Patient Candidates for Spironolactone and When to Do a Hormonal Work-Up

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Disclosure of Relationships with Industry
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F015: Practical Guidelines for Using Spironolactone
Patient Candidates and When to Do a Hormonal Work-Up

Elorac, Galderma: Investigator, Fees to Institution
Decision Support in Medicine, UpToDate®: Author, Honoraria
Allergan: Advisory Board, Speaker, Honoraria
Off-label use of medication will be discussed.

When Should Spironolactone Be Considered for the Treatment of Acne?


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
When to Consider Hormonal Therapy

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

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

Endocrinologic Evaluation

- Total testosterone
- Free testosterone
- Dehydroepiandrosterone sulfate (DHEAS)
- 17OH-progesterone
- Thyroid-stimulating hormone
- Prolactin

Evaluation for Hyperandrogenemia

- Total 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

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)

Clinical Features of “Hormonal” Acne

Clinical Profile of “Hormonal” Acne

- Acne that persists beyond 25yo
  – Change in morphology, distribution
- New onset acne ≥ 25yo

Acne in Adult Women

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

<table>
<thead>
<tr>
<th>Ages</th>
<th>Study</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-58</td>
<td>Clinical exam</td>
<td>21%</td>
</tr>
<tr>
<td>25-40</td>
<td>Survey</td>
<td>41%</td>
</tr>
<tr>
<td>&gt;23yo</td>
<td>F:M</td>
<td>&gt;23yo F:M</td>
</tr>
<tr>
<td>&gt;23yo</td>
<td>5% of woman 40-49yo</td>
<td>5%</td>
</tr>
</tbody>
</table>

Overall Prevalence of Clinical Acne

- 21-30yo 45%
- 31-40yo 26%
- 41-50yo 12%

Clinical Profile of “Hormonal” Acne

- Acne that persists beyond 25yo
  – Change in morphology, distribution
- New onset acne ≥ 25yo
- Lower face, “U distribution” predominance
- Comedonal acne with seborrhea
**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
- Perimenstrual flare

**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.

**Spironolactone for Acne**

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

Recurrent Acne Status-Post Isotretinoin

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 & Relapse Incidence (further medical tx) & 2nd Course of Isotretinoin

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Relapse Incidence</th>
<th>2nd Course of Isotretinoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>22/292 (7.5%)</td>
<td>24/77 (31.3%)</td>
</tr>
<tr>
<td>Males</td>
<td>22/113 (19.5%)</td>
<td>7/22 (31.8%)</td>
</tr>
<tr>
<td>Age &lt; 20yo</td>
<td>27/155 (17.4%)</td>
<td>4/27 (14.8%)</td>
</tr>
<tr>
<td>Age ≥ 20yo</td>
<td>67/290 (23.1%)</td>
<td>27/67 (40.3%)</td>
</tr>
</tbody>
</table>

- Hormonal therapy was not part of regimen

Adult Female Acne and Isotretinoin
- Stainforth et al\(^1\)
  - 299 patients, followed 5 years post-isotretinoin
  - Risk factors: female > 25yo, persistent acne
- Coloe et al\(^2\)
  - 102 patients, followed ≥ 1 year
  - 16 relapse of isotretinoin
  - Mean cumulative dose by weight (mg/kg): 268.69 vs 216.72 (p 0.009)
  - Isotretinoin relapse 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 = ≤ comedones, ≤ 2 inflammatory
- 56% prior isotretinoin; 75% prior OCP

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
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<tr>
<td>High # inflammatory lesions at inclusion</td>
<td>1.08 (1.03-1.13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Relapse with previous isotretinoin</td>
<td>2.46 (1.09-5.54)</td>
<td>0.03</td>
</tr>
<tr>
<td>OCP containing 1st or 2nd generation progestin</td>
<td>2.77 (1.35-5.71)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

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
**Combination 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**

- Pregnancy
  - Breastfeeding (breast-feeding or postpartum)
- Current breast cancer
  - Postpartum (< 21 days)
- Breastfeeding < 6wk postpartum
  - Age ≥ 35 and light smoker (< 15 cigarettes/day)
- Age ≥ 35y and heavy smoker (≥ 15 cigarettes/day)
  - Previous hypertension (including pregnancy)
- Hypertension (SBP ≥ 160, DBP ≥ 100)
  - Hypertension (SBP 140-159, DBP 90-99)
- Diabetes with end-organ damage
  - Migraine w/o aura < 35yr
- Diabetes ≥ 20 years duration
  - Known hyperlipidemia should be assessed
- Previous CVA
  - History of breast cancer ≥ 5 years of no disease
- Migraine w/ local neurologic sx, w/o aura if ≥ 35yr
  - Bilary tract disease
- Major surgery with prolonged immobilization
  - History of cholestasis related to OCP use
- Active von Willebrand's disease
  - Concurrent drug use affecting liver enzymes
- Severe decompensated cirrhosis
  - Liver tumor (benign or malignant)
- Liver tumor (benign or malignant)

**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

**Patients with Contraindications to Combined Oral Contraceptives**

- Pregnancy
- Breastfeeding
- Current breast cancer
- Postpartum (< 21 days)
- Breastfeeding < 6wk postpartum
- Age ≥ 35 and light smoker (< 15 cigarettes/day)
- Age ≥ 35y and heavy smoker (≥ 15 cigarettes/day)
- Previous hypertension (including pregnancy)
- Hypertension (SBP ≥ 160, DBP ≥ 100)
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- Liver tumor (benign or malignant)

**Spironolactone and Thrombosis**

- Aldosterone is PROthrombotic
  - Arterial and venous thrombosis models
  - Endothesial dysfunction (↓ nitric oxide)
  - Fibrinolytic disorders (↑ PAI-1)
- Spironolactone improves this profile
  - Hepatic vein thrombosis, protein C deficiency
  - Portal vein thrombosis in HepB+ cirrhosis
Patients Unable to Take/Access/Afford Other Acne Medications

Affordability of Systemic Acne Therapies

- Spironolactone 50mg $0.58 per pill
- Doxycycline hyclate 100mg $1.55 per pill
- Doxycycline monohydrate 100mg $1.04 per pill
- Minocycline 100mg $2.87 per pill
- Isotretinoin 40mg $5.54 per pill

Data obtained from Pharmacychecker.com for zipcode 60091 on February 16, 2018.

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.**

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.