Southern California CSU DNP Consortium

California State University, Fullerton
California State University, Long Beach
California State University, Los Angeles

TREATING PERSISTENT ACNE IN ADULT WOMEN IN THE ERA OF ANTIBIOTIC RESISTANCE

A DOCTORAL PROJECT

Submitted in Partial Fulfillment of the Requirements

For the degree of

DOCTOR OF NURSING PRACTICE

By

Daniela Moura Leslie, DNP, RN, FNP-C

Doctoral Project Committee:

Beth Keely, PhD, RN, Project Chair
Dana Rutledge, PhD, RN, Committee Member

May 2018
Problem: Most providers treat adult women with moderate to severe acne with oral antibiotics. Often a chronic condition, acne may require long-term management. Therefore, the potential for antibiotic resistance secondary to long term oral antibiotic use is a concern. Spironolactone (SPL), an anti-androgenic medication, is safe and effective in treating chronic acne without the risk of antibiotic resistance. Besides its safety in long-term use without the risk of antibiotic resistance, spironolactone can be a more cost-effective alternative in the treatment of acne in adult women.

Method: The purpose of this project was to disseminate evidence regarding acne management in adult women to nurse practitioners and other health care providers who treat patients affected. This was achieved through development of a manuscript, that if published, will enhance provider’s awareness and initiative to approach acne treatment in women with alternatives, such as spironolactone, to decrease antibiotic overuse and enhance antibiotic stewardship.

Results: The manuscript was developed, reviewed by the project committee and submitted to The Clinical Advisor.

Discussion: If the manuscript raises awareness of providers about new ways to think of acne management, these providers may educate their colleagues and patients, who in turn can share this information with their family and friends; all of these avenues
may help reduce antibiotic resistance when acne management is done in a responsible manner.

**Recommendations:** Education of providers and patients regarding antibiotic resistance and implementation of alternative acne treatments can achieve and maintain acne clearance while preserving antibiotic effects.
# TABLE OF CONTENTS

ABSTRACT .......................................................................................................................... iii

ACKNOWLEDGMENTS ........................................................................................................ vii

INTRODUCTION .................................................................................................................. 1

Acne Vulgaris .......................................................................................................................... 1
Problem Identification ........................................................................................................... 2
Significance ............................................................................................................................ 2
Supporting Framework .......................................................................................................... 3
  Innovation ............................................................................................................................ 4
  Adopter ................................................................................................................................. 5
  Communication Channels ................................................................................................. 5
  Time ..................................................................................................................................... 6
  Social System ...................................................................................................................... 6
Innovation-Decision Process ................................................................................................. 7
  Knowledge ........................................................................................................................... 7
  Persuasion ........................................................................................................................... 8
  Decision ............................................................................................................................... 8
  Implementation .................................................................................................................... 9
  Confirmation ........................................................................................................................ 9
  Purpose ............................................................................................................................... 9

REVIEW OF LITERATURE .................................................................................................. 11

Pathophysiology of Acne ....................................................................................................... 11
Hormones and Acne .............................................................................................................. 11
Clinical Practice Guidelines ................................................................................................. 13
  First Line Treatment ......................................................................................................... 13
  Second Line Treatment (with First Line Failure) .............................................................. 14
  Maintenance Treatment ................................................................................................. 14
  Guideline Differences ...................................................................................................... 15
Antibiotic Resistance and Potential Side Effects .................................................................... 16
Spironolactone Effectiveness ................................................................................................. 18
Provider Use of Antibiotics ................................................................................................. 19
Summary .............................................................................................................................. 20
METHODS .................................................................................................................................. 22
  Design ..................................................................................................................................... 22
  Ethical Considerations ........................................................................................................... 22
  Procedures ............................................................................................................................... 23
  Journal Selection .................................................................................................................... 24
  Manuscript Preparation ......................................................................................................... 24
  Evaluation ................................................................................................................................. 25

RESULTS .................................................................................................................................... 26

DISCUSSION .............................................................................................................................. 27

REFERENCES ............................................................................................................................. 29

APPENDIX A: TABLE OF EVIDENCE FOR PROPOSAL ....................................................... 34

APPENDIX B: AUTHOR GUIDELINES .................................................................................... 47

APPENDIX C: MANUSCRIPT ................................................................................................. 50
ACKNOWLEDGMENTS

My deepest gratitude goes to my parents for their unconditional love and support throughout this journey. And especially to my most treasured gift, the king of all kings, my little super hero named Keegan, who has been beyond patient for seeing very little of his mommy – your wisdom far exceeds your 9 years of age with an amazing sense of wonder and zest for life like no other. You fill my heart with so much love and joy. I love you with all my being! To Scott for being an amazing and involved dad – thank you! To Laura, Kristin and Julie for often having Keegan over for play dates and always being so kind and loving to him – I will always remember that. This accomplishment is yours, too. I am eternally grateful to all of you! To Jennifer and Carolyn for being my partners in creating and launching the PV League of Extraordinary Businesswomen around my tight schedule. Despite the madness of the demands of life, we managed to grow and make a difference. Thank you both for your support, vision and willingness to step with me into the unknown.

To my amazing friends, The Brus, who walked with me through the thick and thin and remained present even when I was not – I love you forever. To my CSUF DNP family as we held hands through laughter, tears, sweat and blood while uplifting and pulling each other up when the going got tough and celebrated each successfully (or not!) completed assignment. To Jennah, who bravely handled my schedule, accommodated every patient and worked insane hours with me – I can’t express how much I appreciate you and all you do for me. You are my rock! To Britt, who kept me physically and
mentally strong – thank you! To Armando, who shared such insightful life experiences with me – you inspired me by reminding me that possibilities are not bound to logic or reality whatsoever. My belief that all things are possible transcended into knowing – thank you! To Marijano, who opened my eyes to a whole other world – thank you! And thank you for showing up with the perfect technological solution exactly when I needed it! Michael, Bob, Laurie, and Susie – you each had such a profound impact on me. As life would have it, I jumped and the ground did appear. And there you were…

Dr Scott Rackett, who taught me everything I know about general dermatology and gave me the opportunity to learn and grow in my professional unfoldment: I deeply appreciate your support, guidance, and most of all, for being patience in human form! Besides being an outstanding dermatologist, you overflow with calmness and kindness regardless of circumstances. When most saw me as a conflict of interest for having a practice, you saw me as an opportunity to collaborate. Because of that, I was able to fulfill my aspirations. Eight years later, we are still growing strong. I am forever grateful to you.

Dr Penny Weissmuller and Sarah Douville, thank you for working out my credits to transfer to CSUF. I am so happy and thankful to be here! Your warmth and positivity always made me feel welcome. Thank you Dr Brady for your encouragement, support, calmness, grace and feedback. Many thanks to Dr Beth Keely who suggested and directed me through the best-fitting supporting framework for the manuscript. Thank you for helping me stay on track and complete this project! And to the one who pushed me beyond my perceived limits, when at times, I thought there was nothing left to give in the process of writing this project (and she proved me wrong!) – thank you! She led me from
wordy, to average, to better, to the best finished product with the utmost dedication, in a
tough yet fair and caring manner. When I think of parsimony, I think of her! She is able
to reduce a whole page into a few sentences in the most eloquent and clear way. Her
name is Dr Dana Rutledge and I am incredibly and forever grateful to have had the
privilege of being her student. Thank you from the bottom of my heart!
INTRODUCTION

Most providers treat adult women with moderate to severe acne with oral antibiotics. Acne can be a chronic condition that may require long-term management (Collier et al., 2008). Therefore, the potential for antibiotic resistance secondary to long-term oral antibiotic use is a concern (Goh et al., 2015). Spironolactone (SPL), an anti-androgenic medication, is safe and effective in treating acne without the risk of antibiotic resistance (Lessner et al., 2014). Besides its safety in long-term use without the risk of antibiotic resistance, spironolactone can be a more cost-effective alternative in the treatment of acne in adult women (Hassoun, Chahal, Sivamani, & Larsen, 2016; J. C. Shaw & White, 2002).

Acne Vulgaris

Acne vulgaris is an inflammatory disorder of the pilocebaceous unit of the skin. This multifactorial condition includes follicular plugging and microcomedone formation, bacteria *Propionibacterium acnes* (*P. acnes*), inflammation of skin structures, and excess sebum production (Harper, 2009). Acne severity is classified by the type and number of lesions (comedones, papules, pustules, nodules) and degree of scarring. Grade I, or mild acne, consists of comedones and few inflammatory papule and pustules. Grade II, or moderate acne, presents with numerous comedones, few to many papule and pustules and few small nodules with marked inflammation. Grade III, or severe acne, shows numerous large painful inflamed nodules and pustules. Grade IV is severe acne with many large inflamed nodules and pustules along with scarring (Kraft & Freiman, 2011).
Problem Identification

The conventional treatment for moderate to severe acne is oral antibiotics (Roman, Cifu, & Stein, 2016). In a southwestern United States dermatology practice, 764 women between the ages of 20 to 40 years of age were being treated for acne. A large challenge facing providers of such patients is that women successfully treated for moderate to severe acne resist discontinuation of oral antibiotic therapy fearing the acne lesions will return.

Long term use of oral antibiotics (i.e., more than three to four months) may cause antibiotic resistance (Zaenglein et al., 2016). Antibiotic resistance is not just limited to *P. acnes*. The risk of resistance extends to the resident flora of patients treated with oral antibiotics as well as their contacts. When managing acne, providers and patients must take into consideration risks and benefits on a community level. For individuals, long term antibiotics may result in clear skin, at the cost of microbial drug resistance that may affect an entire population (Eady, Cove, & Layton, 2003).

Significance

Sixty million Americans suffer from active acne vulgaris (AV), and more than half are women. Twelve percent of women will continue to have acne up to their fourth decade and beyond (Lynde, 2004). Americans spend close to 1 billion dollars a year on prescription and over the counter acne products (Kraft & Freiman, 2011). Although AV is perceived as a condition of teenagers, office visits by patients in their twenties and older are not unusual (Kim & Michaels, 2012). A subset of patients experiences persistent AV from adolescence throughout adulthood, with some developing new onset
AV in adulthood - particularly women. The majority of adult patients presenting with AV is women.

Late onset AV (20+ years old) occurs in 18.4% of women and 8.3% of men (Collier et al., 2008). While men show a higher prevalence of AV before the age of 16 years, women demonstrate a higher prevalence of AV after 23 years of age. Approximately 82% of adult women with persistent AV failed therapy with multiple courses of antibiotics (Yemisci, Gorgulu, & Piskin, 2005) and 32% relapsed after treatment with one or more courses of isotretinoin (Goulden, Stables, & Cunliffe, 1999).

Adult women with AV may respond to antiandrogenic hormonal agents such as spironolactone (SPL). SPL may be safely used long term for acne treatment without the risk of bacterial resistance; it is also cost effective - about $43 per month (Hassoun et al., 2016; Epocrates, 2016) when compared to the cost of oral antibiotic treatment, which can cost up to $1,500 a month (Epocrates, 2016)

**Supporting Framework**

The framework chosen for this project was the Diffusion of Innovations theory by Everett Rogers. Rogers (2003) defines innovation as an “idea, practice, or object that is perceived as new by an individual or other unit of adoption” (p. 475). Through diffusion, information about an innovation is communicated over time to the members of a social system (Rogers, 2003). This theory describes how, why and the speed to which new ideas unfold and propagate (Adams, Tranfield, & Denyer, 2011). The following were the key elements comprising the diffusion theory:
Innovation

Potential adopter views the attributes of the innovation in terms of its relative advantage (effectiveness and cost efficiency compared to other options, or the degree to which an innovation is perceived as an improvement), complexity (if innovation is easy to understand), compatibility (how the innovation fits what is to be accomplished and the degree to which the innovation coincides with values and needs of potential adopters), observability (how visible the outcomes are), and trialability (the adopter’s level of commitment for full adoption and the ability to gradually adopt the innovation overtime) (Rogers, 2003).

The innovation in this project was using SPL concurrently with tretinoin, BPO and oral or topical antibiotic treatment as opposed to long term antibiotics. Oral antibiotics were to be discontinued after 12 weeks of treatment, and SPL could have been continued for maintenance. If patients were opposed to taking two oral medications (i.e., oral antibiotic and SPL), SPL could have been initiated as the 12th week of oral antibiotic is completed. SPL, as previously mentioned, may be a safe, effective and low-cost option to treat acne. This innovation is simple to understand and implement as providers educate female patients on the benefits of SPL over long term oral antibiotics, as it can avoid antibiotic resistance. Clearer skin is a visible outcome, which will lead providers as well as patients to continue their regimen with SPL.

Possible barriers with the project are several. These include provider clinical inertia (inaction) to change medication, lack of time to explain to patients the need/importance of change, lack of knowledge regarding medication or need to change current practice, disagreement with treatment guidelines, non-compliance from patients regarding
medication adherence and showing up for appointments (Roumie et al., 2007). A major innovation-related barrier is that SPL is not FDA approved to treat acne. Its anti-androgenic effect is used off label to treat acne in women (Lessner et al., 2014); however, it is covered by insurance to treat acne.

**Adopter**

Especially important is understanding the readiness of each adopter relative to others in adopting the innovation (Bowen, Stanton, & Manno, 2012). In this project, the first level adopters are health care providers and second level adopters are patients. Each adopter has different levels of awareness of the global issue of bacterial resistance and readiness to try SPL for acne in adult women.

Possible barriers with this project follow. If, prior to implementing the innovation, provider and patient are both satisfied with patient response (clear skin) with oral antibiotics, both adopters may not be inclined to change a treatment regimen. However, skin clearance from acne lesion is not the only goal. It is important to change the treatment regimen to address potential bacterial resistance as a result of long term use of oral antibiotics (Eady, Cove, & Layton, 2003; Walsh, Efthimiou, & Dréno, 2016).

**Communication Channels**

To allow transmission of information from one entity to another, communication channels must be established between adopters and those attempting to make a practice change (innovation) for diffusion to take place (Bowen et al., 2012). In this project, the initial communication channel is from the doctoral student to the providers, and then, from providers to patients. The communication channel chosen by the student is a manuscript aimed at nurse practitioners. Subsequent communication through conferences...
and meetings are means for providers to communicate to other providers about their experience with SPL in treating acne in adult women.

Potential barriers related to communication channels exist with this project. Providers who do not look beyond acne lesion clearance for those patients who achieve and maintain skin clearance with long term oral antibiotics. Such providers need to communicate and educate patients on the ramifications of bacterial resistance, and may need teaching tools if this is new to them. Once made aware, providers using SPL in acne treatment may share their experience with other providers in dermatology as well as other medical specialties; this will provide communication about the innovation to others. If a manuscript is published about the innovation, providers would get to learn about it.

Time

Often, innovations are not immediately adopted. It takes time for the communication processes to instill change in systems. In this project, it will take time to educate patients and providers about SPL, its advantages, safety profile and cost. It may take time for patients who have been on long-term oral antibiotics to be willing to try SPL. Potential barriers to this project include clinical inertia, lack of provider knowledge regarding SPL and awareness of bacterial resistance, and lack of time to educate patients on SPL.

Social System

Practice changes occur within a social system, which includes all of the components of the health care arena. In such a system, media as communication, opinion leaders (i.e., providers of all specialties, with and without SPL experience, aware and unaware of antibiotic resistance, who treat acne) and potential adopters who question the
need to adopt. In this project, it is assumed that when SPL has been used successfully to treat acne in adult women and its benefits are apparent, providers and patients will talk about it; then, other patients and providers will get to know about it, may search for further information, and hopefully implement changes where and when needed.

Potential barriers in this project: provider lack of knowledge regarding SPL, lack of awareness of antibiotic resistance due to long term use of oral antibiotics in the treatment of acne, and lack of provider access to recent articles regarding SPL and the ramifications of long term oral antibiotic use in the treatment of acne.

**Innovation-Decision Process**

The innovation-decision process unfolds from individuals gaining knowledge of an innovation, to developing a viewpoint about it, to deciding to adopt or reject it, to implementing it, and to confirm this decision (Rogers, 2003). There are five steps to this process.

**Knowledge**

Knowledge is the first exposure to the existence of an innovation without further information about it; knowledge is necessary for awareness to occur. In this project, first level adopters (providers) must first be aware of the ripple effects of long-term oral antibiotic use and alternatives to it, such as SPL. Concurrently, second level adopters (patients) will be individually counseled by providers on the effectiveness, safety and cost of SPL as opposed to long term oral antibiotics in the treatment of acne in adult women.
**Persuasion**

Following awareness, adopters can be persuaded that an innovation can be useful; in this phase, there is interest in the innovation, formation of positive opinion about it and curiosity to gain further information about it (Bowen et al., 2012). In this project, providers are aware of efficacy and safety of SPL and educate their patients about it. Education starts on the consequences of long-term oral antibiotic use and how SPL fits in the treatment and maintenance of acne. The manuscript will contain information that may persuade readers that addressing antibiotic resistance in acne management is important.

At this stage, patients may be given written information about SPL and encouraged to voice their concerns and ask further questions to the providers. Patients also begin to understand and consider the effects of individual behavior (long term antibiotic use) on public health (antibiotic resistance).

**Decision**

Once persuaded, adopters consider using the innovation; here, they consider the practice change given the pros and cons to adopt or reject it (Bowen et al., 2012). In this project, providers should become more informed and comfortable in using SPL with their female acne patients. They exchange information with other providers who have had longer experience in treating patients with SPL and continue to educate and use it with their patients. It is anticipated at this stage that patients become more informed about SPL, learning how it is well tolerated, effective and cost-effective. They may also begin to see improvement of skin lesions in other patients treated with SPL in their search for
further evidence. Consequently, patients who have not received treatment with SPL may be more inclined to try it to manage their own acne.

**Implementation**

Once the innovation is being used, its effectiveness is assessed (Bowen et al., 2012). In this project, it is anticipated that once patients start taking SPL to treat their acne, see decrease or clearance of lesions, they will be inclined to stay on SPL for maintenance or long-term treatment if necessary and their providers will be more likely to try SPL with other patients. Their satisfaction will be positive feedback to providers.

**Confirmation**

With an evaluation of effectiveness, the adopter decides to maintain or discontinue the innovation based on the value and benefits it generated (Bowen et al., 2012). In this project, providers will be familiar with the most common questions asked by patients and confidently address these verbally as well as handing patients written materials on SPL. This way, patients can refer to these anytime and ask further questions as they arise. Patients may recognize the value and benefits of SPL based on the communication with the provider and come to a decision to continue or stop treatment with SPL to manage their acne.

**Purpose**

The purpose of this project was to disseminate evidence to nurse practitioners (NPs) and other health care providers related to acne management in adult women. This was done through a manuscript. Important elements in the manuscript will be pathophysiology of acne in women, standard acne management based upon published clinical practice guidelines, a discussion of antibiotic overuse, evidence about SPL
(spironolactone), and an algorithm to assist in treating adult women with moderate to severe acne. The Centers for Disease Control and Prevention (CDC), is a good resource for educating health care providers and patients regarding antibiotic use, how it works and effects of overuse (www.cdc.gov/getsmart). If published, this manuscript should enhance awareness by providers of practice changes that may decrease the chances that women with acne will add to the global problem of antibiotic resistance.
REVIEW OF LITERATURE

This section includes: (a) review of the pathophysiology of acne, and syntheses of (b) the (recommendations from on current guidelines to treat acne, (c) findings about (1) antibiotic resistance, (2) efficacy of spironolactone, and (3) provider use of antibiotics.

Pathophysiology of Acne

In the United States, about 60 million people suffer from acne (Roman et al., 2016). Sufferers include 85% of all adolescents and 12% of adult women. Acne is a chronic inflammatory condition of the piloceanous units resulting in comedones (blackheads/whiteheads), papules, pustules, and nodules (Kraft & Freiman, 2011). The pathogenesis of acne is multifactorial including androgen-induced sebum production, follicular hyperkeratinization (follicular plugging), inflammation, and colonization by Propionibacterium acnes (P. acnes) in the pilosebaceous unit (Harper, 2009). Follicular plugging results from sebum in the follicles that leads to comedone formation. P. acnes then colonizes in the follicle, which triggers the release of cytokines resulting in inflammatory lesions, such as papules and pustules (Kumar et al., 2016). Despite not being a fatal disease, acne impacts patients physically with pain and scarring, and emotionally/psychologically with depression and anxiety; these sequelae can lead to low self-esteem (Roman et al., 2016).

Hormones and Acne

In women, the sex hormones, dehydroepiandrosterone (DHEAS) and dihydrotestosterone (DHT), and metabolic hormone insulin-like growth factor 1 (IGF-1) play a role in acne by increasing the lesion count. These hormones work synergistically as the influence of androgens on acne depends upon the presence of IGF-1 (Barros &
Thiboutot, 2017). Produced by adrenal glands and ovaries, androgens (testosterone, DHT, DHEAS) affect the sebaceous glands by increasing their size and sebum production. Androgens are also produced by sebaceous glands themselves when type 1 5-alpha-reductase converts testosterone to DHT (Barros & Thiboutot, 2017).

In women, one of the main purposes of androgen is to be converted to estrogen. Androgens are a major factor in acne pathogenesis because they enhance follicular keratosis and influence sebum production. There is no acne without sebum as it is a nutrient source for *P. acnes*. Increased sebum production in acne patients may be due to increased circulating androgens or hyper-responsiveness of pilosebaceous units, or both (Bettoli, Zauli, & Virgili, 2015). Persistent or severe acne may be the only clinical sign of androgen excess in women (Collier et al., 2008).

Anti-acne hormonal therapy works by lowering circulating and local androgen levels and blocking their effects on the sebaceous glands. Spironolactone (SPL) is an androgen receptor blocker that has anti-androgenic properties. SPL decreases steroid production in adrenal and ovarian tissue. Additionally, SPL also acts as an antiandrogen peripherally by blocking androgen receptors in the sebaceous glands (Friedman, 2015). This means it prevents testosterone and DHT from connecting to the androgen receptors. As a result, sebum production from the sebaceous glands gets reduced (Bettoli et al., 2015). SPL is also a potassium-sparing diuretic. Because hyperkalemia is uncommon in healthy adults with acne, unless cardiac or renal issues exist, altered serum potassium is not usually an issue (Plovanich, Weng, & Mostaghimi, 2015).
Clinical Practice Guidelines

PubMed database and Google Scholar were utilized to search for articles. Key words used were “acne guidelines.” Limiters included peer reviewed, abstract, English language, humans, and publish date within 5 years to review the most current information available. Sixty-seven articles were retrieved; two guidelines were selected for review. The other 65 were review articles focusing on other diagnosis such as polycystic ovarian syndrome and rosacea, which deviates from the scope of this project.

Three sets of current guidelines were evaluated, those of The American Academy of Dermatology (AAD), the South-East Asia Study Alliance (SASA) group and French multidisciplinary group. These current professional guidelines address the treatment of moderate to severe acne in women very similarly. All three recommend acne grading and classification systems to help providers assess the severity of the disease (Goh et al., 2015; Le Cleach et al., 2017; Zaenglein et al., 2016). Each also suggests strategies to determine appropriate treatment and allocate ways to document baseline status and subsequent clinical changes (e.g., improvement) during treatment (Zaenglein et al., 2016). While there is no universally accepted grading system (Zaenglein et al., 2016), the AAD classifies acne severity on number and type of lesions: mild to severe (Goh et al., 2015). The SASA group uses the AAD acne grading system (Goh et al., 2015). The French guidelines use a global acne severity scale that ranges from almost clear to very severe including clinical photography (Le Cleach et al., 2017).

First Line Treatment

In all three sets of guidelines, oral antibiotics are recommended for treatment of adult acne for up to 12 weeks along with topical benzoyl peroxide (BPO) and retinoid.
Limiting the treatment duration with oral antibiotics may reduce associated conditions of antibiotic overuse, such as upper respiratory infections (URI) (Zaenglein et al., 2016). It is reported that acne patients treated with oral antibiotics are more susceptible to URIs than those not treated with oral antibiotics (Goh et al., 2015). An alternative treatment consists of hormonal therapy for women (Goh et al., 2015; Zaenglein et al., 2016). The French guidelines recommend hormonal therapy only if birth control is required, but not to treat acne alone (Le Cleach et al., 2017).

**Second Line Treatment (with First Line Failure)**

The AAD guidelines recommend the following alternative treatments following first line failure in women: consider change in oral antibiotic or add oral contraceptive with or without an anti-androgen or SPL (Zaenglein et al., 2016). SASA group recommends oral contraceptive with or without an anti-androgen (Goh et al., 2015). The French group recommends isotretinoin (Le Cleach et al., 2017).

**Maintenance Treatment**

Recommendations for maintenance treatment are the same for all three (Goh et al., 2015; Le Cleach et al., 2017; Zaenglein et al., 2016) and include retinoids and BPO (Appendix A Table 1). Further, AAD and SASA recommend hormonal therapy as an alternative treatment, without stating length of time (Goh et al., 2015; Zaenglein et al., 2016). The AAD guidelines recognize that patients who are on topical medications and are not candidates for alternative therapies may need to stay on oral antibiotics longer than recommended. In this case, BPO and retinoids must be used in conjunction with antibiotics to reduce antibiotic resistance to *P. acnes*, as it will not address the commensal flora (Zaenglein et al., 2016). AAD and SASA agree that topical or oral antibiotics
should not be used as monotherapy, as that contributes to the development of antibiotic resistance (Goh et al., 2015; Zaenglein et al., 2016). If dermatological management does maintain acne clearance, the French group recommends hormonal therapy for maintenance that is also in agreement between the patient and her gynecologist (Le Cleach et al., 2017).

**Guideline Differences**

While similar, there are some points where the three guidelines differ. The AAD guidelines recommend as an option for first line treatment, concurrent use of oral and topical antibiotics along with topical retinoid and BPO (Zaenglein et al., 2016). Conversely, the SASA guidelines state that topical and oral antibiotics should not be used concomitantly to prevent antibiotic resistance (Goh et al., 2015). The French group does not recommend topical antibiotics for moderate to severe acne. They recommend oral antibiotics – doxycycline or lymecycline; the latter is not available in the US. Further, they do not consider minocycline as an option since French health authorities retracted its use for acne due to its low safety profile (Le Cleach et al., 2017). AAD recommends reevaluation of antibiotic response in 3-4 months to reduce bacterial resistance before trying a different oral antibiotic, adding or switching to hormonal therapy or starting on oral isotretinoin (Zaenglein et al., 2016). SASA recommends reassessment after 6-8 weeks on oral antibiotics before switching to hormonal therapy or starting on oral isotretinoin (Goh et al., 2015). The French guidelines recommends oral isotretinoin if oral antibiotics fail after 3 months of treatment (Le Cleach et al., 2017).

The AAD supports the use of hormonal therapy in women as an alternative to first line treatment based on available evidence, provider experience, and expert opinion.
(Zaenglein et al., 2016). On the other hand, SASA states that hormonal therapy can be used as first line of therapy for women with moderate acne in addition to topical medication (tretinoin and BPO) (Goh et al., 2015). The French guidelines do not recommend use of combined oral contraceptives (COC) for acne unless birth control is required. They also do not mention SPL as an antiandrogen option, instead, recommending use of the antiandrogen/estrogen combination cyproterone/ethinylestradiol if birth control is required (Le Cleach et al., 2017). Cyproterone, an antiandrogen used in the treatment of androgen dependent conditions such as acne, is not approved for use in the US but is recommended by the French combined with ethinylestradiol group for persistent acne unresponsive to dermatological treatment (topical or systemic antibiotics) (Le Cleach et al., 2017).

Although the AAD states that a system of grading and classifying acne, including the number, type and severity of acne lesions, guides providers in determining the best treatment options and monitoring progress, it does not recommend a specific one (Zaenglein et al., 2016). SASA recommends the acne classification system developed by the AAD Acne Consensus Conference, which is based on the number and type of lesions present (Goh et al., 2015). The French guidelines utilize a detailed grading system based on type of lesion global assessment including extent of affected area of the face (i.e., more or less than half of the face or full face) as well as photographic documentation (Le Cleach et al., 2017).

Antibiotic Resistance and Potential Side Effects

PubMed database and Google Scholar were utilized to search for articles. Limiters included peer reviewed, abstract, English language, humans and publish date
within 5 years to review the most current information available. Key words used were antibiotic resistance in acne. The search yielded 69 articles, of which 64 were excluded. Included were five studies and one systematic review.

Although antibiotics are essential in the treatment of many skin diseases and other infections, antibiotic resistance is an emerging national and global concern (Del Rosso et al., 2015). In dermatology, oral and topical antibiotics are frequently prescribed, especially to treat acne. *P. acnes* resides on normal skin as part of the microflora, but it is found in aberrantly high numbers in the sebaceous follicles of acne patients. It is also the key inflammatory factor as it releases chemical mediators that promotes inflammation which is proliferated by the rupture of comedones into the surrounding dermis. Such inflammation induces papule, pustule, nodule, and cyst formation (Kumar et al., 2016). Although acne is not an infectious disease, it is treated with antibiotics because of their dual effects: antibacterial and anti-inflammatory; the result is decreased number of *P. acnes* as well as inflammation (Kumar et al., 2016).

The use of topical and oral antibiotics targets bacteria all over the body and not just *P. acnes*. The result of long-term use is transfer of resistant genes to potentially pathogenic bacteria (Walsh et al., 2016), as conditions caused by such organisms are listed on Appendix A, Table 2. Therefore, guidelines recommend not using oral antibiotics concomitantly with topical antibiotics (Walsh et al., 2016) but instead with a topical BPO and retinoid. Such topicals may be used for maintenance treatment as well (Walsh et al., 2016). This practice decreases the likelihood of antibiotic resistance. Additionally, the Centers for Disease Control and Prevention (CDC) advises antibiotic stewardship to all prescribing providers; such stewardship infers selecting the correct
antibiotic for the correct condition to maximize patient outcomes in order to avoid antibiotic resistance (Zaenglein et al., 2016).

Although antibiotics are used to treat acne, there are some significant concerns with their use aside from antibiotic resistance. For instance, side effects may include photosensitivity, gastrointestinal upset, and vaginal yeast infections (Zaenglein et al., 2016). Further, the cost of oral antibiotic treatment can be up to $500 to $1,500 a month (Epocrates, 2016).

**Spironolactone Effectiveness**

The terms spironolactone and acne, hormonal therapy for acne in women, acne management in adult women with limiters English language, clinical trial, review, peer reviewed between 1998 and 2017 were entered on PubMed database and Google Scholar to search for articles. Out of 218 articles retrieved, 171 articles were excluded, 47 were reviewed; seven articles were used. The sample size of most studies was small and there were no randomized clinical trials.

Studies reviewed consistently reported that SPL 50 to 100 mg taken daily demonstrates efficacy in the treatment of moderate to severe acne in adult women (James C Shaw, 2000). A long term (8-year) use of spironolactone study concluded that SPL was not associated with serious side-effects; the most common side effects noted were irregular menses, lightheadedness and diuresis, which usually subsided as treatment progressed and generally did not cause patients to discontinue SPL (J. C. Shaw & White, 2002). Incidence of side effects seemed to be dose dependent and tend to improve as treatment progresses. Most side effects occur in the first few months of treatment and generally do not cause patients to discontinue treatment. Further, SPL demonstrated
effectiveness as monotherapy or in conjunction with oral antibiotics, topical antibiotics, or oral contraceptives (Krunic, Ciurea, & Scheman, 2008; Lessner et al., 2014; Sato et al., 2006; James C Shaw, 2000; J. C. Shaw & White, 2002; J. Tan, 2004; Yemisci et al., 2005).

Limitations of studies were small sample size and all but one study lacked a control group.

**Provider Use of Antibiotics**

PubMed and Google scholar were utilized to search for articles on this topic with key terms “provider overuse antibiotics.” Limiters were peer reviewed, English language and publish date within 5 years to review the most current information available. Twenty articles were retrieved, 16 were excluded, 3 were reviewed; two articles were used.

In a cross-sectional study, Ab Rahman, Teng, and Sivasampu (2016) examined antibiotic prescribing behaviors of primary care providers in public and private clinics in Malaysia (see Appendix A or B Table 4). The authors utilized data from the National Medical Care Survey (NMCS), a national cluster sample of private and public primary care clinics in 2014. The findings were as follows: out of 28,000 visits, 5,800 (21%) resulted in antibiotics prescription; in 197 (3.4%), more than one antibiotics was prescribed; there was a higher rate (31%) of antibiotics prescribed in private clinics compared to public clinics (7%). Half of antibiotics prescribed was for URI, which are mostly viral and not bacterial infections (17% in public clinics, 58% private clinics) (Ab Rahman, Teng, & Sivasampu, 2016). The authors concluded that antibiotics were excessively and inappropriately prescribed in primary care, especially private clinics. They recommended education of the public as well as health care providers via social
media and professional organizations to limit antibiotic resistance (Ab Rahman et al., 2016).

A limitation of this study was that even though prescriptions for antibiotics were given at public as well as private clinics, pharmacy records were not checked to confirm if those prescriptions were filled. Therefore, it is evident that antibiotics were overprescribed, and it can only be assumed that such prescriptions were filled and the medication takes as directed. Also, the findings may not generalize to other geographic locations.

**Summary**

Acne is a common inflammatory skin condition which can affect women for many years. Current clinical practice guidelines recommend first line treatment of moderate to severe acne with oral antibiotics up to 12 weeks along with topical BPO and retinoid to avoid antibiotic resistance. Alternative treatment includes the addition of hormonal therapy to first line treatment or hormonal therapy (oral contraceptives with or without an antiandrogenic) with or without topical therapy.

Oral antibiotics are not limited to treat *P. acnes*, it also targets the commensal flora which can cause antibiotic resistance anywhere in the body, not just where *P. acnes* resides. Resistant organisms can be passed to other individuals making antibiotic resistance a public health concern. Therefore, an alternative treatment for acne without the risk of antibiotic resistance is imperative to ameliorate this public health issue.

SPL is a safe and effective option to treat moderate to severe acne in adult women as well as to maintain results long term. It is cost effective and although side effects (SE), such as menstrual irregularities and frequent urination, are common, they tend to
subside as treatment progresses. Generally, SPL SE do not cause patients to stop the treatment. Further, lower doses, 50 – 100 mg/day as an adjunct or monotherapy, deliver effective results (clearance or marked improvement of lesions and produce less SE.

Prescribers, especially in the private setting, are inclined to excessively and inappropriately prescribe antibiotics. This prescribing behavior further contributes to the development and expansion of antibiotic resistance. Educating and raising awareness regarding antibiotic resistance to providers as well as the public via professional organizations and social media can remedy this issue.
METHODS

The purpose of this project was to disseminate evidence regarding acne management in adult women to nurse practitioners and other health care providers who treat patients affected. This was achieved through development of a manuscript, that if published, will enhance provider’s awareness and initiative to approach acne treatment in women with alternatives, such as spironolactone, to decrease antibiotic overuse and enhance antibiotic stewardship. This section focuses on the steps that led to submission of the manuscript to a journal for primary care providers: The Clinical Advisor.

Design

The goal of this project was to fill gaps in provider knowledge regarding acne management and long-term maintenance while enhancing awareness of the ripple effects of antibiotic overuse. The developed manuscript described best treatment practices for acne management in adult women based on evidence.

One important component in the manuscript was an algorithm delineating step-by-step management: from assessment of acne severity, treatment, as well as length of treatment, which was a key focus of the manuscript. This algorithm may guide providers to treat acne without contributing to the growing issue of antibiotic resistance.

Ethical Consideration

No human subjects or data from the DNP student workplace were described in the manuscript. According to California State University, Long Beach (CSULB) Director Research Integrity and Compliance, Jason Wang, no institutional review board approval was necessary for this project.
Procedures

Based on the literature review and the author’s eight years of clinical experience in a dermatology practice, an algorithm illustrating the treatment guidelines was created. Although no specific acne scale is currently recommended by professional organizations, use of the severity scale endorsed by the AAD provided clinicians with a system to determine the best treatment course. The following is an outline of the information on the algorithm:

Step 1: Acne severity scale

- Grade I
  - Mild acne: comedones (open and closed) and few inflammatory papules and pustules
- Grade II
  - Moderate acne: numerous comedones, few to many papule and pustules and few small nodules with marked inflammation
- Grade III
  - Severe acne: numerous large painful inflamed nodules and pustules
- Grade IV
  - Severe acne with many large inflamed nodules and pustules along with scarring

Step 2: Select treatment for:

Mild acne:

- BPO or topical retinoid
  
or
  
  - BPO + topical retinoid + topical antibiotic

Moderate to severe acne:

- Topical therapy:
- BPO + retinoid + antibiotic

- Oral and topical therapy
  - Oral antibiotic (up to 3 months) + topical retinoid + BPO

  Important to consider: although the AAD included concurrent use of topical and oral antibiotic, SASA guidelines recommend not using them concurrently to prevent antibiotic resistance.

- Alternative therapy:
  - SPL + topical retinoid + BPO

  This may also be used for maintenance therapy as it does not promote antibiotic resistance. Additionally, an 8-year study supports the long term use of SPL.

Severe acne:
- Same as moderate to severe acne regimen
  or

- Oral Isotretinoin

**Journal Selection**

Implementation consisted of reviewing several clinical journals which had the potential to publish articles focused on primary care. *Journal of Nurse Practitioners, The Nurse Practitioner Journal*, and *The Clinical Advisor* were considered and the respective author guidelines are in Appendix B. The last two years of publication for these three journals were assessed to determine whether acne management had been covered. This helped determine the ultimate journal for submission. The journal selected was *The Clinical Advisor*. Once the project committee determined that the appropriate journal was selected, the manuscript was prepared according to the author guidelines.

**Manuscript Preparation**

The outline for the manuscript is as follows:
Abstract

Treating persistent acne in adult women in the era of antibiotic persistence. Why is it important?

What is acne and its significance?

Pathophysiology and psychological impact
  - Hormones and acne

Guidelines: AAD, SASA and French multidisciplinary group
  - Similarities
  - Differences
  - Treatment recommendations

How are providers utilizing antibiotics?

Antibiotic resistance and potential side effects: what is the evidence?
  - Antibiotic resistance in acne
  - Spironolactone and acne: how does it work?

Managing acne: how to assess and treat it
  - Treatment algorithm
    - Mild acne
    - Moderate to severe acne

Summary

Evaluation

The project committee reviewed and evaluated the article to make sure it met the guidelines for the selected journal: The Clinical Advisor.
RESULTS

The manuscript was developed (see Appendix C) reviewed by the project committee and submitted to The Clinical Advisor on March 9, 2018.
DISCUSSION

The framework for this project, Diffusion of Innovations theory (Rogers, 2003), helped me understand how to implement and disseminate an innovation that took into account potential barriers to adopters (providers and patients). The more someone understands the problem and the consequences of it (enhanced awareness), the more he or she is inclined to adopt the innovation/change. Time is an important factor in diffusion of new information. It takes time for people to recognize a problem, consider a strategy to take for solving it, and then, to take action. For instance, inertia may be a roadblock for clinicians to fully change how they treat acne. It takes effort and time to become familiar and comfortable with a medication that is used off label (i.e., SPL), and then, to explain to patients why it is necessary to stop oral antibiotics and have patients be willing to accept this change, especially when their acne is under control. Approaching acne management in the context of global antibiotic resistance, allows providers and patients to consider that individual accountability regarding antibiotic use can reduce antibiotic resistance. This mindset enables them to become part of the solution and contribute to better health worldwide.

If providers across specialties that treat acne implement the recommendations put forth in the manuscript, fewer antibiotic prescriptions will be written, less antibiotics will be used, clinicians will be more vigilant of the length of time patients will be kept on antibiotics, and patients will be better informed of the ripple effects of long-term use of antibiotics. Additionally, patients can be more active partners in their care. This is especially important if they change providers; the new provider may not be aware of, or practice, antibiotic stewardship. Ultimately, if the manuscript raises awareness of
providers about new ways to think of acne management, these providers may educate their colleagues and patients, who in turn can share this information with their family and friends; all of these avenues may help reduce antibiotic resistance when acne management is done in a responsible manner. All involved in providing and receiving acne treatment can be valuable agents of change.

Reading the evidence needed to write this manuscript has expanded my understanding of how antibiotics are utilized in this country and abroad. It was alarming to know that 80% of antibiotic exposure in the US comes from agricultural use and 20% from human exposure. Antibiotic resistance can affect people who consume animals that have been treated with antibiotics. This can make them more susceptible to antibiotic resistant infections. As providers, we must make our colleagues and patients aware of this so they can reduce exposure to possible antibiotic resistant sources. Through knowledge, awareness and implementing changes, we can achieve and maintain acne clearance while keeping the effects of antibiotics intact.
REFERENCES


# APPENDIX A

## TABLE OF EVIDENCE

### Table 1

**Clinical Practice Guidelines**

<table>
<thead>
<tr>
<th>Purpose (Author(s), year)</th>
<th>Design, Key Variables</th>
<th>Sample &amp; Setting</th>
<th>Measures</th>
<th>Results</th>
<th>Conclusions/ Limitations/Appropriateness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describes evidence-based recommendations for tx of moderate to severe acne (Zaenglein et al., 2016)</td>
<td>Systematic reviews, meta-analyses</td>
<td>Systematic search PubMed and Cochrane Library from 2006-2014 to address clinical questions on previous to address new clinical questions for this guideline.</td>
<td>Abx</td>
<td>Systemic abx (tetracyclines) 1st line of tx mod to severe acne</td>
<td>Abx: remains first line of tx for mod-severe acne, but should not be used as monotherapy or more than 3-4 mos to avoid bacterial resistance.</td>
</tr>
<tr>
<td></td>
<td>IV: oral abx + topical retinoid + BP</td>
<td>SPL</td>
<td>No measures mentioned</td>
<td>Re-assess and possibly discontinue oral abx after 3-4 mos to ↓ bacterial resistance. Combine w topical retinoid and BPO to avoid bacterial resistance.</td>
<td>Limitations: comparative studies of length of tx w and w/o topical therapy</td>
</tr>
<tr>
<td></td>
<td>DV: acne</td>
<td>Group of 17 acne experts, 1 GP, 1 pediatrician and 1 patient to discuss scope and clinical questions for dx and mgmt of AV</td>
<td>SPL</td>
<td>CDC rec abx stewardship limiting it to 3-4 mos</td>
<td>SPL: although studies were small, results showed efficacy of SPL in acne tx. experts who developed the guidelines, agree with use of SPL in acne tx based on evidence and experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1) 2 small placebo-controlled prospective studies SPL 50-200 mg daily</td>
<td></td>
<td>1) statistically sig imp in acne severity and sebum production</td>
<td>Limitations: more studies and larger samples needed to determine tx duration and efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Retrospective chart review 85 pts SPL 50-100 mg/daily</td>
<td></td>
<td>2) Japanese study 116 pts, SPL 200 mg daily x 8wks, ↓ 50 mg q 4 wks for a total of 20 wks</td>
<td>These guidelines fit project addressing long term oral abx use</td>
</tr>
<tr>
<td>Purpose (Author(s), year)</td>
<td>Design, Key Variables</td>
<td>Sample &amp; Setting</td>
<td>Measures</td>
<td>Results</td>
<td>Conclusions/ Limitations/Appropriateness</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------</td>
<td>-----------------</td>
<td>----------</td>
<td>---------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2) 66% achieved clearance or marked imp</td>
<td>3) 64 pts had good to excellent imp</td>
<td>Mod acne rec: BPO, retinoid, and oral abx. Assess response x 6-8 wks and do not exceed 12 weeks. Hormonal tx may be added as needed and used for maintenance tx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Severe acne: mod acne tx for 6-8 wks. If no imp, start isotretinoin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Meta-analysis demonstrated hormonal therapy to be likely better than oral antibiotics for long term tx of acne in women</td>
</tr>
<tr>
<td>Purpose (Author(s), year)</td>
<td>Design, Key Variables</td>
<td>Sample &amp; Setting</td>
<td>Measures</td>
<td>Results</td>
<td>Conclusions/Limitations/Appropriateness</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------</td>
<td>-----------------</td>
<td>----------</td>
<td>---------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Develop rec to manage acne with appropriate abx use while avoiding abx resistance in <em>Propionibacterium acnes</em> (Goh et al., 2015)</td>
<td>Group of experts from Asia identified clinical differences between Caucasian and Asian skin to tailor tx guidelines to SEA ppn bases on current guidelines and current practices</td>
<td>13 dermatologists developed treatment guidelines for SEA ppn based on evidence, current guidelines, practices, collective experience</td>
<td>Experts discussed current guidelines, practice and new progress to decide on best practices and rec to treat acne based on evidence, experience and expertise</td>
<td>Oral abx should be used for less than 12 wk w topical retinoids and BPO to ↓ abx resistance</td>
<td>Oral abx should not be used as monotherapy or maintenance tx to avoid abx resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Limitations: no information of extent of time hormonal therapy may be used for</td>
<td>This study fits the project addressing long term oral antibiotic use</td>
</tr>
<tr>
<td>Purpose (Author(s), year)</td>
<td>Design, Key Variables</td>
<td>Sample &amp; Setting</td>
<td>Measures</td>
<td>Results</td>
<td>Conclusions/ Limitations/Appropriateness</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------</td>
<td>------------------</td>
<td>----------</td>
<td>---------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Update French best practice guidelines from 2007 due to abx resistance issue (Le Cleach et al., 2017)</td>
<td>Group of experts of different specialties reappraised new evidence published since 2007</td>
<td>WG of 7 dermatologists, 1 drug safety specialist, 1 endocrinologist, 1 infectious disease specialist, 1 microbiologist, 1 psychiatrist, 1 pediatrician, 2 gynecologists, 2 GPs, 2 methodologists appraised new published information</td>
<td>WG reviewed published articles from 2007 to 2014 that were previously analyzed by 6 physicians w methodology skills. Guidelines and recs were developed. 4 acne experts gave their opinion. WG made further revisions. PRG of 51 physicians reviewed the info. Rec &lt; 90% mean score were revised by WG</td>
<td>No topical antibiotics due to ↓ efficacy and ↑ risk of bacterial resistance</td>
<td>Oral abx should always be limited to 3 months and combined w topical BPO and retinoid</td>
</tr>
</tbody>
</table>

Notes: Abx = antibiotics; AV = acne vulgaris; BPO = benzoyl peroxide; CDC = Centers for Disease Control; dx = diagnosis; GP = general practitioner; imp = improvement; mgmt = management; mod = moderate; mos = months; P. acnes = Propionibacterium acnes; ppn = population; PRG = Peer Review Group; pts = patients; q = every; rec = recommends; SE = Side Effects; SEA = South East Asian; sig = significant; tx = treat/treatment; URI = upper respiratory infection; w = with; WG = Working Group; w/o = without; wk/wks = week/weeks; x = for
# Table 2

**Antibiotic Resistance**

<table>
<thead>
<tr>
<th>Purpose (Author(s), year)</th>
<th>Design, Key Variables</th>
<th>Sample &amp; Setting</th>
<th>Measures</th>
<th>Results</th>
<th>Conclusions/Limitations/Appropriateness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describes consequences of abx resistance secondary of abx use in acne tx based on evidence (Walsh et al., 2016)</td>
<td>Systematic review</td>
<td>Articles from January 1954-March 2015 on PubMed with specific keywords</td>
<td>Articles pertaining to different combinations of these key words acne, resistance (not insulin), macrolides, antibiotics</td>
<td>Topical and oral abx may result in abx resistance. Limiting use up to 3 mos along w topical BPO and retinoids to ↓ resistance. should not be used as monotherapy or w topical abx</td>
<td>Abx resistance as a result of abx use to treat acne is of growing concern. Abx use should be limited to 3 mos for mod to severe acne along with topical retinoid and BPO. Such topicals may be used for maintenance as well</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV: abx use</td>
<td></td>
<td></td>
<td></td>
<td>Abx resistance can happen w/o abx tx because resistant bacteria spread to skin of untxd individuals</td>
</tr>
<tr>
<td></td>
<td>DV: abx resistance</td>
<td></td>
<td></td>
<td></td>
<td>Acne with poor/no response to abx or relapses can be result of resistant <em>P. acnes</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>S. pyogenes</em> is 3x more likely to colonize in oropharynx of acne pts tx’d w abx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85% of <em>S. pyogenes</em> cultured from abx tx’d pts resistant to tetracycline abx compared to 20% of pts not tx’d w abx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral abx use can cause abx resistance to commensal flora anywhere in body</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Spread of <em>S. aureus</em>, MRSA with abx resistance secondary to acne tx is major concern</td>
</tr>
</tbody>
</table>

Limitations: few studies addressing and comparing abx length of time to tx acne have been done. Even less studies involving microbiology and outcomes available.

More evidence needed regarding *P. acnes* resistance in other specialties besides dermatology.

This systematic review meets the needs of the project regarding long term use of oral antibiotics.
<table>
<thead>
<tr>
<th>Purpose</th>
<th>Design, Key Variables</th>
<th>Sample &amp; Setting</th>
<th>Measures</th>
<th>Results</th>
<th>Conclusions/ Limitations/Appropriateness</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. acnes can cause endocarditis, mediastinitis post cardiac surgery, prosthetic joint infections, and breast implant infections, secondary infections reported to resistant to abx for such infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Notes:* Abx = antibiotics; BPO = benzoyl peroxide; mos = months; MRSA = methicillin resistant *Staphylococcus aureus*; *S. pyogenes* = *Streptococcus pyogenes*; P. acnes = Propionic bacterium; tx = treatment; untxd = untreated
Table 3

*Effectiveness of Spironolactone (SPL)*

<table>
<thead>
<tr>
<th>Purpose (Author(s), year)</th>
<th>Design, Key Variables</th>
<th>Sample &amp; Setting</th>
<th>Measures</th>
<th>Results</th>
<th>Conclusions/ Limitations/Appropriateness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigated therapeutic effect low doses of SPL alone or adjunct tx acne in adult women (James C Shaw, 2000)</td>
<td>Retrospective study</td>
<td>IV: SPL 50 mg - 100 mg/day x 2-24 months</td>
<td>Oral antibiotics OC DV: acne severity</td>
<td>Monthly or bimonthly visits to evaluate level of response and tolerance SPL 50-100 mg/day evaluated using physician examination and interim pt history</td>
<td>17 pts (20%) SPL 50-100 mg/d only 5 pts clear of acne 5 pts &gt; 50% imp over 2-24 months 46 pts (54%) SPL + systemic antibiotics 10 pts clear of acne 14 pts &gt; 50% improvement 10 pts (12%) SPL + OC 4 pts clear of acne 3 pts &gt; 50% improvement 12 pts (14%) SPL, oral antibiotics and OC 5 pts clear of acne 2 pts &gt; 50% improvement None: 46 pts (57.5 %) Menstrual irreg: 14 pts (17.5 %) SI hyperkalemia: 10 pts (13.7 %)</td>
</tr>
<tr>
<td>Describes long term safety and tolerance of SPL in adult women</td>
<td>Retrospective study</td>
<td>Survey was mailed 210 18-52 yo women who received</td>
<td>Survey questionnaire (regarding acne history, SPL use, 10 categories of adverse)</td>
<td>Response rate was 43% (91/210) From group who received survey 52% responded (91/173)</td>
<td>No serious conditions thought to be related to SPL were reported during the 8 year follow up. Long term</td>
</tr>
<tr>
<td>Purpose</td>
<td>Design, Key Variables</td>
<td>Sample &amp; Setting</td>
<td>Measures</td>
<td>Results</td>
<td>Conclusions/ Limitations/Appropriateness</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------</td>
<td>------------------</td>
<td>----------</td>
<td>---------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>with acne who were followed up to 8 years (J. C. Shaw &amp; White, 2002)</td>
<td>DV: adverse events attributed to SPL</td>
<td>SPL for mild to moderate inflammatory acne. Urban dermatology practice in Chicago</td>
<td>SE, general medical/gynecological health) sent to pts who received SPL for adult acne between 1988 and 1996. A comparison chart review survey respondents/non-respondents to confirm length of tx w SPL.</td>
<td>Tx duration: 28.5 mos survey respondents 16.3 mos chart review incl survey respondents, non-respondents FU period from 1st exposure: mean 70.5 mos (range 15.3 to 122 mos) SE from survey respondents: ↑urination: 29% menstrual irregularities: 22% fatigue: 17% HA: 14% Dizziness: 12% Lightheadedness: 11% Br tenderness: 17% ↓libido: 15% ↑libido: 6%</td>
<td>use of SPL for acne tx appears to be safe. Although SE are common, usually not a reason to stop SPL. Limitations: Retrospective study No control group 43% survey response rate may leave the possibility that non-responders may have had different outcomes and SE good point This study fits the project in which SPL shows long term safety profile to treat acne in adult women long term</td>
</tr>
<tr>
<td>Investigated the efficacy and safety of SPL to treat acne in Asians (Sato et al., 2006)</td>
<td>Prospective study</td>
<td>116 females and 23 males 15-46 yo w severe acne Ritz Medical Clinic in Japan</td>
<td>Infl acne severity was measured using a scale from Grade 1 to Grade 7 to assess lesion type and inflammation Global response to treatment scale Excellent: Improved 3 or ore grades or no infl lesions Good</td>
<td>64 female patients completed regimen with clinical improvement 34 patients (53.1%) with excellent imp 30 patients (46.9%) with good imp SE: Menstrual irreg 80% Urinary freq changes &lt; 10% No changes noted: lethargy, fatigue, dizziness and HA</td>
<td>SPL monotherapy is effective and demonstrated safety as no serious SE other than menstrual irregularities for Asian women with acne and unsafe for male patients due to gynecomastia. SPL is an option for recurrent, severe, resistant or wide spread types of acne. Limitations: No control group</td>
</tr>
<tr>
<td>Purpose</td>
<td>Design, Key Variables</td>
<td>Sample &amp; Setting</td>
<td>Measures</td>
<td>Results</td>
<td>Conclusions/ Limitations/Appropriateness</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Investigated safety and efficacy of SPL and contraceptive containing drosiprenone</td>
<td>Prospective</td>
<td>27 women 18-43 yo w severe papular or nodulocystic facial acne</td>
<td>Acne severity (moderate to severe – severe papular or nodulocystic facial acne)</td>
<td>11% full clearance</td>
<td>SPL efficacious and well tolerated as it showed mild SE which did not require discontinuation of tx in moderate to severe acne when given with EE/DRSP</td>
</tr>
<tr>
<td>(Krunic et al., 2008)</td>
<td>IV: SPL + EE/DRSP (Yasmin)</td>
<td>outpatient clinics from 2002-2006 in Chicago</td>
<td>Serum potassium pre tx and between 4-6 weeks after starting on meds</td>
<td>74% excellent clearance (&gt;75% clearance)</td>
<td>No increased levels of serum potassium post tx</td>
</tr>
<tr>
<td></td>
<td>DV: acne, Serum potassium</td>
<td></td>
<td></td>
<td>7.4% mild clearance (&gt;25% clearance)</td>
<td>Limitations: Small prospective study; subjective evaluation of clearance through clinical appearance without defining which measurement scale used</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.4% no change</td>
<td>No control group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>serum potassium ranged 3.8-4.8 mmol/L; mean of 4.35 mmol/L at follow-up (reference range 3.5-5.3 mmol/L)</td>
<td>This study fits the project as it addresses the effectiveness of SPL</td>
</tr>
<tr>
<td>Investigate SPL and topical retinoids efficacy</td>
<td>Retrospective chart review</td>
<td>41 female pts 19-57 yo w mild to severe acne were treated with 50 mg of</td>
<td>Women w mild to severe acne were treated with 50 mg of</td>
<td>No response: 1 pt (2.4%) 50 mg/d x 2 mos</td>
<td>The addition of SPL to topical retinoids indicates superior response to</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purpose (Author(s), year)</td>
<td>Design, Key Variables</td>
<td>Sample &amp; Setting</td>
<td>Measures</td>
<td>Results</td>
<td>Conclusions/ Limitations/Appropriateness</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------</td>
<td>------------------</td>
<td>----------</td>
<td>---------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>in the tx of cyclical acne in adult women (Lessner et al., 2014)</td>
<td>IV: SPL 50-200mg/day x2-102 months and Topical tretinoin 0.025% or adapalene 0.1% cream</td>
<td>DV: acne response</td>
<td>SPL. If no improvement within 3-6 mos, dose held or ↑ in 25 mg increments every 3 mos</td>
<td>Minimal response: 5 pts (12.2%) Good: 9 pts (22%) Excellent: 12 (29.3%) Clear: 14 (34.1%)</td>
<td>Se: Lightheadedness: 1 pt (2.4%) on SPL 50 mg, SE subsided as tx progressed Irregular periods: 2 pts (4.9%) on 50 mg and 200 mf of SPL Orthostatic hypotension: 1 pt (2.4%) on SPL 50 mg. No serious SE during tx</td>
</tr>
<tr>
<td>Investigated the efficacy, safety and tolerability of SPL (Grandhi &amp; Alikhan, 2017)</td>
<td>Retrospective Chart review IV: SPL 50-100mg/day SPL + topical + oral SPL + oral SPL only SPL + Topical</td>
<td>400 pts 12-62 yo Department of Dermatology, University of Cincinnati</td>
<td>Response to SPL as improved, no change, worsened, or indeterminate SPL + topical + oral Improved: 188 (88%) Indeterminate: 3 (1%) Unchanged: 14 (7%) Worsened: 8 (4%) SPL + oral Improved: 25 (81%) Indeterminate: 2 (6%) Unchanged: 3 (10%) Worsened: 1 (3%) SPL only Improved: 35 (85%) Indeterminate: 0 (0%) Unchanged: 5 (12%)</td>
<td>86 % of patients improved on SPL with low incidence of SE, which supports the safety of SPL Limitations: No control group No clear description of acne severity No clear definition of response This study fits the project as it demonstrated the effectiveness of SPL</td>
<td></td>
</tr>
<tr>
<td>Purpose (Author(s), year)</td>
<td>Design, Key Variables</td>
<td>Sample &amp; Setting</td>
<td>Measures</td>
<td>Results</td>
<td>Conclusions/ Limitations/Appropriateness</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------</td>
<td>-----------------</td>
<td>----------</td>
<td>---------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worsened: 1 (2%)</td>
<td>SPL + topical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improved: 108 (95%)</td>
<td>Improved: 108 (95%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Indeterminate: 2 (2%)</td>
<td>Indeterminate: 2 (2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unchanged: 2 (2%)</td>
<td>Unchanged: 2 (2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worsened: 2 (2%)</td>
<td>Worsened: 2 (2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SE:</td>
<td>SE:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Estrogen dependent cancers: 0</td>
<td>Estrogen dependent cancers: 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Breast tenderness: 1</td>
<td>Breast tenderness: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heavy menses: 1</td>
<td>Heavy menses: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperkalemia: 6</td>
<td>Hyperkalemia: 6</td>
</tr>
</tbody>
</table>

Notes: assmt = assessment; CNS = central nervous system; DV = dependent variable; EE/DRSP = ethinyl estradiol/drospirenone; FU = follow-up; HA = headache; IM = intramuscular; Imp = improvement; Incl = including; Infl = inflammatory; IV = independent variable; Mod = moderate; mos = months; No = number; OC = oral contraceptives; pts = patients; QOL = quality of life; SE = side effects; sx = symptom(s); SPL = spironolactone; tx = treatment; wt = weight; w = with; w/o = without; yo = years old
Table 4

*Provider Use of Antibiotics*

<table>
<thead>
<tr>
<th>Purpose (Author(s), year)</th>
<th>Design, Key Variables</th>
<th>Sample &amp; Setting</th>
<th>Measures</th>
<th>Results</th>
<th>Conclusions/ Limitations/ Appropriateness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigated abx prescribing in public and private practice in primary care (Ab Rahman et al., 2016)</td>
<td>Cross-sectional</td>
<td>Data from NMCS incl public and private clinics in 2014</td>
<td>Abx rx frequency, type and reason (dx) in public and private clinics</td>
<td>416 private clinics 16,415 pt encounters 15,119 total rx 5242 systemic abx rx 30.79% abx rx rate</td>
<td>Abxs are overused to tx self-limiting conditions, such as URTI, particularly in private practice. Such improper and excessive use of abx indicate the need to educate prescribers and consumers on antibiotic resistance. Limitations: only primary care was studied. No other specialties that commonly abx were included, such as dermatology. This study fits the purpose of the project as it demonstrates overuse of antibiotics by providers.</td>
</tr>
<tr>
<td>Investigated abx tx duration for acne by GP (Barbieri, Hoffstad, &amp; Margolis, 2016)</td>
<td>Retrospective cohort study</td>
<td>Data from HIND United Kingdom</td>
<td>Abx duration with or without topical retinoids</td>
<td>3 – 6 mos 27.7% 6 – 12 mos 16.7% 1-2 years 9.5% &gt;2 years 2.5%</td>
<td>GP prescribing practices deviates the current recommendations. Topical retinoids use and alternative therapy (i.e. hormonal therapy, isotretinoin) reduce antibiotic use/long-term and therefore resistance.</td>
</tr>
<tr>
<td>Purpose (Author(s), year)</td>
<td>Design, Key Variables</td>
<td>Sample &amp; Setting</td>
<td>Measures</td>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------</td>
<td>------------------</td>
<td>----------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Limitations: no acne severity described, BPO use or acne improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>This study fits the purpose of the project as it demonstrates overuse of antibiotics by providers</td>
<td></td>
</tr>
</tbody>
</table>

*Notes:* abx = antibiotic(s); dx = diagnosis; GP = general practitioner; HIND = Health Improvement Network Database; incl = included; NMCS = National Medical Care Survey; pt = patient; rx/rx’d = prescription(s)/prescribed; rcvd = received; Tx/Tx’d = treatment/treated; URTI = upper respiratory tract infections
APPENDIX B

AUTHOR GUIDELINES

The following journals will be considered: *Journal of Nurse Practitioners, The Nurse Practitioner Journal*, and *The Clinical Advisor*

The following are the submission requirements for the *Journal of Nurse Practitioners*:

1. **Abstract** - create a concise and factual abstract that does not exceed 100 words and that summarizes the article content. References should be avoided.

2. **Keywords** - list at least 5 words that best describe your article and would identify it through a standard search engine.

3. **Cover letter** - indicate who you are, a very brief summary of your article, and why you believe it would fit with *JNP*’s mission; also state that the manuscript has not been and will not be submitted elsewhere for publication.

4. **Conflict of interest statement** - submit a signed copy of the "Conflict of Interest" form that is found on the website as you move through the submission process. Use a separate form for you and each coauthor.

5. **Title page** - include title of the manuscript; name of authors in order in which they should appear; an affiliation, address, phone number, and e-mail address for each author; author byline; and funding sources. Please identify the corresponding author who will receive all correspondence. Student authors should indicate their anticipated date of graduation.
6 Word count - create a page that lists only the total number of words in the submission—not just the main text.

7 Blinded manuscript - make no reference to the geographic location, the institution at which the work or study was conducted, or any of the names or affiliations of the authors. Generic terms should be used instead (region, university, medical center, etc).

8 Tables and figures (if appropriate) - separately label and save each table and high-resolution figure file. Figure legends (number and explanation) should be included at the end of the blinded manuscript, not as part of the figure file. Identify sources for all tables and submit written permission to publish copyrighted tables or images that you wish to reprint or adapt.

The following are the writer’s guideline for *The Nurse Practitioner Journal*:

Manuscripts:

Double-space manuscripts, using 12-point type and 1-inch margins. Style should conform to *The Chicago Manual of Style*. Manuscripts are received with the understanding that they have not been previously published and are not currently under consideration for publication in any other journal. All manuscripts are subject to editing. The author assumes final responsibility for the content of the manuscript, including responding to author queries. Confine text to a maximum of 12 pages.

In addition to the title, include the full name, degrees, and hospital or university affiliation of each author on the title page. At the bottom of the title page, include the mailing address and the telephone and fax numbers of the author to whom
communications and proofs should be sent. The title page is page 1.

The abstract, not exceeding 100 words, should be factual and complete in itself so that the reader may quickly obtain the essence of the article. Avoid abbreviations and reference citations in the abstract. The abstract is page 2.

The text should be clear and concise, avoiding jargon. Spell out acronyms on first use. Use generic drug names and provide up to three examples of trademark drugs in parentheses following the generic name.

The following are the writer’s guidelines for *The Clinical Advisor*:

Share your knowledge and experience with your colleagues by submitting your article to Clinical Advisor. If we accept your submission, we'll be glad to work with you to develop your ideas into compelling narratives.

As for length, that depends on which kind of article you submit. Read the descriptions below to see which is right for you.

**CLINICAL FEATURES**

We update our readers with the latest information about conditions seen in everyday practice. Running no more than 4,000 words, features can be written either as regular narratives or as a series of questions and answers. Topics should be selected with the busy primary-care clinician in mind; specialists should review specialty topics from the primary-care point of view.

Articles should be accompanied by clinical photos. Charts, tables, and algorithms are also encouraged. References are necessary and may include books, articles and websites. In addition, include your curriculum vitae, which should list all current titles and affiliations.
APPENDIX C
MANUSCRIPT

Treating Persistent Acne in Adult Women in the Era of Antibiotic Resistance

Daniela M. Leslie, DNP, FNP-C
Beth Keely, PhD, RN,
Dana Rutledge, PhD, RN,

Southern California Doctor of Nursing Practice Consortium

Author Note

Daniela M. Leslie, DNP, FNP-C, General and Cosmetic Dermatology Nurse Practitioner, Dana Rutledge, PhD, RN California State University Fullerton Beth Keely, PhD, RN, California State University Long Beach

Correspondence concerning this article should be addressed to Daniela Leslie

E-mail: DLeslieNP@CSU.Fullerton.edu
DLeslieNP@gmail.com

Abstract
Most providers treat adult women with moderate to severe acne with oral antibiotics. Often a chronic condition, acne may require long-term management. Therefore, the potential for antibiotic resistance secondary to long term oral antibiotic use is a concern. Spironolactone (SPL), an anti-androgenic medication, is safe and effective in treating chronic acne without the risk of antibiotic resistance. Besides its safety in long-term use without the risk of antibiotic resistance, SPL can be a more cost effective alternative in the treatment of acne in adult women.

Treating persistent acne in adult women in the era of antibiotic resistance
Why is this important?

The Centers for Disease Control and Prevention (CDC) state that antibiotic resistance is a global threat. The leading culprit? Antibiotic use. It is estimated that per year, antibiotic-resistant bacteria affect 2 million people or more claiming at least 23,000 lives as a direct result.¹ This number does not include deaths from other conditions secondary to antibiotic-resistant infections. While antibiotics are frequently prescribed medications, they are misused almost 50% of the time.¹ Either patients who do not need antibiotics receive prescriptions, or when prescribed, antibiotics are not effective. Antibiotics are also unnecessarily used to promote growth in food animals such as cattle and chickens, which magnifies the resistance issue.¹ Agriculture (livestock, poultry) accounts for 79% of antibiotic exposure compared to 19% from human exposure.² Contrary to the US Food and Drug Administration (FDA) recommendations for cautious antibiotic use in agriculture, 29,000,000 tons of antibiotics are utilized to promote animal growth and reduce infections.² Since people who eat these animals also ingest antibiotic residues, antibiotic-resistant bacterial strains and antibiotic-resistant genes from consuming them, those consumers may become more susceptible to antibiotic-resistant infections.¹,²

Given current American Academy of Dermatology (AAD) guidelines,³ most US providers utilize oral antibiotics to treat adult women with moderate to severe acne. However, acne can be a chronic condition that requires long-term management.⁴ Therefore, the potential for antibiotic resistance secondary to long term oral antibiotic use is a concern.⁵

What is acne and its significance?
Acne vulgaris is a chronic inflammatory condition of the pilocelebaceous unit of the skin resulting in comedones (blackheads/whiteheads), papules, pustules, and nodules. This condition includes follicular plugging and microcomedone formation, bacteria Propionibacterium acnes (P. acnes), inflammation of skin structures, and excess sebum production. Acne severity is classified by the type and number of lesions and degree of scarring.

In the US, about 60 million people suffer from acne and more than half are women. Americans spend close to 1 billion dollars a year on prescription and over the counter acne products. While 85% of adolescents are affected, 12% of adult women continue to have acne up to their fourth decade and beyond. Although acne vulgaris (AV) is perceived as a condition of teenagers, office visits by patients in their twenties and beyond are not unusual. A subset of patients experiences persistent AV from adolescence throughout adulthood; some -- particularly women -- can develop new onset AV in adulthood. The majority of adult patients presenting with AV is women.

Late onset AV (20+ years old) occurs in 18.4% of women and 8.3% of men. While men show a higher prevalence of AV before the age of 16 years, women demonstrate a higher prevalence of AV after 23 years of age. Approximately 82% of adult women with persistent AV fail therapy with multiple courses of antibiotics and 32% relapse after treatment with one or more courses of isotretinoin.

Pathophysiology

The multifactorial pathogenesis of acne includes androgen-induced sebum production, follicular hyperkeratinization (follicular plugging), inflammation, and colonization by P. acnes in pilocelebaceous units. Follicular plugging from sebum leads to
comedone formation. *P. acnes* then colonizes in follicles, triggering the release of cytokines and resulting in inflammatory lesions such as papules and pustules.\textsuperscript{13} Despite not being a fatal disease, acne impacts patients with pain and scarring, and concurrently with depression and anxiety. Patients can suffer from low self-esteem, isolation, and suicidal ideation.\textsuperscript{8}

**Hormones and Acne**

In women, the sex hormones, dehydroepiandrosterone (DHEAS) and dihydrotestosterone (DHT), and the metabolic hormone insulin-like growth factor 1 (IGF-1) play a role in acne by increasing lesions. These hormones work synergistically; the influence of androgens depends upon the presence of IGF-1.\textsuperscript{14} Produced by adrenal glands and ovaries, androgens (testosterone, DHT, DHEAS) enlarge the sebaceous glands and increase sebum production. Also, androgens are produced by sebaceous glands themselves when type 1 5-alpha-reductase converts testosterone to DHT.\textsuperscript{14}

Androgens are a major factor in acne pathogenesis because they enhance follicular keratosis and influence sebum production. *P. acnes* thrives on sebum; therefore, acne development depends on the presence of sebum. Increased sebum production in acne patients may be due to increased circulating androgens or hyper-responsiveness of pilosebaceous units, or both.\textsuperscript{15} Persistent or severe acne may be the only clinical sign of androgen excess in women.\textsuperscript{4} Although androgens are involved in acne pathogenesis, endocrinologic evaluation is not necessary as most acne patients have normal hormone levels. Infrequent menses, hirsutism, androgenic alopecia, infertility, polycystic ovaries, clitoromegaly, and truncal obesity do require hormonal workup.\textsuperscript{3}

**What are the current practice guidelines?**
Three sets of current guidelines were evaluated, those of the AAD, South-East Asia Study Alliance (SASA) group, and the French multidisciplinary group. Each similarly addresses the treatment of moderate to severe acne in women. All three recommend acne grading and classification systems to help providers assess disease severity. Each also suggests strategies to determine appropriate treatment and allocate ways to document baseline status and subsequent clinical changes (e.g., improvement) during treatment. While there is no universally accepted grading system, the AAD classifies acne severity on number and type of lesions: mild to severe. The SASA group uses the AAD acne grading system. The French guidelines use a global acne severity scale that ranges from almost clear to very severe including clinical photography.

**Guideline Differences**

While similar, there are some points where the three guidelines differ. As an option for first line treatment, AAD recommends concurrent use of oral and topical antibiotics along with topical retinoid and benzoyl peroxide (BPO). Conversely, SASA states that topical and oral antibiotics should not be used concomitantly in order to prevent antibiotic resistance. The French group does not recommend topical antibiotics for moderate to severe acne. They recommend oral antibiotics – doxycycline or lymecycline; the latter is not available in the US. Further, they do not consider minocycline as an option since French health authorities retracted its use for acne due to its low safety profile. AAD recommends reevaluation of antibiotic response in 3-4 months to reduce bacterial resistance before trying a different oral antibiotic, adding or switching to hormonal therapy or starting on oral isotretinoin. SASA recommends reassessment after 6-8 weeks on oral antibiotics before switching to hormonal therapy or
starting on oral isotretinoin. The French guidelines recommend oral isotretinoin if oral antibiotics fail after 3 months of treatment.

The AAD supports the use of hormonal therapy in women as an alternative to first line treatment based on available evidence, provider experience, and expert opinion. On the other hand, SASA states that hormonal therapy can be used as first line of therapy for women with moderate acne in addition to topical medication (tretinoin and BPO). The French guidelines do not recommend use of combined oral contraceptives (COC) for acne unless birth control is required. They also do not mention SPL as an antiandrogen option, instead, recommending use of the antiandrogen/estrogen combination cyproterone/ethinylestradiol if birth control is required. Cyproterone, an antiandrogen used in the treatment of androgen dependent conditions such as acne, is not approved for use in the US but is recommended by the French combined with ethinylestradiol group for persistent acne unresponsive to dermatological treatment (topical or systemic antibiotics).

Although the AAD states that a system of grading and classifying acne, including the number, type and severity of acne lesions, guides providers in determining the best treatment options and monitoring progress, it does not recommend a specific one. SASA recommends the acne classification system developed by the AAD Acne Consensus Conference, which is based on the number and type of lesions present. The French guidelines utilize a detailed grading system based on type of lesion global assessment including extent of affected area of the face (i.e., more or less than half of the face or full face) as well as photographic documentation.

**Figure 1: Treatment recommendations**
Treatment Recommendations

Figure 1 refers to treatment recommendations based on all three guidelines. First line of treatment for moderate to severe acne is oral antibiotics, specifically tetracyclines except when contraindicated (i.e., pregnancy or allergy). Tetracyclines inhibit protein synthesis by binding the 30S subunit of the bacterial ribosome and have significant anti-
inflammatory properties. Antibiotics should be concurrently used with benzoyl peroxide (BPO) and retinoid. BPO is an antibacterial agent that kills *P. acnes* and has some comedolytic action. Further, adding BPO to topical or oral antibiotic regimen may enhance results while reducing the development of antibiotic resistance.³ If initial treatment is effective, patients are started on maintenance treatment with topical BPO and tretinoin. Since acne can be chronic, maintenance treatment can be long-term.³,⁵

As shown in the figure and recommended by AAD, “changing” oral antibiotic is done if the first line therapy does not work. For instance, if a patient is initially treated with doxycycline 100-200 mg per day without improvement, the provider may try minocycline 100-200 mg per day and determine if it yields a better response before considering oral isotretinoin. Another alternative for moderate inflammatory acne is sub-antimicrobial dosage of doxycycline (i.e., 40 mg daily).³ In the event of contraindication or intolerance to tetracycline, macrolides can be an option as they also possess some anti-inflammatory effects.³ Hormonal therapy, which consists of COC and/or spironolactone (SPL) may be added as well if the patient is willing to try it.

COCs contain an estrogen and progestin component; their effectiveness in acne treatment stems from their anti-androgenic properties. Specifically, they act by decreasing androgen production by the ovaries and increasing sex hormone-binding globulin, which then binds to free circulating testosterone disabling binding and activating androgen receptors.³ Providers should be prepared for cultural/religious or fear issues for women when recommending oral contraceptives. If a patient smokes, or has high blood pressure or a history of venous thromboembolic events, COCs are
contraindicated. Hormonal therapy may be used long-term for maintenance along with topical BPO and tretinoin.\textsuperscript{3,5}

**How are providers utilizing antibiotics?**

In 2010, a total of 258 million courses of oral antibiotics were prescribed in the US. Dermatologists contributed to 8.2 million of those prescriptions, making them the highest prescribers compared to other specialties.\textsuperscript{2} In the US, dermatologists write an average of 8 to 9 million antibiotic prescriptions a year, which is about 20% of all prescriptions by dermatologists. Up to 66.7% of antibiotic prescriptions are to treat acne.\textsuperscript{2} Clindamycin is the most common topical antibiotic prescribed by dermatologists, accounting for 25% of acne prescriptions. Tetracyclines, particularly doxycycline and minocycline, account for 75% of all oral antibiotics prescribed by dermatologists.\textsuperscript{2} Oral antibiotics may cost up to $1,500 per month.\textsuperscript{16}

Although seemingly high, these percentages are in alignment with conditions that are frequently seen and treated in dermatology (i.e., acne and rosacea). While acne, like rosacea, is an inflammatory and not an infectious condition, it requires longer courses of antibiotic treatment and consequently longer exposure to oral/topical antibiotics. This explains the high volume, frequency and length of antibiotic use in dermatology compared to other specialties and can further contribute to bacterial resistance.\textsuperscript{2}

In Europe, primary care providers write 80-90% of antibiotic prescriptions, primarily for respiratory tract infections. Since such infections tend to be viral and not bacterial, antibiotics are ineffective in treatment. This type of practice further contributes to the global issue of antibiotic resistance.\textsuperscript{17}
Antibiotic resistance and potential side effects: what is the evidence?

Antibiotic resistance is a global threat to humans. For instance, methicillin-resistant *Staphylococcus aureus* claims more lives annually in the US than emphysema, HIV/AIDS, Parkinson’s disease and homicide combined. Worldwide, 3.7% of newly diagnosed and 20% of previously treated cases of tuberculosis are believed to be caused by resistant strains to isoniazid and rifampicin. Historically, those medications were effective, but have become ineffective with new strains of infectious agents. Diseases linked to antibiotic resistance in primary care include tuberculosis, gonorrhea, typhoid fever and Group B streptococcus. The World Health Organization recommends that broad-spectrum antibiotics should be avoided when narrow-spectrum antibiotics are effective; this minimizes the risk of *Clostridium difficile* infection, MRSA, and resistant urinary tract infection.

The issue of resistance does not only affect individual patients; it affects the community and the world. Respiratory and urinary tract infections treated with antibiotics may result in individual resistance that may last up to 12 months after treatment completion. This means that a second line of antibiotics may be required along with those resistant organisms being passed on to others.

In the US, 20% of drug-related emergency room visits result from adverse effects of antibiotic prescriptions. Approximately 80% of such visits entail adverse or allergic reactions, with effects that range from gastrointestinal to neurologic and psychiatric disorders. Although most adverse reactions may be mild, some can be life-threatening such as hepatotoxicity secondary to amoxicillin and clavulanate.
Antibiotic resistance in acne

Linked to antibiotic use, incidence of *P. acnes* resistance increased from 20% in 1978 to 62% in 1996. Countries that restrict antibiotic use have low antibiotic resistance levels. Antibiotic treatment is not necessary for antibiotic resistance to take place. Resistant *P. acnes* exists on the skin on untreated individuals. This means that resistant *P. acnes* spreads from acne patients exposed to antibiotics to anyone in contact with them, which is strongly associated with antibiotic prescribing patterns. Topical clindamycin when used as monotherapy, can cause a significant proliferation of resistant *P. acnes* to over 1600% of baseline values by week 16. Concomitant use of BPO can counter this.

While topical antibiotics can cause antibiotic resistance confined to the skin of the treated area, oral antibiotics can lead to resistance to the intrinsic microbiome of the body. Those resistant organisms can spread to others and potentially cause infections.

Another important issue to consider is that while clindamycin and doxycycline are frequently used to treat acne, they also treat MRSA. MRSA causes illnesses such as skin and wound infections, pneumonia and bloodstream infections that can lead to sepsis and death. Consequently, the development of resistance to these antibiotics secondary to continuous use to treat acne, eventually can limit their efficacy and ability to treat potentially fatal infections.

Spironolactone and acne: how does it work?

Anti-acne hormonal therapy works by lowering circulating and local androgen levels and blocking their effects on the sebaceous glands. Spironolactone (SPL) is an androgen receptor blocker with anti-androgenic properties. SPL decreases steroid
production in adrenal and ovarian tissue. Additionally, SPL acts as an antiandrogen peripherally by blocking androgen receptors in the sebaceous glands. This action disallows testosterone and DHT from connecting to androgen receptors. As a result, sebum production is reduced. SPL is also a potassium-sparing diuretic; because hyperkalemia is uncommon in healthy adults with acne, unless cardiac or renal issues exist, altered serum potassium usually does not occur. Consequently, serum levels of potassium need not be checked in healthy adults.

Consistent evidence supports that SPL 50 to 100 mg taken daily demonstrates efficacy in the treatment of moderate to severe acne in adult women. The cost per month of SPL 50 mg and 100 mg, is $26 and $43 respectively. A long term (8-year) study found that SPL was not associated with serious side-effects; those that occurred in fewer than 30% of women were irregular menses, lightheadedness, and diuresis; side effects usually subsided as treatment progressed and generally did not cause patients to discontinue SPL. Incidence of side effects seemed to be dose dependent. Most side effects occurred in the first few months of treatment and generally did not cause patients to discontinue treatment. Further, SPL demonstrated effectiveness both alone and when used with oral antibiotics, topical antibiotics, or oral contraceptives. Limitations of studies were small sample sizes and all but one study lacked a control group.

**Managing acne: how to assess and treat it**

In order to treat acne appropriately, acne severity must be evaluated. In the AAD system which is used by SASA, acne severity is classified by the type and number of lesions (comedones, papules, pustules, nodules) and degree of scarring. Grade I, or
mild acne, consists of comedones and few inflammatory papules and pustules. Grade II, or moderate acne, presents with numerous comedones, few to many papules and pustules and few small nodules with marked inflammation. Grade III, or severe acne, shows numerous large painful inflamed nodules and pustules. Grade IV is severe acne with many large inflamed nodules and pustules along with scarring.\textsuperscript{6}

Mild acne can be treated with one or a combination of topical medications: retinoids (nightly application), BPO (once or twice daily), topical antibiotics up to 12 weeks (most commonly clindamycin – once or twice daily). See Figure 2. Moderate to severe acne is treated with oral doxycycline/minocycline (100 to 200 mg/day) up to 12 weeks along with topical BPO and retinoid. Hormonal therapy may be added and continued after completing antibiotic course. When unresponsive to treatment, severe acne may be managed with isotretinoin (0.5 to 1mg/kg/day) for about 24 weeks.\textsuperscript{3,5} See Figure 3.

Since relapse may occur after treatment discontinuation, maintenance beyond 12 weeks is important. Maintenance treatment consists of topical retinoid and BPO. Hormonal therapy may also be added and can be used long-term.\textsuperscript{3,5,24}
Figure 2: Mild Acne Treatment

Mild Acne
Comedones and few inflammatory papule and pustules

Treatment
Topical retinoids
Topical BPO
Topical retinoid + BPO

Maintenance
Topical retinoids + BPO
Figure 3: Moderate to Severe Acne Treatment

**Moderate to Severe Acne**
Numerous comedones, few to many papule and pustules and few small nodules with marked inflammation

**1st Line Treatment**
Oral antibiotics x 12 weeks
+ Benzoyl Peroxide
+ Retinoid

**2nd Line Treatment**
Consider change in oral antibiotic
or Add Combined Oral Contraceptive and/or SPL
or Consider oral isotretinoin

**Maintenance**
Retinoids
+ Benzoyl Peroxide
+/- Hormonal Therapy
Summary

Initial acne management involves assessments of types of lesions present as well as their severity. This drives the optimum course of treatment. Antibiotics are integral to treatment of a noninfectious dermatologic condition such as acne. However, prudent antibiotic prescribing is necessary to minimize antibiotic resistance. Treating acne as a condition that requires long term management points to use of alternatives to antibiotic treatment (i.e., hormonal therapy) in order to provide safe, cost effective, and ethical care.
References