# The Efficacy and Tolerability of Electrolyzed Oxidized Water in Treating Mild to Moderate Acne

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The purpose of this study was to determine the efficacy and the tolerability of the Charme™ system, a hand-held device that electrolyzes a water-based sodium chloride solution and delivers electrolyzed oxidized water (EOW) to the skin, in the treatment of mild to moderate acne. A total of 31 patients with mild to moderate acne vulgaris were enrolled in this 8-week, open-label, split-face pilot study. Acne lesion counts and physician global assessments were taken at each visit, as well as patient satisfaction and global assessments and high-resolution digital photographs. Statistical analysis of the results for treatment versus baseline scores was performed using a Hotelling T test and repeated - measures analysis of variance. Values of .04 or less were considered statistically significant. A total of 25 patients (mean age, 24.7 years, ranging from 15 to 47.years) completed the study. The mean reduction in total acne lesion counts from baseline to the end of treatment was 40.9 for the EOW - treated side (right side) and 18 for the untreated side (Heft side) (P=.04). Investigators observed a significant mean reduction in inflammatory lesions, both papules and pustules (P<01), as well as in the number of individual papules (75.7 vs 19.4) and pustules (42 vs 7.38) on the treated side versus the untreated side (P=.Q2). The mean reduction of the noninflammatory lesions, however, was not significant (P=.336). Physician global assessment indicated that 100 of the patients showed clinical improvement of 25 or more, while 50 of the patients observed a moderate improvement of 50 or more at the end of the treatment period. Interestingly. 75 of the patients preferred the EOW delivery system to other conventional treatment modalities. Only 5 patients had transient, cutaneous adverse effects, such as pruritus, erythema, buming/stingfng, and/or peeling, that ceased by week 2. Patient satisfaction with the EOW system was rated high, with 80 of the patients in the study assessing the EOW device as good or excellent, while 16 rated the device as fair. Only 4 of the patients were dissatisfied with the device. The pilot study demonstrated that the EOW system is an effective and well-tolerated method of treatment for patients with acne. The device appeared to be effective primarily on inflammatory acne lesions. This is most likely attributed to the antimicrobial properties of the EOW that reduce the Propionibacterium acnes populations.

**ANTIMICROBIAL EFFECTS OF LOW pH WATER IN A LABORATORY SETTING*†[33,36]**

| Bacteria | Count Prior to Testing (million) | 5 sec | 10 sec | 30 sec |
|---|---|---|---|---|
| *Escherichia coli* | 3.94 | <100 | <100 | <100 |
| *Staphylococcus aureus* | 12.5 | <100 | <100 | <100 |
| *Streptococcus pyogenes* | 8.95 | <100 | <100 | <100 |
| *Pseudomonas aeruginosa* | 17.82 | <100 | <100 | <100 |
| MRSA* | 11.24 | <100 | <100 | <100 |
| *Salmonella* | 13.80 | <100 | <100 | <100 |
| Sporular species | 11.40 | <100 | <100 | <100 |

*Methicillin-resistant *Staphylococcus aureus*.
†Bacteria broth: low pH acidic water=1:100.
Testing agency: Food and Drug Safety Center, Tokyo, Japan.

Acne vulgaris is an extremely common condition that affects more than 40 to 50 million individuals annually in the United States alone.[1] Although more prevalent in teenagers, acne can also have an impact on every age group.[2] Both sexes and all races are prone to this often distressing skin condition.[3] Many physicians trivialize this condition, .but considerable research has explored the psychosocial impact and quality of life for patients with acne. A study by Mallon et al[4] assessed the quality of life for patients and compared it with other chronic conditions. They found that patients with acne have social, psychological, and emotional problems of the same magnitude as those with chronic asthma, epilepsy, diabetes, back pain, or arthritis. Acne contributes to low self-esteem and self-confidence and often leads to anger, frustration, and social withdrawal.[5] A key factor in the pathogenesis of inflammatory acne is the proliferation of Propionibacteiium acnes.[6-8] During adolescence, hormonal changes cause increased activity of the sebaceous glands.[9,10] This results in excess sebum production and abnormal keratinization in the sebaceous gland duct leading to the follicle.[11-12] Obstruction of the follicle then occurs, providing a favorable environment for P acnes proliferation.[7,13] Additionally, excess sebum serves as an excellent nutritional source for P acnes populations.[14] This process leads to inflammation and the resultant papules and pustules observed in patients with inflammatory acne.[13] Many treatment options for acne currently exist, and a significant amount of money is spent by Americans each year on prescription and nonprescription medications.[15-16] These treatment options, however, have limitations. Topical acne preparations, such as benzoyl peroxide and retinoids, often irritate the skin and lead to decreased patient compliance.[17-18] The mainstay treatment for mild to moderate acne is topical and/or oralantibiotics, but in recent years antibiotic resistance has become a major concern.[19-22] In addition/oral antibiotic therapy is not effective for many patients, and a new therapeutic modality is needed for their acne. Topical retinoids often are selected for their effect on keratinization and anti-inflammatory properties.[19-21] But these agents commonly cause a great deal of skin irritation, such as peeling, dryness, erythema, stinging, burning, and photosensitivity, precluding their use for many patients.[23-25] Isotretinoin is an effective treatment for acne; however, it has numerous side effects and is reserved for severe or refractory cases.[26-27] Chemical peels, laser ablation, and surgery generally are not directed to combat active disease but rather to mitigate the resultant scars and hyperpigmentation.[28-29] That is why an effective, safe, nonirritating, and easy-to-use modality is highly desirable and needed.

This study examined the Charme™ system, a hand-held device that electrolyzes a water-based sodium chloride solution and delivers etectrolyzed oxidized water (EOW) to the skin. The system produces fine particles, 40 urn or less in diameter, that are able to penetrate the epidermis and upper dermis. EOW has been used for many years in Japan for its antimicrobial properties in the treatment of thermal injury, pressure ulcers, and nosocomial infections.[30-32] In addition, EOW has been used for cleaning and disinfecting medical equipment, such has hemodialysis units.[33-35] Studies show that the device is active against a wide range of bacteria, including anaerobes, gram-positive and gram-negative species, and even viruses, including HIV and hepatitis[33,36] (Table). Furthermore, the device uses a naturally occurring substance, eliminating the need for artificial substances.

By producing an electrolyzed, low pH solution that is active against a wide variety of bacteria and delivering it to the skin, the device offers a potential treatment modality for mild to moderate acne. The purpose of this open-label pilot study was to determine the efficacy and tolerability of the device in the treatment of mild to moderate acne.

## METHODS

A total of 31 subjects qualified and were enrolled in this split-face, open-label, clinical study. To be included, patients had to present with 5 to 50 facial noninflammatory lesions (open and closed comedones), 5 to 60 inflammatory lesions (papules and pustules), and no more than 3 cystic lesions on each side of the face. No other dermatologic disease could be present on the face. Patients were excluded from the study if they used topical acne medications in the preceding 14 days, systemic antibiotics in the past 30 days, or systemic retinoids in the last 6 months prior to initiation of treatment. Pregnant and lactating women, as well as women using oral contraceptives, were excluded from the study. Patients were not allowed to use any over-the-counter acne medications or washes during the study period. Only mild moisturizers and sunscreens were permitted throughout the study. Informed consent was obtained from all patients. For minors, a parent or legal guardian cosigned the informed consent and accompanied the minor patient on each visit during the treatment period.

At baseline, each patient in the study gave a medical history and had a physical examination. A thorough assessment of the severity of acne was made, and the number and type of acne lesions were noted. Patients were given detailed information on how to use the EOW study device. This included demonstrations on how to pour the base solution (a low concentration of 2500 ppm sodium chloride) into the device. The evaluator also gave demonstrations on the distance (approximately 10 cm from the face) and duration (a minimum of 10 seconds to a maximum of 30 seconds) for using the device. Each patient was given an EOW device, 3 bottles of base solution, and 2 unscented, mild soap bars. At each visit, empty solution bottles were retrieved and recorded.

Each patient was instructed to use only the unscented, mild soap to cleanse the entire face twice a day. After the face was washed and dried, the EOW device was to be used only on the right side of the face for 10 to 30 seconds continuously twice daily (morning and night), while the left side of the face remained untreated (control). A log sheet was provided to each patient to keep track of the time, date, and duration of each treatment and any adverse effects experienced.

Efficacy and cutaneous tolerance were assessed 4 times over the trial period: at baseline and weeks 2, 4, and 8. At each of these visits, the number and type of acne lesions were evaluated, and patient and physician assessments were recorded. Vital signs and adverse effects also were recorded at each visit, and device compliance was reviewed. Telephone calls were made to each patient at 2-week intervals to stress device compliance and to assess the general well-being of the patient.

Cutaneous tolerance was assessed by determining the degree of erythema, peeling, stinging/burning, and pruritus. All cutaneous tolerance evaluations were graded on a 0 to 3 scale: 0=none; 1 =mild; 2=moderate; and 3=severe. Global improvement compared with baseline was graded by the physician at each follow-up visit, using this 6-point scale: 0=no signs of acne; 1=markedly (75) improved; 2=moderately (50) improved; 3=slightly (25) improved; 4=no improvement; and 5=worse. Using the same scale, patients graded improvement in their acne over the course of the treatment period. At the conclusion of the study, patient satisfaction with the EOW device was measured using a 0 to 3 scale: 0=not satisfied; 1=fair; 2=good; and 3=excellent. This patient questionnaire also included assessment of the EOW device, compared with conventional acne treatments, based on a numerical scale. Patients were photographed by a standardized method, using high-resolution digital photography at baseline and at each subsequent visit. Results of treatment versus baseline scores were assessed using a Hotelling T test and repeated-measures analysis of variance. All statistical tests were 2-sided, and values of .04 or less were considered statistically significant.

## RESULTS

### Patients

A total of 25 of 31 patients completed the 8-week efficacy and tolerability study; 2 patients were disqualified for treating the entire face with the EOW device, and 4 were lost to follow-up or moved to another geographic region. The mean age was 24.7 years, with a range of 15 to 47 years. The ethnicity groups represented in this study were: white (32), Asian (32), Hispanic (20), and African American (16).

**Clinical Assessment**
There were no significant differences between the right and left side of the face at baseline in any of the parameters to be evaluated. The mean reduction in the total number of acne lesions from baseline to the end of treatment (8 weeks) was 40.9 for the EOW-treated side (right side) and 18 for the untreated side (left side) (P=.04). There was a consistent reduction in total lesion count in the EOW-treated side, with clinically relevant reductions at week 8, compared with an inconsistent clinical response in the untreated side (Figures 1 and 2).

The mean reduction in the number of inflammatory lesions (pustules and papules) from baseline to the end of treatment was 49.1 in the EOW-treated side, compared with 9.9 in the untreated side (P<.01). The mean reduction in each specific type of inflammatory lesion was also clinically significant. The treated side had a mean reduction of 75.7 and 42.0 in the number of pustules and papules, respectively. The untreated side showed only a mean reduction of 19.4 and 7.38 in the number of pustules and papules, respectively (P=.002) (Rgures 3 and 4).

There was not a statistically significant reduction in the number of noninflammatory acne lesions (open/closed comedones) or cysts between the treated and untreated side of the face (P=.336).

Physician-assessed global improvement increased steadily, as noted in the percentage of patients improving from baseline, with 100 of patients showing 25 or more improvement by week 8 (Figure 5). Patient-assessed global improvement in acne also steadily increased during the course of the study period. At week [8, 50] of the patients graded overall their improvement as moderate, with improvement of 50 or more for the right side of the face (Figure 6). .In addition, 75 of the patients in the study indicated that they preferred the EOW delivery system over conventional topical acne medications.

**Safety Assessment**
The EOW system was well tolerated by an overwhelming majority of patients in the study. No patients stopped or temporarily ceased treatment due to side effects. One patient had transient pruritus, and 2 others had mild erythema during the first 2 days of treatment. Two additional patients experienced burning/stinging and treatment-associated peeling. All cutaneous side effectsresolved by the week 2 visit (Figure 7).

**Patient Satisfaction Assessment**
In their assessments, 80 of the patients in the study rated their satisfaction with the EOW device as good or excellent, while 16 rated the study device as fair. Only 4 were dissatisfied with the EOW device (Figure 8).

## COMMENT

EOW is produced with an anode current by electrolyzing salt-containing water through a diaphragm.[37] EOW which has a high posrtive oxidation-reduction potent (ORP) and high concentrations of dissolved chloride and oxygen, functions as a bactericide and is used clinically for the treatment of various types of infection and for cleaning and disinfecting medical equipment.[37,39] Since the 1990s, electrolyzed sodium chloride solutions, which contain high free-chloride concentrations, have been investigated for various ctinical applications in Japan. Currently, 2 types of electrolyzed solutions are available: electrolyzed weak acid water (EWW) and electrolyzed strong acid water (ESW). The study device generated ESW by electrolysis of an NaCI solution, using positive and negative electrodes in compartments separated by a cationic membrane; ESW was obtained from the well of the positive electrode (Rgure 9).[37] This process can be summarized in the following chemical formula.[37-39]

**Positive electrode:**

$$H_20 \rightarrow ½O_2 + 2H^+ + 2e^-$$

$$2Cl^- \rightarrow Cl_2 + 2e^-$$

$$CI_2 + H_2O \leftrightarrow H^+ + Cl^- + HClO$$

**Negative electrode:**

$$2H_2O + 2e^- \rightarrow H_2 + 2OH^-$$

The water at the positive electrode becomes EOW, which has a low pH and a high ORP and contains high concentrations of dissolved chloride, oxygen, and hydroxyi radicals. Water at the negative electrode becomes a basic aqueous solution that has a high pH and a tow ORP and high concentrations of alkaline minerals.

All microorganisms require a certain mitochondrial environment for survival; a pH in the range of 2 to 12 and ORP from -400 to +850 mV are needed to survive and proliferate.[40] In this study, the EOW device produced a solution that has a pH in the range of 2.3 to 3.0 and a high ORP in the range of +1100 to +1300 mV.[37] It also generated high concentrations of hypochlorous acid, dissolved oxygen (9-15 ppm), and hydroxyl radicals.[37] This was the solution that was emitted in a fine mist by the EOW device after the electrolysis process.

The EOW produced by the study device falls outside the required parameters for the mitochondrial function of microorganisms. This served as the basis for the proposed mechanism of action against the P acnes population. Additionally, the high concentrations of hypochlorous acid and hydroxyi radicals produced by the treatment solution are well documented antimicrobial agents that markedly increase in low pH solution. Moreover, a study by Shimizu et al[41] reported that almost all organisms will perish within 10 seconds in EOW because of the synergistic activity of the resultant radicals (eg, $Cl^-$, hydroxyl radical, hydrogen peroxide) generated in EOW.[42] These radicals react with oxygen and destroy P acnes by damaging its cell lipid membrane, denaturing proteins, and preventing replication by severing its DNA.[43] Because EOW does not provide a long-lasting antibacterial effect after application, repeated applications are necessary.[37,44-46] In this study, patients were instructed, to use the EOW device twice daily for at least 10 seconds.

To further analyze the bactericidal effect of EOW research studies on inhibiting Pseudomonas aeruginosa growth by EOW can be used as a model. Using electron microscopy, P aerugi'nosa growth was completely inhibited by EOW. Morphological changes noted on electron microscopy showed that EOW induced breaks and blebs in the outer membrane cell wall (average diameter of bleb was 28 nm), which were not seen in unelectrolyzed sodium chloride solution.36 To assess whether or not the effect of EOW penetrated deep into the bacterial cells, the presence of chromosomal DNA was detected by restriction fragment length polymorphism, or RFLP, assay.36 No bands were detected using EOW, while bacterial samples treated with unelectrolyzed sodium chloride revealed strong band formation.36

The study showed that the EOW treatment, administered twice daily for 8 weeks in patients with mild to moderate acne, resulted in an overall reduction of 40.9% in mean acne lesion counts. A similar reduction was noted in the mean inflammatory acne lesion counts measured independently (49.1%). A greater decrease was observed when measuring individual inflammatorylesions—75.7% for pustules and 42.0% for papules.

The mechanism by which the study treatment improved inflammatory acne lesions is most likely the EOW. The EOW is antimicrobial and decreases P acnes colony populations. This proposed mechanism of action is supported by the observation of the authors that pustules, followed by papules, had the most significant reductions.

The study demonstrated that the EOW system is potentially effective on inflammatory lesions but is not an effective comedolytic agent. To treat patients with inflammatory acne, the authors suggest oral and topical antibi otics can be eliminated by using a strong comedolytic agent, such as a topical retinoid, in combination with the EOW treatment. Moreover, the EOW device, working in conjunction with topical retinoids, could possiblydecrease common cutaneous side effects associated with topical retinoids.

Patient satisfaction with the EOW treatment was rated very high, with 80% of the patients in the study assessing satisfaction with the study device as good or.excellent. Only 4% of the patients were dissatisfied with the device. Moreover, 50% of the patients reported a moderate improvement at week 8. Of particular note, 75% of the patients indicated that they would rather use an EOW delivery system than conventional forms of treatment.

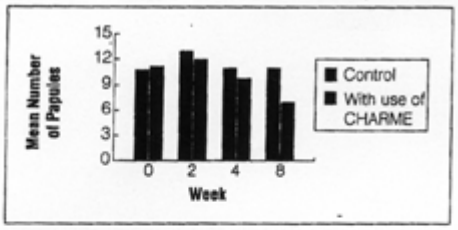


Figure 3. The number of papules over an 8-week period with electrolyzed oxidized water treatment and with control.

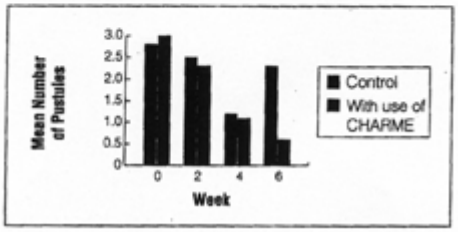


Figure 4. The number of pustules over an 8-week period with electrolyzed oxidized water treatment and with control.


Figure 5. Physician evaluation of global improvement from baseline with electrolyzed oxidized water treatment.


Figure 6. Patient self-assessment: percentage of patients who indicated overall acne improvement from baseline to week 8.

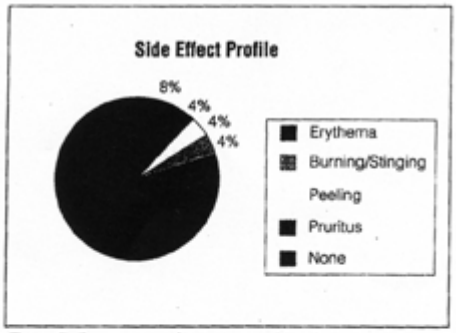


Figure 7. Percentage of cutaneous side effects experienced with electrolyzed oxidized water treatment after 8 weeks.

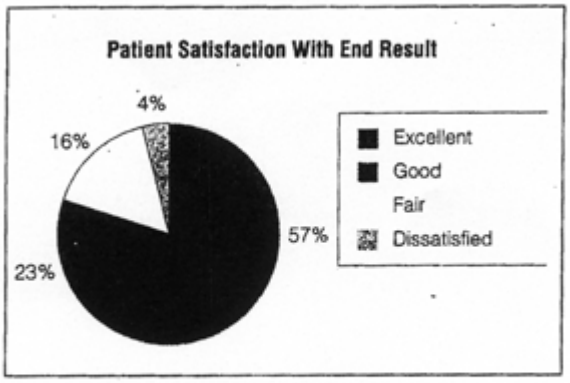


Figure 8. Patient satisfaction with the electrolyzed oxidized water device after treatment.

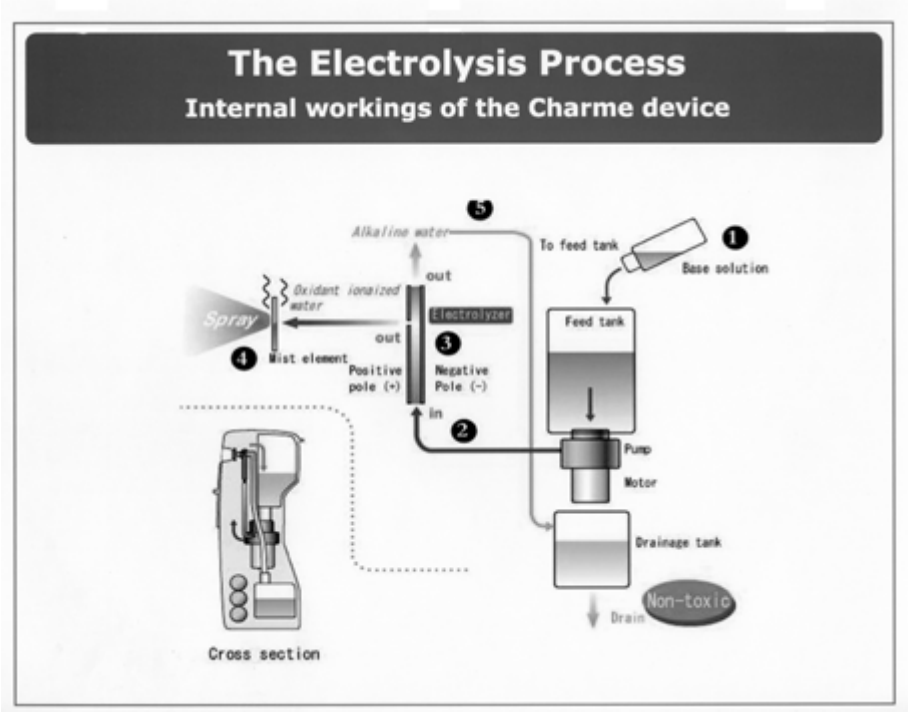


Figure 9. The process of electrolysis (steps 1-5): After the water-based, sodium chloride solution (base solution) is Introduced into the electrolyzed oxidized water (EOW) device, the electrolysis process begins. Within seconds, EOW is emitted as a fine mist to the skin. Nontoxic alkaline solution is collected in the drainage tank and emptied after use.

In contrast to the likelihood of side effects from other antiacne products, such as topical retinoids and benzoyf peroxide, the EOW treatment and its delivery system did not produce significant clinical signs or subjective symptoms of skin irritation, stinging/burning, erythema, pruritus, or peeling. In fact, 96% of the patients did not experience any burning/stinging or peeling. Only 4% experienced pruritus, and 8% experienced treatment-associated erythema. All side effects experienced by patients during the treatment period were completely resolved by the week 2 visit.

From a pharmacoeconomic perspective, the EOW system appears to be cost-effective, though it is difficult to conduct a cost-effectiveness analysis comparing the EOW treatment to current acne therapies because of the multitude of factors to consider in assessing acne treatment costs. When evaluating the estimated costs of various acne therapies in 2001, however, the study device afforded the patient with a more cost-effective method in treating acne.[16-46] For instance, 40% of patients in 2001 spent an average of $293.03 on acne treatments, and 20% of patients spent an average of $813.24 per year on acne medications.[16-46] Tolerability of these medications can also influence the overall cost because more office visits are required, and alternative medications may be prescribed to increase compliance.

Clinical studies have repeatedly shown that combination therapy yields the best results when treating acne.[19-21, 47]. A common approach is to use topical or systemic antibiotics with topical retinoids.[19-21] Topical and oral antibiotics, however, often are associated with the emergence of resistant bacteria and adverse effects, such as gram-negative folliculitis, vaginal candidiasis, discoloration of teeth, headaches, depression, gastrointestinal upset, and dose-related phototoxic effects.[48-55] Other antibiotic options, such as trimethoprim and sulfamethoxazole, clindamycin, and ciprofloxacin are effective but are limited by toxicities.[56] The study suggested that EOW treatment is effective in combating inflammatory acne and is a possible alternative to oral/topical antibiotics in the management of this condition. Oral and topical antibiotics could be used as a second-line therapy, an option that would most likely help reduce the resistance of P acnes and antibiotic-associated toxicities.

## CONCLUSION

The EOW device and its delivery system to the skin is an alternative modality for treating acne. Although it has never been studied specifically for acne, scientific evidence from other applications makes this device a practical and logical consideration. Used for many years in Japan, EOW has been shown to be effective against many different types of bacteria, viruses, and fungi. This study showed that the EOW device can reduce inflammatory acne lesions, namely papules and pustules.

Patient assessments indicated satisfaction with and acceptance of the EOW system, which may be attributed to its ease of use and relatively few of the side effects commonly experienced with topical acne regimens. In addition, a possible cost savings makes this device an even more attractive option for patients. Other advantages of EOW treatment include: a relatively short duration of therapy (8 weeks), good patient compliance, and lack of antibiotic resistance. Although this is the first study illustrating the efficacy and tolerability of the EOW device in treating acne, the results and patient satisfation seem promising. Future studies are needed to see if EOW has additional mechanisms of action in treating inflammatory acne.

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## REFERENCES

1. White GM. Recent findings in the epidemiologic evidence, classification, and subtypes of acne vulgaris. J Am Acad Dermatol. 1998;39(SUDpl):34-37.
2. Stern RS. The prevalence of acne on the basis of physical examination. J Am Acad Dermatol. 1992:26:931 -935.
3. Cunliffe WJ, Gould DJ. Prevalence of acne in late adolescence and in adutts. fir Med J. 1979:1:1109-1110.
4. Mallon E, Newton JN, Klassen A, et al. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. BrJ Dermatol. 1999:140:672-676.
5. Koo J. The psychosocial impact of acne: patients' perceptions. J Am Acad Dermatol. 1995;32(suppl): 26-30.
6. Lee WL, Shalita AR, Suntharalingam K, et al. Neutrophil chemotaxis by Propionibactenum acnes lipase and its inhibition. Infect ImmunA 982:35:71 -78.
7. Allaker RP, Greenman J, Osborne RH. The production of inflammatory compounds by Propionibactenum acnes and other skin organisms, fir J Dermatol. 1987,117:175-183.
8. Toyoda M, Morohashi M. Pathogenesis of acne. Med Bectron Microsc. 2001:34:29-40.
9. Strauss JS, Thtooutot DM. Diseases of the sebaceous glands. In: Freedberg IM. Einsen A2, Wotff K, eds. Fitzpatrick's Dermatology in General Medicine. 5th ed. New York, NY: McGraw-Hill; 1998:769-784.
10. Thiboutot D. Hormones and acne: pathophysiology, clinical evaluation. and therapies. Semin Cutan Med Surg. 2001:20: 144-153.
11. Jenkinson DM, Elder HY, Montgomery I, et al. Comparative studies of the uttrastructure of the sebaceous gland. Tissue Cell. 1985:17:683-698.
12. Norris JFB, CLnliffe WJ. A histotogical and immunocytochemical study of eariy acne lesions. BrJ Dennatol. 1988:118:651-659.
13. Webster GF. Inflammation in acne vulgaris. J Am Acad Dermatol. 1995:33:247-253.
14. Stewart ME. Sebaceous gland lipids. Sem/'n Dermatol. 1992:11:100-105.
15. Suh DC. Okpara IR, Agnese WB, et al. Application of pharmacoeconomics to formulary decision making in managed care organizations. Am J Manage Care. 2002:8:161 -169.
16. Bergfeld WF. The evaluation and management of acne: economic considerations. J Am Acad Dermatol. 1995;32(suppl, pt3):52-56.

17. Bershad SV. The modem age of acne of acne therapy: a review of current treatment options. Mt Sinai J Med. 2001 ;68:279-286.
18. Gollnick H, Schramm M. Topical drug treatment in acne. Dermatology. 1998:196:119-125.
19. Soto P, Cunliffe W, Meynadier J, et al. Efficacy and safety of lymecydine 300 mg plus adalpene 0.1% gel versus lymecycline 300 mg plus adapalene gel vehicle in subjects with acne vulgaris. In: Program and abstracts of the 60th Annual Meeting of the American Academy of Dermatology; February 22-27, 2002; New Orleans. La. Abstract P36.
20. Zouboulis CC, Demmeaux L, Decroix J, et al. A multicentre, single-blind, randomized comparison of a fixed dindamycin phosphateAretinoin gel formulation (velac) applied once daily and a dindamyin lotion formulation (Daiacin T) applied twice daily in the topical treatment of acne vulgaris. Br J Dermatol. 2000; 143: 498-505.
21. Czemielewski J, Loesche C, Poncet M. Efficacy and safety comparison of adapalene gel, 0.1 % and clindamycin topical lotion 1 % in the treatment of acne vulgaris. In; Program and abstracts of the 60th Annual Meeting of the American Academy of Dermatology; February 22-27, 2002; New Orleans, La. Abstract P33.
22. Dreno B, Reynaud A, Moyse D, et al. Erythromycin-resistance of cutaneous bacterial flora in acne. Eur J Dermatol. 2001 ;11: 549-553.
23. Leyden JJ. Therapy for acne vulgaris. N EngI J Meet. 1997;336: 1156-1162.
24. Gollnick H, Schramm M. Topical drug treatment in acne. Dermatology. 1998;196:119-125.
25. Johnson BA, Nunley JR. Topical therapy for acne vulgaris: how do you choose the best drug for each patient? Postgrad Med. 2000; 107:69-80.
26. Ortonne JP. Oral isotretinoin treatment policy: do we all agree? Dermatology- 1997:195(suppl):34-37. Discussion 38-40.
27. Meigel WN. How safe is oral isotretinoin? Dermatology. 1997,195(suppl):22-28. Discussion 38-40.
28. Jacob 0, Dover JS, Kaminer MS. Acne scarring: a classification system and review of treatment options. J Am Acad Dermatol. 2001:45:109-117,
29. Solish N, Raman M, Pollack SV. Approaches to acne scarring: a review. J Cut Med Surg. 1998;2(supp! 3):24-32.
30. Shiba A, Shiba K. The current situation of application in medicine. In; Johosha I, ed. Strong Electrolyzed Solution Handbook. Tokyo, Japan; 1995:105-114.
31. Okuda R, Sasazaki H, Kanebira M, et al. Bectron microscopical study of bactericidal action of high oxidation potential water. Jpn J Conservation Dent. 1994:37:755-765.
32. Otoguro K, Suzuki F, Akimaru Y, et al. Hand disinfectant activities of two kinds of etectrolyzed acid aqueous solution by Globe Juice Method. Environ Toxicol Water Quality. 1996;11:117-122.
33. Tanaka N, Fujisawa T, Daimon T, et al. The effect of electrolyzed strong acid aqueous solution on hemodialysis equipment. Artif Organs. 1999:23:1055-1062.
34. Tanaka N, Yamamoto M, Daimon T, et al. The use of electrotyzed strong acid aqueous solutions in dialysis equipment. Jpn J Clin Dial. 1997:13:113-118.
35. Sakurai Y. Electrolyzed water and endoscopy disinfection. In; Functional Water Symposium. Yokohama, Japan; 1998:12-13.
36. Kiura H, Sano K, Morimatsu S, et al. Bactericidal activrty of electroiyzed acid water from solution containing sodium chloride at tow concentration, in comparison with that at high concentration. 2002:49:285-293.

37. Kumon K. What is functional water? Artif Organs. 1997:21:2-4.
38. Tanaka N, Fujisawa T, Daimon T, et al. The cleaning and disinfecting of hemodialysis equipment using electrolyzed strong acid aqueous solution. Artif Organs. 1999:23:303-309.
39. Shirahata S, Kabayma S, Nakano M, et al. Electrolyzed-reduced water scavenges active oxygen species and protects DMA from oxidative damage. Biochem Biophys Res Common. 1997:234: 269-274.
40. Hajime N, Inaba H. Effectiveness of electrolyzed oxidized water irrigation in a bum-wound infection model. J Trauma Inj Infect Crit Care. 2000:49:511-514.
41. • Srwnizu Y, Sugawara H. Virucidal and bactericidal effects of etectrolyzed oxidizing water: comparison of disinfectant effect with electrolyzed oxidizing water and hypochlorous acid. Jpn J'Oral Btol. 1996:38:564-571.
42. Hotta K. What is the main sterilizing component? In: Kenkyukai W, ed. The Basic Knowledge ofESAAS. Tokyo, Japan: Ohmsha; 1997:26-31.
43. Kohno M. Bectrolytic water as a solution. In: Kenkyukai W, ed. The Basic Knowledge of ESAAS. Tokyo, Japan: Ohmsha; 1997:40-44.
44. Inoue Y, Endo S, Kondo K, et al. Trial of electrolyzed strong acid aqueous solution lavage in the treatment of peritonitis and intraperitoneal abscess. Arttf Organs. 1997;21:28-31.
45. Sekiya S, Ohmori K. Harii K. Treatment of infectious skin defects or ulcers with etectrolyzed strong acid aqueous solution. Artif Organs. 1997;21:32-38.
46. Wessds F, Anderson AN, Kropman K. The cost-effectiveness of isotretinoin in the treatment of acne: a chronic medication plan profiling study. SAfrMedJ. 1999;89(7 pt 2):785-790.
47. Leyden J. Are 2 combined antimicrobial mechanisms better than 1 for the treatment of acne vulgans?: clinical and antimicrobial results of a topical combination product containing 1 % clindamycin and 5% benzoyl peroxide. Cutis. 2001 ;67(suppl 2):5-7.
48. Meynadier J, Allrezal M. Systemic antibiotics for acne. Dermatology. 1998:196:135-139.
49. Vibramycin [package insert]. New York, NY: Pfizer Inc; 1993,
50. Greenwald RA, Golub LM. Preface: nonantibiotic properties of tetracyclines. Adv Dent Ffes. 1998; 12:1.
51. Layton AM, Cunliffe WJ. Phototoxic erupttons due to doxycydine: a dose-related phenomenon. CSn Exp Dermatol. 1993:18:425-427.
52. Espersen F. Resistance to antibiotics used in dermatological practice. BrJ Dermatol. 1998;139(suppl):4-8.
53. Sturkenboom MC, Meter CR, Jick H, et al. Minocycline and lupus-like syndrome in acne patients. Arch Intern Mod. 1999;159: 493-497.
54. MacNeil M, Haase DA, Tremaine R, et al. Fever, lymphadenopathy, eosinophilia, lymphocytosis, hepatitis and dermatitis: a severe adverse reaction to minocydine. JAm Acad Dermatol. 1997;36(pt 2):347-350.
55. Somech R, Arav-Boger R, Assia A, et al. Complications of minocydine therapy for acne vulgaris: case reports and review of the literature. Pecfa&-Z3ew»afo/. 1999:16:469-472.
56. Leyden JJ. The evoMng role of Propionibactenum acnes in acne. Semin Cutan Med Surg. 2001 ;20:139-143.

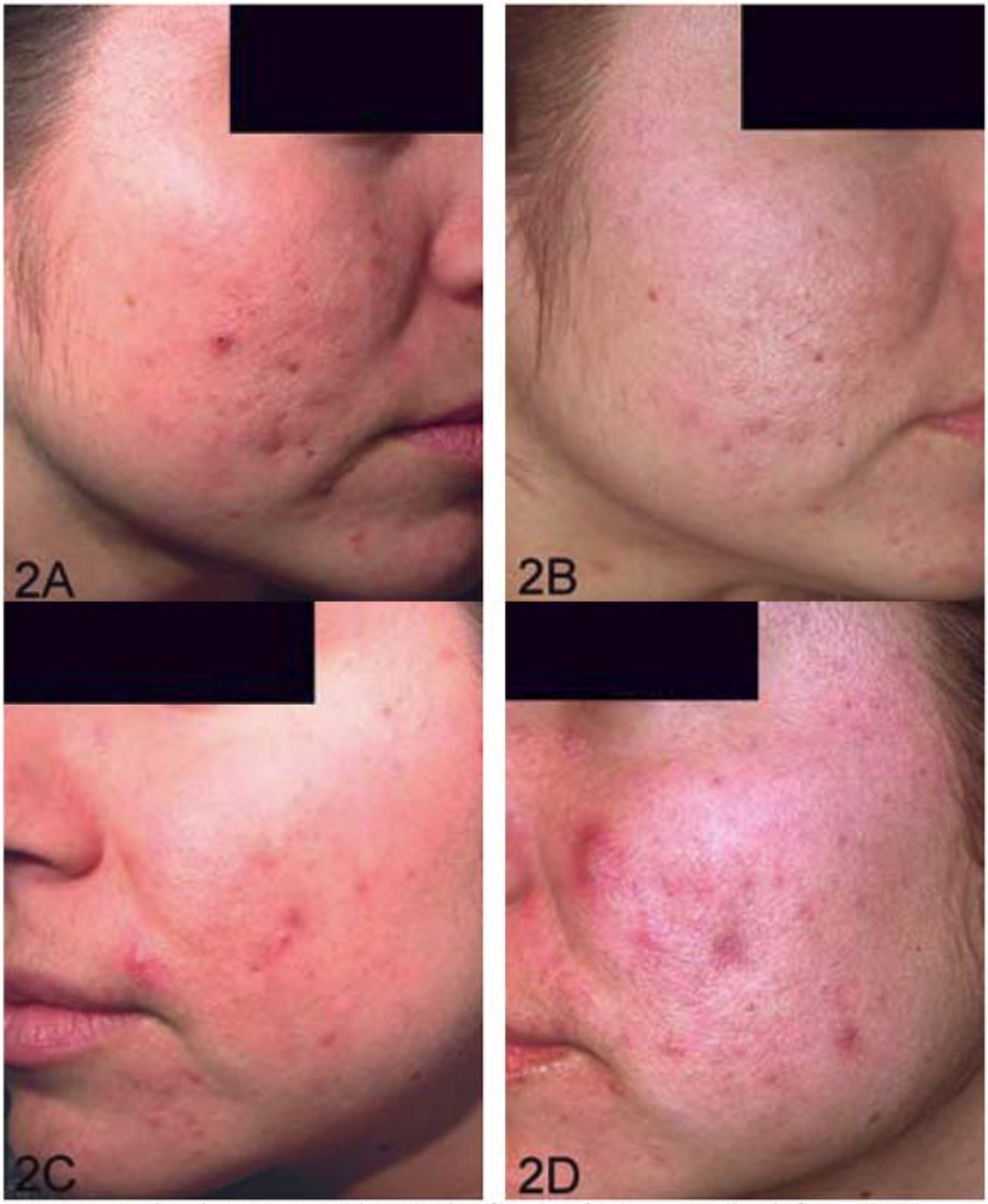


**Figure 2.** Patient is a 28-year old Caucasian female with long-standing inflammatory acne refractory to oral and topical antibiotics, topical retinoids and benzoyl peroxide. **2A.** Before treatment, numerous inflammatory acne lesions are noted. **2B.** After 8 weeks of treatment with CHARME twice daily, significant improvement is noted with minimal irritation. **2C.** Same patient at baseline without treatment on left side of face (control). **2D.** Control at 8 weeks. No improvement observed in acne lesion counts.