Use of Antibiotic Therapy in Acne

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Disclosures

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Outline

• Antibiotic stewardship
• Evidence for resistance
• Guidelines for antibiotic use
• Maintenance
• Future
Antibiotic Stewardship\textsuperscript{1,2}

• This is to ensure that the patient gets the \textbf{right dose} of the \textbf{right antibiotic} at the \textbf{right time} and for the \textbf{right duration}

Antibiotic Stewardship in Dermatology

• Limiting antibiotics for acne
• **Monotherapy (topical or oral) is not recommended** due to better regimens being available
• Systemic antibiotics should be used for **limited duration** (3 months)
• **Benzoyl peroxide** should be used with topical antibiotics to ward off resistance

Dreno B, Thiboutot D, Gollnick H, Bettoli V, Kang S, Leyden JJ, Shalita A, Torres V.
• Eur J Dermatol. 2014 Apr. 11
Antibiotic resistance around the world

- *P. acnes* resistance has been studied around the world.
- USA, UK, Spain, Singapore, Sweden, Italy, Hong Kong
- India
- Reviewed in reference below


Other Specialties Experiencing Resistance

• *P. acnes* infections after orthopedic surgery
• Shoulder surgery
• Men more than Women
• Difficult to treat

What’s new with respect to resistance?

Hidradenitis Suppuritiva
Antibiotic Resistance in Hidradenitis Suppurativa (HS)

- A cross-sectional analysis
- 239 patients with HS seen at the Johns Hopkins Medical Institutions from 2010 through 2015.

Antibiotic Resistance in Hidradenitis Suppurativa (HS)

• Patients using **topical clindamycin** were more likely to grow clindamycin-resistant *Staphylococcus aureus* compared with patients using no antibiotics (63% vs 17%; P = .03).

• Patients taking **ciprofloxacin** were more likely to grow ciprofloxacin-resistant methicillin-resistant *S. aureus* compared with patients using no antibiotics (100% vs 10%; P = .045).

Antibiotic Resistance in Hidradenitis Suppurativa (HS)

• Patients taking trimethoprim/sulfamethoxazole were more likely to grow trimethoprim/sulfamethoxazole-resistant *Proteus* species compared with patients using no antibiotics (88% vs 0%; P < .001).

• No significant antimicrobial resistance was observed with tetracyclines or oral clindamycin resistance.
Antibiotic Resistance in Hidradenitis Suppurativa (HS) - Limitation

Data on disease characteristics and antimicrobial susceptibilities for certain bacteria were limited

Antibiotic Resistance in Hidradenitis Suppurativa (HS)

• Antibiotic therapy for HS treatment may be inducing antibiotic resistance.

• Support the importance of antibiotic stewardship.

What is the evidence of antibiotic resistance in acne?

How does the resistance affect treatment?

What is the Evidence?

• 5 clinical trials
• None were randomized
• 120,008 patients
What is the Evidence?

• The clinical efficacy of topical erythromycin has decreased from the 1972 to 2002, and this is attributed to antibiotic resistance\(^1\)

• Resistant *P. acnes* is found on the skin of untreated contacts of acne patients prescribed antibiotics\(^2\)

• Resistant strains of *P. acnes* are reported to cause severe infections\(^1\)

• After discontinuation of therapy, resistance may persist\(^1\)

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What is the Evidence?

• OFF TARGET EFFECTS

• Use of topical antibiotics is associated with resistance in *S. aureus* \(^3\)

• In a retrospective cohort of those treated with topical or oral antibiotics for at least 6 weeks, were more likely to develop upper respiratory infections during the one year follow up than those who did not receive antibiotics \(^4\)

• In a prospective cohort of university students who received oral antibiotics for acne, they were more than 3 times likely to report pharyngitis during the year follow up than untreated individuals \(^5\)

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3 Fanelli M, Kupperman E, et al. Arch Dermatol 2011;147(8);917-921.


How might you experience resistance?

- Slow responses
- Relapses
Guidelines of care for the management of acne vulgaris

Topical Antibiotics
Topical Antibiotics

- Topical antibiotics (eg, erythromycin and clindamycin) are effective acne treatments, but are **not recommended as monotherapy** because of the risk of bacterial resistance.
Topical Antibiotics

• Benzoyl peroxide or combinations with erythromycin or clindamycin are effective acne treatments and are recommended as monotherapy for mild acne, or in conjunction with a topical retinoid, or systemic antibiotic therapy for moderate to severe acne.
Topical Antibiotics

- Benzoyl peroxide is effective in the prevention of bacterial resistance and is recommended for patients on topical or systemic antibiotic therapy.
Benzoyl Peroxide

• NO REPORTED RESISTANCE TO BENZOYL PEROXIDE

• Prevents development of antibiotic- resistant *P. acnes* strains
• Treats non-inflammatory and inflammatory acne
• Mild anticomedolytic activity
• Can be a cleanser and leave-on product
Systemic Antibiotics
Systemic Antibiotics

- Systemic antibiotics are recommended in the management of moderate and severe acne, and forms of inflammatory acne that are resistant to topical treatments.
Systemic Antibiotics

• Doxycycline and minocycline are more effective than tetracycline, but neither is superior to each other
Systemic Antibiotics

• Although oral erythromycin and azithromycin can be effective in treating acne, its use should be limited to those who cannot use the tetracyclines (i.e., pregnant women or children under 8 years of age).
• Erythromycin use should be restricted due to its increased risk of bacterial resistance.
Systemic Antibiotics

• Use of systemic antibiotics, other than the tetracyclines and macrolides, is discouraged as there is limited data for their use in acne.

• Trimethoprim-sulfamethoxazole and trimethoprim use should be restricted to patients unable to tolerate tetracyclines or in treatment resistant patients.
Systemic Antibiotics

• Systemic antibiotic use should be limited to the shortest possible duration, **typically 3 months**, to minimize the development of bacterial resistance.

• **Monotherapy with systemic antibiotics is not recommended.**
Systemic Antibiotics

- **Concomitant topical therapy** with **benzoyl peroxide and/or a retinoid** should be used with systemic antibiotics, as well as for maintenance after completion of systemic antibiotic therapy.
Systemic Antibiotics

• Tetracyclines
• Macrolides
• Trimethoprim (with or without sulfamethoxazole)
Evidence supports the use of:

- Tetracycline
- Doxycycline
- Minocycline
- Trimethoprim/Sulfamethoxazole
- Trimethoprim
- Erythromycin
- Azithromycin
- Amoxicillin
- Cephalexin
Systemic Antibiotics

• Lipophilic antibiotic (tetracyclines [TCNs], macrolides, trimethoprim)
• TCN class – generally first line
• For Gram negative folliculitis (after treatment with antibiotics for months) consider gram negative coverage – rarer than we think
Routine Microbiologic Testing is Not Recommended

• **Routine microbiologic testing** is **NOT** recommended in the evaluation and management of patients with acne

• Those who exhibit acne-like lesions suggestive of Gram-negative folliculitis **MAY BENEFIT** from microbiologic testing
Efficacy and Safety with the first line medications

Doxycycline Versus Minocycline
Safety of Doxycycline and Minocycline: A Systematic Review

• Medline, EMBASE and Biosis databases 1996-2003

• MedWatch Adverse Events (AE)

• AEs very low for both drugs with fewer for doxycycline despite 3 fold greater number of prescriptions

• Immunological AEs are rare and seen with minocycline

• Smith and Leyden Clinical Therapeutics 2005; 27:1329-1342
Cochrane Review on Minocycline

• 39 Randomized controlled trials
• 6013 patients treated for acne

• Minocycline an effective treatment but no evidence of superiority versus other antibiotics

• Minocycline safe but associated with rare more serious side effects such as Drug induced Lupus (8.8 cases per 100,000 patient years)

• Garner et. Al. Cochrane Database of Systematic Reviews 2012
Comparison of the Tetracycline Class for Safety

- **French** Pharmacovigilance Database, literature
  - Minocycline Adverse Events more common and more serious than other tetracyclines

- Gastrointestinal disorders, particularly esophageal, predominated with doxycycline

- Autoimmune disorders, DRESS and other hypersensitivity reactions more frequent with minocycline
Minocycline controversy

Anything new with respect to oral antibiotics?

Which is better?
Which is better?

• A systematic search of MEDLINE was conducted to identify randomized controlled clinical trials, systematic reviews, and meta-analyses evaluating the efficacy of oral antibiotics for acne.

• 41 articles examined

Which is better?

• **Tetracyclines, macrolides, and trimethoprim/sulfamethoxazole** are effective and safe in the treatment of moderate to severe inflammatory acne.

• The **combination with a topical therapy** is superior to oral antibiotics alone.

• There is insufficient evidence to support one type, dose, or duration of oral antibiotic over another in terms of efficacy.

How can we limit antibiotics in daily practice..

• Maintenance
• Maintenance
• Maintenance
Maintenance Reminder

• Retinoids
• Benzoyl Peroxide
• Dapsone
Retinoid Maintenance
Adapalene

Retinoid Maintenance with Adapalene Gel 0.1% as Maintenance Therapy after Use with Doxycycline

Thiboutot et.al. Arch. Derm.2006;142:597-602
Retinoid Maintenance

Tazarotene 0.1% gel after Minocycline

- Leyden and Thiboutot, *Arch Dermatol*, 2006; 142(5), 605-612
Retinoid and Benzoyl Peroxide Maintenance

Adapalene and Benzoyl Peroxide after Doxycycline

Tan et al. J. Drugs Derm. 2012;11: 174-180
Dapsone maintenance

After Doxycycline, Dapsone 5% gel twice daily with Doxycycline 100mg

• Kircik LH. Use of Dapsone 5% Gel as Maintenance Treatment of Acne Vulgaris Following Completion of Oral Doxycycline and Dapsone 5% Gel Combination Treatment. J Drugs Dermatol. 2016 Feb 1;15(2):191-5.
What else can we use?
What else can we use?

- Niacinamide
- Azelaic Acid
- Light therapy
Niacinamide

• Topical Niacinamide¹
• Oral Niacinamide²
• Oral Niacinamide in combination with Azelaic Acid³


Niacinamide

• Yes it works in moderate inflammatory acne
• Efficacy comparable to clindamycin 1% gel

What’s the latest on how we are doing with respect to antibiotic usage?

• Systemic agents in the treatment of acne were evaluated in the United States between 2004 and 2013.

• The median duration of therapy with oral antibiotics was
• 126 days by dermatologists
• 129 days by nondermatologists
What’s the latest on how we are doing with respect to antibiotic usage?

• The number of courses of spironolactone increased from:
  • 2.08 to 8.13 for dermatologists
  • 1.43 to 4.09 for non-dermatologists

• The median duration of therapy with oral antibiotics was
  • 126 days by dermatologists
  • 129 days non-dermatologists

What’s the latest on how we are doing with respect to antibiotic usage?

• Conclusions
• Look for alternative therapies
  • Spironolactone
  • Oral contraceptives
  • Isotretinoin
• Represents an opportunity to improve the care of patients
Latest study to access resistance, the cheeks, the nose and the toes...

- Comparison to two previous studies accessing resistance in acne patients
- This one in Lincoln County, UK
- Others in Leeds County, UK and Philadelphia, PA, USA
- Areas accessed were the cheeks, nares, and toe webs
- Isotretinoin use resulted excellent improvement in acne as well as...
- Reductions in the number of P. acnes of the skin, including resistant isolates possibly acquired from previous treatment with antibiotics, on the cheek, but not the nares or the toe webs.

- Consider isotretinoin for treatment of patients with significant acne
What’s on the horizon?
What’s on the horizon?

- Phage therapy against *P. acnes*
- Bacteriophages are bacterial viruses that naturally control microbial populations
- Known phages that can work against *P. acnes*
- Need more knowledge
- May play a role in the future in the treatment of acne

“Exit plan”

• Envision and discuss with the patient from the beginning an anticipated “exit plan” to discontinue the antibiotics.

• This can always be modified, but it speaks to expectations.

SUPPORT!!

American Acne & Rosacea Society™
Thank You!