Patient Candidates for Spironolactone and When to Do a Hormonal Work-Up
Bethanee J. Schlosser, MD, PhD
bschloss@nm.org
Depts of Dermatology and OB/GYN
Northwestern University
Chicago, IL
03/02/2019

Strength of Evidence for Hormonal Therapy

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined oral contraceptives</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>B</td>
<td>II, III</td>
</tr>
<tr>
<td>Flutamide</td>
<td>C</td>
<td>III</td>
</tr>
</tbody>
</table>

A. I = Recommendation based on consistent and good-quality patient-oriented evidence
B. II = Recommendation based on inconsistent or limited quality patient-oriented evidence
C. III = Recommendation based on consensus, opinion, case studies or disease-oriented evidence

Recommenion Strength of Recommendation Level of Evidence

When Should Spironolactone Be Considered for the Treatment of Acne?

When to Consider Hormonal Therapy

- Hyperandrogenism
- Late-onset or persistent (>25yo)
- Prominence of acne at lower face, neck
- Perimenstrual flare
- Comedonal acne with seborrhea
- Resistant to “conventional” therapies
- Alternative to repeat isotretinoin

Hyperandrogenism: When to Suspect and How to Evaluate

Triggers for Endocrinologic Evaluation

- Hirsutism
- Androgenetic alopecia
- Virilization (clitoromegaly, deep voice, muscular habitus)
- Acanthosis nigricans
- Central/abdominal obesity
- Oligomenorrhea/amenorrhea
- Infertility
- Perimenstrual flare of acne
- Sudden onset, severe acne
- Acne recalcitrant to traditional therapy (isotretinoin)

Endocrinologic Evaluation

- Total testosterone
- Sex hormone binding globulin
- Free testosterone (calculated)
- Dehydroepiandrosterone sulfate (DHEAS)
- 17OH-progesterone
- Thyroid-stimulating hormone
- Prolactin
Evaluation for Hyperandrogenemia

- Total/free testosterone
  - Most sensitive for hyperandrogenemia
  - 2/3 ovarian, 1/3 adrenal
  - Mean [testosterone] F with acne > controls
- Dehydroepiandrosterone sulfate (DHEAS)
  - Marker of adrenal androgen production
  - Positive correlation between [DHEAS] and acne severity

Dehydroepiandrosterone (DHEA)
- Marker of adrenal androgen production
- Positive correlation between [DHEAS] and acne severity

Endocrinologic Evaluation

- Off all hormonal therapies for ≥ 4 weeks
- Obtain early in follicular phase (with onset of menses)
- Avoid mid-cycle evaluation
- Obtain early in morning (diurnal variation)

Acne in Adult Women

- 2895 women ages 10-70
- Photographs for acne, scars, dyschromia
- Sebum, pore size measurements

Overall Prevalence of Clinical Acne

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-30yo</td>
<td>45%</td>
</tr>
<tr>
<td>31-40yo</td>
<td>26%</td>
</tr>
<tr>
<td>41-50yo</td>
<td>12%</td>
</tr>
</tbody>
</table>

Clinical Profile of “Hormonal” Acne

- Acne that persists beyond 25yo
  - Change in morphology, distribution
- New onset acne ≥ 25yo
Clinical Profile of “Hormonal” Acne

- Acne that persists beyond 25yo
  - Change in morphology, distribution
- New onset acne ≥ 25yo
- Lower face, “U distribution” or “O” distribution

Clinical Profile of “Hormonal” Acne

- Acne that persists beyond 25yo
  - Change in morphology, distribution
- New onset acne ≥ 25yo
- Lower face, “U distribution” or “O” distribution
- Comedonal acne with seborrhea

Adult Female Acne: Hormonal Factors

- Shaw and White\(^1\)
  - Survey of 173 adult women with acne
  - 83% exacerbation with menses
  - 65% change in acne during pregnancy
- Collier et al\(^2\)
  - 225 premenopausal women
  - 62.2% + perimenstrual exacerbation
  - 10.5% postmenopausal women + benefits from systemic HRT

\(^1\) Shaw JC, White LE. Arch Dermatol 2001; 137: 1252.

Adult Female Acne: Hormonal Factors

- 18-44yo women with regular menses (n=40)
- Mild+ severity acne vulgaris
- No acne treatment
- Acne lesion counts
  - Late follicular phase (days 7-12)
  - Late luteal phase (days 22-28)

Lucky AW. Arch Dermatol 2004; 140: 423.

# Inflammatory lesions: + 25.3% (p 0.02)
# Comedonal lesions: +21.2 (p 0.05)
Resistant to “Conventional” Acne Therapies

Spironolactone for Acne

- 85 adult women → 73 evaluable
- 79% failed oral antibiotic
- 14% failed isotretinoin
- 50-100mg/day
- Mean duration = 10 mos


Adult Female Acne and Isotretinoin

- Retrospective review of 405 pts
- History of isotretinoin ≥ 150mg/kg total dose
- 72.1% female, 71.6% > 20yo, 80.9% relapse within 2 yr

Demographic

<table>
<thead>
<tr>
<th>Gender</th>
<th>Relapse Incidence</th>
<th>2nd Course of Isotretinoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>72/292 (24.6%)</td>
<td>24/72 (33.3%)</td>
</tr>
<tr>
<td>Males</td>
<td>22/113 (19.5%)</td>
<td>702 (31.8%)</td>
</tr>
<tr>
<td>Age &lt; 20yo</td>
<td>27/115 (33.9%)</td>
<td>437 (14.8%)</td>
</tr>
<tr>
<td>Age ≥ 20yo</td>
<td>67/290 (33.1%)</td>
<td>2787 (40.3%)</td>
</tr>
</tbody>
</table>

- Hormonal therapy was not part of regimen


Adult Female Acne and Isotretinoin

- Stainforth et al¹
  - 299 patients, followed 5 years post-isotretinoin
  - Risk factors: female > 25yo, persistent acne
- Coloe et al²
  - 102 patients, followed ≥ 1 year
  - 16 retrial of isotretinoin
  - Mean cumulative dose by weight (mg/kg): 268.69 vs 216.72 (p 0.009)
  - Isotretinoin retrial for F vs M: OR 4.109 (p 0.018)


Predicting Response to Spironolactone

- Retrospective review, 70 F ≥ 20yo with facial acne
- Spironolactone ≤ 150mg/day x 6 months
- Remission = ≤ 5 comedones, ≤ 2 inflammatory
- 56% prior isotretinoin; 75% prior OCP

Factor | OR (95% CI) | p value
---|------------|--------
High # inflammatory lesions at inclusion | 1.08 (1.03-1.13) | 0.001
Relapse with previous isotretinoin | 2.46 (1.69-5.54) | 0.03
OCP containing 1st or 2nd generation progestin | 2.77 (1.35-5.71) | 0.005

When to Consider Spironolactone Specifically

- Patients on combined OCP but inadequate control of acne
- Patients with contraindications to combined OCP
  - Patients with LAR hormonal contraceptive devices and acne
  - Patients on progestin-only oral contraceptive pill, nursing
- Patients with hypertension and acne (2 birds with 1 stone)
- Patients unable to take/access/afford other acne medications

Patients on Combined OCP but Inadequate Control of Acne


Moderate acne

20µg EE/3mg DSP (n= 266) vs placebo (n=268)

- % reduction greater for treatment group across all lesion types (p<0.0001)
- OR clear/almost clear = 4.31
- At least 3 cycles of use prior to judging efficacy

Inflammatory

Non-inflammatory

Total

Combined OCP Plus Spironolactone Treatment

- N= 27, 18-43yo, severe papular or nodulocystic acne
- 30µg EE/3mg DSP + 100mg spironolactone qday for 6 months
- 11% completely clear
- 74% >75% clearance
- 74.5% >25% clearance
- 7.4% no change
- No vaginal spotting, weight gain, irregular menses
- Serum K = 3.8-4.8mmol/L (mean 4.35)

WHO Combined OCP Use Eligibility

<table>
<thead>
<tr>
<th>CONTRAINDICATIONS</th>
<th>CAUTION OR SPECIAL MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Breastfeeding (6wk – 6mo postpartum)</td>
</tr>
<tr>
<td>Current breast cancer</td>
<td>Postpartum (&gt; 21 days)</td>
</tr>
<tr>
<td>Breastfeeding ≤ 6wk postpartum</td>
<td>Age ≥ 25 and light smoker (&lt; 15 cigarettes/day)</td>
</tr>
<tr>
<td>Age ≥ 35yr and heavy smoker (&gt; 15 cigarettes/day)</td>
<td>Previous hypertension (including pregnancy)</td>
</tr>
<tr>
<td>Hypertension (SBP ≥ 160, DBP ≥ 100)</td>
<td>Hypertension (SBP 140-159, DBP 90-99)</td>
</tr>
<tr>
<td>Diabetes with end-organ damage</td>
<td>Migraine w/o aura &lt; 35yr</td>
</tr>
<tr>
<td>Diabetes &gt; 20 years duration</td>
<td>Known hyperlipidemia should be assessed</td>
</tr>
<tr>
<td>Previous CVA</td>
<td>History of breast cancer ≥ 5 years of no disease</td>
</tr>
<tr>
<td>Migraine w/ focal neurologic sx, w/o aura ≥ 35yr</td>
<td>History of cerebrovascular disease</td>
</tr>
<tr>
<td>Current or previous DVT or PE</td>
<td>Mild compensated cirrhosis</td>
</tr>
<tr>
<td>Major surgery with prolonged immobilization</td>
<td>History of cholestasis related to OCP use</td>
</tr>
<tr>
<td>Active viral hepatitis</td>
<td>Concurrent drug use affecting liver enzymes</td>
</tr>
<tr>
<td>Severe decompensated cirrhosis</td>
<td>Liver tumor (benign or malignant)</td>
</tr>
</tbody>
</table>
**WHO Combined OCP Use Eligibility**

<table>
<thead>
<tr>
<th>NOT RECOMMENDED</th>
<th>CAUTION OR SPECIAL MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Breastfeeding (&lt;6mo postpartum)</td>
</tr>
<tr>
<td>Current breast cancer</td>
<td>Postpartum (&lt;31 days)</td>
</tr>
<tr>
<td>Breastfeeding &lt;6mo postpartum</td>
<td>Age ≥ 35 and light smoker (&lt;15 cigarettes/day)</td>
</tr>
<tr>
<td>Age ≥ 35yr and heavy smoker (≥15 cigarettes/day)</td>
<td>Previous hypertension (including pregnancy)</td>
</tr>
<tr>
<td>Hypertension (SBP ≥ 160, DBP ≥ 100)</td>
<td>Hypertension (SBP 140-159, DBP 90-99)</td>
</tr>
<tr>
<td>Diabetes with end-organ damage</td>
<td>Migraine w/o aura ≤ 35yr</td>
</tr>
<tr>
<td>Diabetes &gt;20 years duration</td>
<td>Known hyperlipidemia should be assessed</td>
</tr>
<tr>
<td>Previous CVA</td>
<td>History of breast cancer ≥5 years of no disease</td>
</tr>
<tr>
<td>Migraine w/ focal neurologic sx</td>
<td>History of cholostasis related to OCP use</td>
</tr>
<tr>
<td>Active viral hepatitis</td>
<td>Concurrent drug use affecting liver enzymes</td>
</tr>
<tr>
<td>Severe decompensated cirrhosis</td>
<td>Liver tumor (benign or malignant)</td>
</tr>
</tbody>
</table>

**Spironolactone and Thrombosis**

- Aldosterone is PROthrombotic\(^1\)
  - Arterial and venous thrombosis models
  - Endothelial dysfunction (↓ nitric oxide)
  - Fibrinolytic disorders (↑ PAI-1)
- Spironolactone improves this profile\(^1\)
  - Hepatic vein thrombosis, protein C deficiency\(^2\)
  - Portal vein thrombosis in HepB+ cirrhosis\(^3\)

\(^1\) AD Struthers, TM MacDonald. *Cardiov Res* 2004; 61: 663.


\(^3\) M Kumar et al. *Eur J Gastro Hepatol* 2011; 23: 617.

**Patients Unable to Take/Access/Afford Other Acne Medications**

- Spironolactone 50mg $0.89 per pill ($0.58)
- Doxycycline monohydrate 100mg $1.04 per pill ($1.04)
- Doxycycline hyclate 100mg $1.67 per pill ($1.55)
- Minocycline 100mg $3.18 per pill ($2.87)
- Isotretinoin 40mg $5.54 per pill ($5.54)

Data obtained from Pharmacychecker.com for zip code 60091 on March 1, 2019.

**Spironolactone: Contraindications**

- Renal insufficiency
- Hyperkalemia
  - ACEIs, ARBs, KCl, NSAIDs
- Pregnancy Category C
  - Feminization of male fetus
- Abnormal uterine bleeding (requires evaluation)
- **Banned substance for NCAA, Olympics, etc.**

Data obtained from Pharmacychecker.com for zip code 60091 on March 1, 2019.
Spironolactone: In My Clinical Practice

- Starting dose: 50mg to 100mg
  - Drospirenone 3mg = 25mg spironolactone
- Once daily dosing until 100mg po BID
  - BID dosing may minimize adverse effects
- Better bioavailability if taken with food
- Assess initial impact in 2 to 3 months
- Dose increase by 25mg or 50mg depending on response
- Once well-controlled for 6 months, consider taper

Conclusions

- Endocrinologic lab evaluation is indicated for females with signs of hyperandrogenism, irregular menses; could also be considered for recalcitrant acne.
- There are multiple groups of patients who may be excellent candidates for spironolactone.
- Spironolactone is a low-cost, effective systemic treatment option for acne.