after mupirocin exposure was used to compare the bactericidal efficiency of different mupirocin treatments. Results showed that each ingredient had the potential to reduce germ reproduction. The mupirocin-coated bandage was the most efficient strategy to kill antibiotic-resistant bacteria, whereas the liquid mupirocin was the least efficient. The mupirocin-coated steroid bandage swiftly killed the tested germs and showed promise against other bacterial strains. Mupirocin might be a therapeutic and prophylactic medication for wound colonization by organisms that hinder healing.

Keywords: mupirocin, wound care, antibiotic resistance

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INTRODUCTION

Despite being home to fungus and bacteria, the human skin functions as a barrier against germ penetration and infection of underlying tissues. Human skin is thicker and more impermeable than other surfaces[1]. Once a wound breaks this barrier, the likelihood of bacterial penetration of an intact tissue rises. In traumatic, thermal, or chronic wounds, the colonization and infection potential rise due to the compromised barrier and the development of avascular eschar, which allows unrestricted microbe growth[2] which leads to uncontrolled microorganism growth that permits germs to proliferate unrestrictedly. Infection is usually related to the kind of wound, wound management, and host factors[3] including the patient's age, diet, immune system health, and underlying sickness. If proper treatment techniques are followed, wound infection rates may be kept low[4].

Antibiotic prophylaxis is necessary to reduce the wound's microbial load and hasten healing. A slow-healing wound increases the patient's medical expenditures and worsens his or her health, leading to recurrent hospitalizations[5]. Antibiotic resistance has increased due to the widespread use of antibiotics, which has led to a rise in the isolation of antibiotic-resistant organisms from wounds. Implementing strategies to minimize patient-to-patient transmission and manage nosocomial outbreaks may result in an antibiotic-resistant wound infection[6]. When treating an antibiotic-resistant illness, it is normal practice to minimize patient contact to prevent the infection from spreading. Infections are often treated with medicines that are effective against the causing organism. Medical treatments are followed. This makes managing resistant organisms with antibiotics problematic. Antibiotics should be used with caution. Hospitals and communities have taken stringent efforts to prevent the spread of antibiotic-resistant microorganisms. To counteract wound colonization or infection by antibiotic-resistant bacteria, a means of prophylaxis that minimizes the risk of resistant organisms must be found. The chosen technique must be effective against many species and destroy intruders quickly[7]. This article discusses the effectiveness of topical antibiotic-resistant bacterial treatments with mupirocin and steroids. As potential topical mupirocin-steroid treatments, a solution, cream, and dressing were studied.

Mupirocin, also known as pseudomonic acid A, is a compound that is synthesized by the soil bacterium *Pseudomonas fluorescens*, which belongs to the Gram-negative group of bacteria. As an antibiotic for the skin, it works by attaching to bacterial isoleucyl-tRNA synthetase (IleRS) and stopping the production of proteins. This medication is used to treat infections caused by microorganisms such as *Streptococci* and *Staphylococci* strains, including those that are resistant to methicillin. It is commonly employed to treat methicillin-

resistant *S. aureus* (MRSA), a bacterium that mostly causes bloodstream infections acquired in hospitals and is a significant contributor to wound infections. Prior studies have indicated that mupirocin has wound healing properties, mostly attributed to its antibacterial action against bacteria commonly seen in wounds. The process of wound healing is multifaceted and involves various cellular activities and molecular interactions, with growth factors playing a significant role. While most wound healing studies have primarily examined the antibacterial properties of mupirocin, a limited number of studies have investigated the impact of mupirocin on inflammation and cell migration. These investigations have revealed that mupirocin promotes the production of tumour necrosis factor (TNF)-α in RAW 264.7 cells. TNF-α has a crucial role as a cytokine in the inflammatory phase of wound healing. In addition, the administration of anti-TNF-α monoclonal antibodies in mice caused a delay in the wound healing process. This delay was accompanied by a reduction in the number of inflammatory cells and fibroblasts in the wound area. In contrast, the administration of TNF-α greatly improved the healing of the wound. This indicates that mupirocin possesses wound healing capabilities that are not only attributed to its antibacterial properties[8].

METHODOLOGY

Microorganisms

Clinical isolates were obtained from Baghdad University and Basra University and Table 1 lists resistance microbes and medications as provided from the source. The strains' stock cultures were preserved at 0°C throughout the operation. The frozen stock was thawed, and the bacterial strains were grown overnight in tryptic soy broth. This made the strains usable. They might then be used. After a day of growth in tryptic soy broth, Gram-negative bacteria were isolated by centrifuging at 13000 rpm for five minutes. After developing in broth, the bacteria were isolated. The bacteria were then washed with physiologic saline and resuspended until their optical density at 750 nm was 0.25 to 0.40. In one test, the bacteria were resuspended in 60% calf serum diluted with physiologic saline. Calf serum is used because it contains low levels of antibodies and other growth-inhibiting components and it can also protect cells from harmful disruptions, including large pH shifts. So, the bacteria's optical density will be compared with calf serum that considered as a control. Gram-positive organisms were washed and resuspended in sterile water to ease recovery. The next paragraphs describe this technique and the recovery of Gram-positive organisms from test materials. After inoculating the organism in Mueller-Hinton Agar plates and examining bacterial growth, high-quality cultures were obtained.

Table 1. Clinical isolates, isolation sites, and resistant antibiotics

Organism	Strain	Sample type	Antibiotic resistance
Burkholderia cepacia	UT363	Wound sample	1,2 3,4,5,7,10,20,22
P. aeruginosa	137366	Traumatic Wound sample	1,2,3,4,5,6,7, 11,13
Pseudomonas spp (P cepacia, P. stutzeri, P. maltophilia and P. putrefaciens)	150938-1	Fluid of body (saliva, blood, interstitial fluids)	5,6,7,8,9,22,23,24
E. faecium	118271	Urine sample	3,4,5,6,716,17,18,22,23
S. aureus	141960	Fluid of body (saliva, blood, interstitial fluids)	1,2 3,4,5,6,7,8,9,10
S. aureus	140277	Urinary catheter	17,18,19,20,21,22,23,24
Acinetobacter	150938-2	Fluid of body (saliva, blood, interstitial fluids)	16,17,18,19,20,21,22,23
Enterococcus faecalis	118271	Feces sample	5,6,7,8,9, 16,17,18,22,23
Citrobacter koseri	150938-3	Fluid of body (saliva, blood, interstitial fluids)	11,12, 13,14,15,16,17,18
Klebsiella pneumoniae	147225	Wound sample	14,15,16,17,18,22,23,24
Alcaligenes	144218	Fluid of body (saliva, blood, interstitial fluids)	1,2 3,4,5,6,7,8,9,10

1- Ampicillin, 2- Ciprofloxacin, 3- Erythromycin 4- Teicoplanin, 5- Tetracycline, 6- Vancomycin, 7- Teicoplanin, 8- Cephazolin, 9- Cloxacillin, 10- Penicillin, 11- Cefazolin, 12- Cefotaxime, 13- Ceftriaxone, 14- Cefuroxime, 15- Gentamicin, 16- Tobramycin, 17- Ceftazidime, Piperacillin, 18- Cephalothin, 19- Clavulan, 20- Clindamycin, 21- Cloxacillin, 22- Ofloxacin, 23- Imipenem, 24- Amikacin

Coating

At each and every step of the product development process, including the conceptualization of the dressings and the determination of the ideal number of antibacterial agents to include, the most current clinical best practices were taken into careful account. The rayon and polyester absorbent core of the dressing that was made for the building of the mupirocin dressing was placed between two sheets of high-density polyethylene mesh. This was done in order to complete the construction of the mupirocin dressing. After that, the dressing was divided into squares with dimensions of about three centimeters each.

The concentration of silver sulfadiazine ultimately reached a value of 0.6 percent after the inclusion of the bacterial inoculum, and it has remained at that value ever since. In order to produce the mupirocin dressing, a dressing was

used that had the very same components and in the exact same proportions as the mupirocin dressing itself. As a coating for the dressing, a very thin layer of mupirocin cream with a concentration of two percent was applied. It was administered as a cream. The layer's overall weight was somewhere around 0.61 grams. The high-density polyethyleneused in the mupirocin-coated dressing was coated with nanocrystalline mupirocin (Neopharma Pharmaceuticals, Abu Dhabi, UAE), but the high- density polyethylene used in the mupirocin nitrate dressing was not. This was the sole difference between the two dressings. The fabrication of both kinds of dressings used the same kinds of components for the rest of the dressing. Both the control dressing and the mupirocin dressing werepreciselythe same size (three centimeters by three centimeters), and they were both constructed using the exact same components.

Design of study

Both the control and test dressings were made in triplicate and placed singly on separate pieces of plastic sheeting that were somewhat larger than the test item. The control dressing served as the standard for comparison. The dressings were inoculated using an aliquot of a bacterial solution of a concentration of 6,200 CFU/ml. Each component of the dressing, with the exception of the mupirocin which did not absorb the inoculum, was covered with an additional piece of plastic sheet and pressed down to ensure that the inoculum came into contact with the active components of the dressing. The inoculate and the dressings were both left to incubate for twenty minutes at a temperature of 37°C. Following the completion of the incubation procedure, the dressings were removed from the incubator and the dressings were then immersed carefully in a bacterial recovery solution that included salt, polysorbate, and sodium thioglycolate [9].

The percentage of sodium chloride in the sodium thioglycolate solution was increased to 10 percent so that the staphylococci and enterococci could be recovered more easily from the dressings. This was done in order to simplify the process of regaining control of the bacteria. In order to gradually dilute the dressings as well as the sodium thioglycolate, vigorous vortexing and the use of phosphate buffered saline were both used. The method that was used to determine the number of viable bacteria that were still present after being exposed to the various dressings was to place the serial dilutions of the bacteria on Mueller-Hinton Agar and count the number of colony-forming units after 24 to 72 hours of incubation at 37°C.

The recovery was verified by simultaneously pouring the same amount of bacterial suspension into a sealed test tube and incubating the culture for a length of time that was comparable to the incubation duration for the inoculum that was applied to the test articles for 24hrs. There was not a discernible difference in the results of the experiment regardless of whether the germs were taken from the test tubes or the control dressing pieces. This would imply that the kind of bacteria that was present at the time may have a significant impact on the degree of healing that a person experienced.

The approach thatwas described above was modified in order to create a time course for the death of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. The dressings were createdin the exact same way as they had been in the past, with the one key difference being that an enough quantity of each form of dressing was manufactured. In order to make it possible to analyze duplicate samples at intervals that had been randomly determined, this step was taken (1, 3, and 4 hours). In addition, the bacteria were first cultivated in the manner that was described earlier, and then they were resuspended to the desired optical density in new tryptic soy broth. This was done so that the tests could be carried out. After everything was accomplished, the inoculum was given to the rats to ensure accurate results.

RESULTS and DISCUSSION

Activity of mupirocin-steroid assay

The bactericidal test that was performed in order to establish the efficacy of topical silver treatments made it possible for an accurate estimate of the impact that the combination of mupirocin and steroid had on the infection. The process also makes it possible to assess the rate of bacterial mortality.

Activity of mupirocin-steroid against bacteria

We investigated whether or not applying silver to wounds using one of three novel approaches was effective against clinical isolates of bacteria that are resistant to antibiotics (Table 2). The mupirocin-steroid coated and mupirocin-steroid cream formulations were able to demonstrate antimicrobial efficacy against a subset of the isolates. However, clinical isolates occurred in each of these varied kinds of mupirocin-steroid treatments, and these products were essentially ineffective against these clinical isolates over the whole-time range of the investigation. The findings also suggest that, with the exception of *Staphylococcus aureus*, mupirocin-steroid sulfadiazine appears to produce a more significant reduction in the number of recoverable live cells than does mupirocin-steroid cream. This is in contrast to the situation with mupirocin-

steroid cream, which produces only a moderate reduction in the number of recoverable live cells as illustrated in the Table 2 which showed that the bacterial number reduced non-significantly after 20 and 30 minutes. When the results of the two therapies were compared, it was clear that this was the case. The nanocrystalline that was included within the mupirocin-steroid-coated dressing was able to exert a significant level of control ($p<0.05$) over the organisms in each of these situations. It is essential to take note of the fact that the method that was employed for the enumeration of live cells did not permitthe detection of less than 200 viable organisms in the dressing material. This is an important pointto take into consideration. Because of this, providing an exact number indicating the degree to which the number of organisms in a particular test was decreased was not possible because it wasnot practical to do so.

In addition, a test was carried out in order to ascertain the impact that serum proteins have on the efficacy of the six distinct formulations of mupirocin and steroid that were used in the study. When the bacteria were suspended in either 60% serum in saline or in 100% normal saline, the results showed that the silver-coated dressing was able to achieve a significant ($p<0.05$) reduction in the number of recoverable organisms that was greater than 8 log10 in magnitude. This was the case despite the fact that a variety of potential solutions were explored (*Pseudomonas aeruginosa 150938-1*). Since this result consistently transpired, the presence or absence of serum in the saline solution was irrelevant to the investigation. When the two different formulations were tested against bacteria that were suspended in serum that was 60% concentration, there was non-significant ($p>0.05$) difference between them.There was no noticeable difference between the two formulations when they were evaluated against each other, and neither mupirocin-steroid cream nor mupirocin-steroid liquid had a significant influence when tested in saline (Table 2).

Table 2. The number of bacteria (CFU) after treatment with antibiotic

Bacteria	Strain	Control	20 min	30 min	p-value
Mupirocin-steroid- coated					
Burkholderia cepacia	UT363	8.1 ± 0.03	<4.0	<3.0	<0.05
P. aeruginosa	137366	8.3 ± 0.02	<4.0	<3.0	<0.05
Pseudomonas spp. (P. cepacia, P. stutzeri, P. maltophilia, and P. putrefaciens).	150938-1	8.2 ± 0.01	<4.0	<3.0	<0.05
E. faecium	118271	8.5 ± 0.04	<4.0	<3.0	<0.05
S. aureus	141960	8.7 ± 0.07	<4.0	<3.0	<0.05
S. aureus	140277	8.3 ± 0.06	<4.0	<3.0	<0.05
Acinetobacter	150938-2	8.9 ± 0.04	<4.0	<3.0	<0.05
Enterococcus faecalis	118271	8.2 ± 0.04	<4.0	<3.0	<0.05
Citrobacter koseri	150938-3	8.8 ± 0.03	<4.0	<3.0	<0.05
Klebsiella pneumoniae	147225	8.6 ± 0.02	<4.0	<3.0	<0.05
Alcaligenes	144218	8.3 ± 0.01	<4.0	<3.0	<0.05
Mupirocin-steroid- cream					
Burkholderia cepacia	UT363	8.1 ± 0.03	<8.0	<6.0	p > 0.05
P. aeruginosa	137366	8.3 ± 0.02	<8.0	<6.0	p > 0.05
Pseudomonas spp. (P. cepacia, P. stutzeri, P. maltophilia, and P. putrefaciens).	150938-1	8.2 ± 0.01	<8.0	<6.0	p > 0.05
E. faecium	118271	8.5 ± 0.04	<8.0	<6.0	p > 0.05
S. aureus	141960	8.7 ± 0.07	<8.0	<6.0	p > 0.05
S. aureus	140277	8.3 ± 0.06	<8.0	<6.0	p > 0.05
Acinetobacter	150938-2	8.9 ± 0.04	<8.0	<6.0	p > 0.05
Enterococcus faecalis	118271	8.2 ± 0.04	<8.0	<6.0	p > 0.05
Citrobacter koseri	150938-3	8.8 ± 0.03	<8.0	<6.0	p > 0.05
Klebsiella pneumoniae	147225	8.6 ± 0.02	<8.0	<6.0	p > 0.05
Alcaligenes	144218	8.3 ± 0.01	<8.0	<6.0	p > 0.05
Mupirocin-steroid- liquid					
Burkholderia cepacia	UT363	8.1 ± 0.03	<15	<10.0	p > 0.05
P. aeruginosa	137366	8.3 ± 0.02	<15	<10.0	p > 0.05
Pseudomonas spp. (P. cepacia, P. stutzeri, P. maltophilia, and P. putrefaciens).	150938-1	8.2 ± 0.01	<15	<10.0	p > 0.05
E. faecium	118271	8.5 ± 0.04	<15	<10.0	p > 0.05
S. aureus	141960	8.7 ± 0.07	<15	<10.0	p > 0.05
S. aureus	140277	8.3 ± 0.06	<15	<10.0	p > 0.05
Acinetobacter	150938-2	8.9 ± 0.04	<15	<10.0	p > 0.05
Enterococcus faecalis	118271	8.2 ± 0.04	<15	<10.0	p > 0.05
Citrobacter koseri	150938-3	8.8 ± 0.03	<15	<10.0	p > 0.05
Klebsiella pneumoniae	147225	8.6 ± 0.02	<15	<10.0	p > 0.05
Alcaligenes	144218	8.3 ± 0.01	<15	<10.0	p > 0.05

Eradication graph

An isolate of methicillin-resistant *S. aureus* and an isolate of vancomycin-resistant *E. coli*, both of which were resistant to vancomycin, were evaluated in order to discover which of the three potential combinations of mupirocin and steroids was the most successful. Both of these bacterialstrains exhibited resistance to the antibiotic vancomycin. The data, which are shown in (Figure 1 and Figure 2), demonstrate the rapidity with which these serious infections were cleared up by using any one of the several mupirocin-steroid therapy protocols studied. In every instance, the use ofmupirocin-steroid cream as well as mupirocin-steroid coated led to a significant decrease ($p<0.05$) in the number of organisms that could be collected and were still alive. This was the case whether or not the organisms had been exposed to the cream or the coated medication. This was the case irrespective of the kind of mupirocin-steroid preparation that was carried out in the experiment. The outcomes were the same regardless of the kind of mupirocin-steroid combination that was used in the experiment.

There was no difference in the result regardless of whether or not the organisms had been given the treatment since this was always the case. There was no difference in the outcome. On the other hand, in none of these situations did the number of organisms reduced to the point where they could no longer be located. Instead, the situation turned out to be the exact reverse of what was expected to occur in accordance with the predictions that were made. As a direct consequence of the mupirocin and the steroid-coated dressing, the number of live organismshad been decreased to an undetectable level in less than twenty minutes. According to these figures, it would appear that using silver in this method makes it easier to quickly eradicate live organisms, which would be consistent with the hypothesis that using mupirocin-steroidin in this manner makes it simpler to quickly eradicate living organisms.

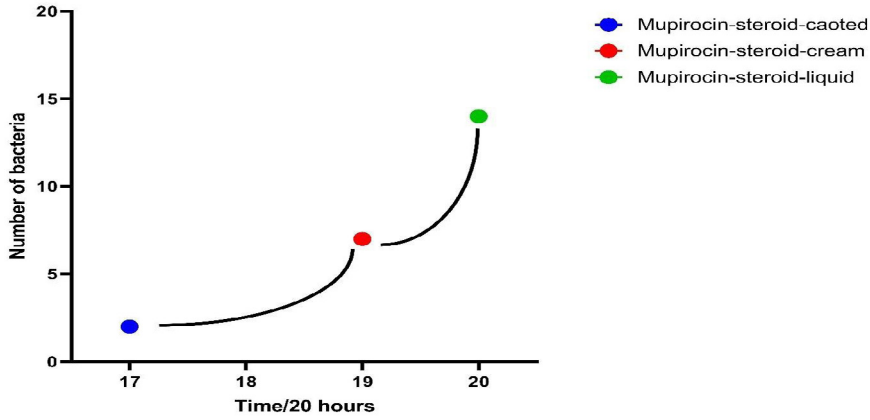

Figure 1. Number of bacteria (CFU) according to the time/ 20 hours

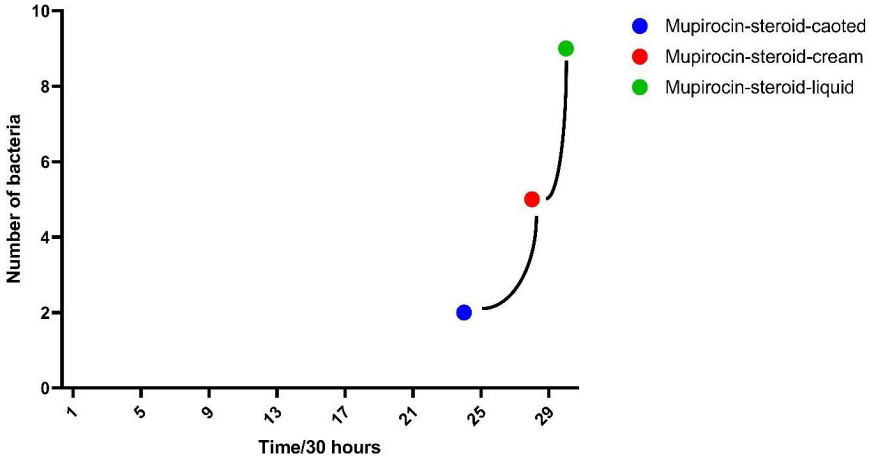

Figure 2. Number of bacteria (CFU) according to the time/ 30 hours

Antibiotic resistance is a worldwide issue that is having the most significant impact on medicine.The identification of organisms that have limited or limited susceptibility to antibiotics is currentlybeing place[1,2]. The issue of antibiotic-resistant microbes colonizing wounds is a concern for the medical profession, particularly in immunocompromised patients. Infections that are resistant to antibiotic treatment are potentially another use for topical mupirocin-steroid[2,3]. This is feasible despite the fact that it is rare for clinical isolates to simultaneously exhibit antibiotic and noble metal resistance[3,4]. The clinical using of isolates for mupirocin-steroid and antibiotic-resistant bacterial strains is not shown in any of the published literature[10]. Since the 19th century, therapeutic

applications of mupirocin-steroid have been carried out. Over the course of a century of clinical use, the safety of mupirocin-steroid combination therapy has been established[11]. Both the mupirocin-steroid cream dressing and the mupirocin- steroid liquid produced no adverse effects when subjected to cutaneous sensitization and irritation tests. Experiments conducted *in vitro* revealed that mupirocin-steroid-coated dressing was muchless hazardous to cells than mupirocin-steroid alone[12]. In a manner similar to that of other heavy metals, mupirocin-steroid poisons respiratory enzymes as well as components of microbialelectron transport systems and interferes with DNA activity[13]. To kill bacteria, mupirocin-steroid must be in the form of a solution, and the efficacy of the solution is directly proportional to the amount of mupirocin-steroid present in it[14]. As a result of their high reactivity, many of the ions found in body fluids, particularly chloride, consume silver ions[15]. In order to treat this condition, topical mupirocin-steroid coated solutions are often used more than one time per day[16]. It's possible that the solution may irritate and tighten the tissues[17]. When using silver nitrate, Klein et al. found that there was limited eschar penetration and browning of the tissue[18]. It was decided to include silver sulfadiazine in order to prevent specific issues that might arise when working with solutions containing silver nitrate[19]. To reduce the number of treatments required to maintain an effective concentration close to a wound, mupirocin-steroid combination medication that isincorporated in a cream base is used[20]. When applied to wounds, mupirocin-steroid coated sulfadiazine causes the tissue to form Pseudo-Eschar and become dry[21]. The removal of cream might be unpleasant for some individuals[22]. Wetting of wounds is encouraged by mupirocin-steroid sulfadiazine, whereas epithelialization is slowed down[23]. Mupirocin-steroid-coated dressings provide a silver concentration that is both effective and long-lasting in the vicinity of a wound[24].

Westaim Biomedical has created a method to sputter silver ions onto a variety of surfaces using their own proprietary technology. It has been shown that an active species of silver included inside the mupirocin-steroid-coated dressing is capable of eliminating a broad variety of germs[25]. According to the data shown in Table 2, physiological chloride concentrations did not have an effect on the efficacy of the mupirocin-steroid-coated dressing. Antimicrobials based on mupirocin and steroids have a reaction with plasma proteins, which disrupts their ability to kill bacteria[26]. In order to determine whether or not serum proteins altered the efficacy of mupirocin-steroid containing wound care products, bacteria suspended in 60% calf serum were studied[27]. As has been stated before, nanocrystalline mupirocin-steroid was shown effective in combating bacterial suspension. According to these findings, serum proteins

may not be able to deactivate nanocrystalline mupirocin-steroid, at least not throughout the time period that was examined[28]. The effect of serum proteins on the other two topicals that were evaluated did not provide any conclusive results since those topicals did not exhibit a significant amount of antibacterial activity after coming into contact with the bacteria under investigation for 20 and 30 minutes[29].

As was hypothesized, Table 2 and Figure 1 and Figure 2 demonstrate that the combination of mupirocin and steroid is effective against a broad variety of antibiotic-resistant bacteria. Because the plasmid for heavy metal resistance, particularly mercury resistance, is associated to antibiotic resistance, other heavy metal antimicrobials are ineffective against antibiotic-resistant bacteria[30]. This is especially true of mercury resistance. In spite of the fact that certain instances of acquired microbiological resistance to silver do occur, particularly with antibiotic, the likelihood of these events happening with mupirocin-steroid coated dressings is much lower[31]. The speed, breadth, and thoroughness with which nanocrystalline mupirocin- steroid kills bacteria should eliminate the possibility of bacterial resistance[5-8]. In the fight to manage antibiotic-resistant infections in wound care, modern mupirocin-steroid treatments may show to be effective tools, particularly those that provide rapid killing of a broad range of bacterialspecies[1-4].

STATEMENT OF ETHICS

The study received approval from the "Scientific Committee in the Department of Pharmacy, Al-Kut University College, Wasit, Iraq" on May 6, 2023 (51/2023).

CONFLICT OF INTEREST STATEMENT

No conflict of interest was declared by the authors.

AUTHOR CONTRIBUTIONS

Design – Joudah MS, Abbood AZA; Acquisition of data – Ajeel ZH, Hadi HS; Analysis of data – Joudah MS, Abbood AZA; Drafting of the manuscript – Abbood AZA, Ajeel ZH; Critical revision of the manuscript – Ajeel ZH, Hadi HS; Statistical analysis – Joudah MS, Abbood AZA; Technical or financial support – Ajeel ZH, Hadi HS; Supervision – Joudah MS, Abbood AZA, Ajeel ZH, Hadi HS.

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