Acne, HS and related disorders

AAD Orlando 2017
Louise Cunningham
Dermatology SpR MMUH
Acne
Pathophysiology

• ↑ P. acnes ribotypes 4 + 5 [Fitz-Gibbon et al. JID 2013]
  • Mutation in 16S gene that infers ↑ resistance to tetracyclines (Phylotype 1A)
  • Most acne pts with these strains no prior expo to tetracyclines
  • ↑ IL17 + IFNγ x 2- 3 in peripheral blood MNCs (vs ↑IL10 with other phylotypes a/w healthy skin)
    • Induction of Th1 + Th17 responses

• Therapeutic implications:
  ➢? Could use healthy strains in a topical probiotic formulation
  ➢?Vaccines
  ➢?Novel drugs targeting type-specific virulence factors

Courtesy of Diane Thiboutot
Acne + Diet

• Ulvestad et al. JEADV 2016
  • 2489 high school students (15) – dairy intake (milk, yoghurt; full fat/skim #glasses)
  • 2469 – subjective acne (18)
  • ♀ OR – 1.8 (total dairy); ♀+♂ OR 1.56 (high full fat); no association for skim/moderate intake

• LaRosa et al. JAAD 2016
  • 120 mod acne; 105 controls (14 – 19) [GAAS + BMI]
  • Random phone survey of 3 day dietary recall, 3 diff points in time
  • Nutrition research software package – dairy, GI + fat
  • Only intake low fat/skim a/w acne (p=0.01)

Courtesy of Diane Thiboutot MD
Genetics

• Is there a relationship between polymorphisms of IGF-1 gene and acne severity (in promoter region may directly influence expression of IGF-1)?

• ?Role → plasma IGF-1 levels + acne + severity [Rahaman et al JAAD 2016]

• Case control study: 80 pts acne + 80 gender- + age-matched
  • ↑ mean plasma IGF-1 levels (p=0.04)
  • Plasma IGF-1 ∝ acne severity (p=0.01)
  • HoZ for 192-bp polymorphism
    • OR - 4.29 acne
    • ↑ mean level IGF-1
    • OR - 3.08 ↑ acne severity

Courtesy of Diane Thiboutot
Topical therapies

- Multicentre dose-finding study – FMX-101 1% + 4%

- Co-primary end points (Wk 12) – Change in baseline lesion count and IGA score

- 150 subjects 1:1:1

- 139 incl in modified intention to treat analysis

- 0.5g face OD x 12 weeks
• Topical Dapsone
  • Am J Clin Derm Feb 2017

- 7.5% Gel OD
- 2 Phase 3 trials; 12 weeks
- ≥ 12 years
- ↓ Acne severity (GAAS) + ↓ Lesion count vs vehicle
- Well tolerated, Low A/Es
Spironolactone

• 25 – 100mg od
• +/- OCP
• Dose dependent A/E: Diuresis, Headache, dizziness, menstrual changes (80%), breast pain, fatigue
• ↑K+: Low usefulness for checking healthy young women
  • 974 healthy women 0.72% vs 0.76%
  • Check if older age, hx renal/cardiac disease, higher doses, co-admin other drugs

• Hypospadias or feminization of male fetus; can stop peri-conception
• Cancer risk not replicated in humans

Courtesy of Julie C Harper MD
Fitzpatrick IV – VI

- Topical retinoids first line
- ? Spironolactone > Abs
- Acne cosmetica, acne pomade (silicone-based hair products); bleaching creams, mechanical exacerbation (eg cocoa butter)

- PIH occurs in 2/3
  - Acne treatment should target both – “treatment failure”
  - Hydroquinone 4% oint prescribed concurrently

Susan C Taylor, MD, FAAD & Valerie D Callendar, MD, FAAD
Hypertrophic/Keloid Scarring

• Intralesional steroids:
  • 25 – 30g needle; 2 – 6 week intervals
  • Body – 30- 40mg/ml triamcinolone (avoid over dilution!)
  • 5 year ResR 50 – 100%; RecR 9 – 50%
  • Sessile/flat/broad
  • Retrograde injection/parallel tunneling for firm lesions
  • Papillary dermis – inhibit collagenase inhibitors

• +/- Use of lasers + cryotherapy (RemR 68-81% + RecR <2%)

Temitayo Ogunleye MD, FAAD
Excision

- Monotherapy – only earlobe
- Adjuvant therapies:
  - ILS (time of surgery + 2 – 4 weeks for min 2 mths +/- repeat every 1 – 2 mths)
  - And/or potent TCS BD x 6 mths
  - Radiotherapy – 1st 2 week post surgery (ResR 65 – 99%)
  - Topical imiquimod BD x 2/12

- Other tips/tricks:
  - Smallest incision possible
  - Monofilament suture
  - Minimize wound tension

Temitayo Ogunleye MD, FAAD
Compression

• Can ↓ RR X 30%

• Most effective if worn 24/7 x 4 - 6 mths

• Recommended level of pressure – 25mmHg

Temitayo Ogunleye MD, FAAD
Visible Results
in as little as 1 week with results improving over time

After 12 weeks

98%  Showed fewer breakouts

94%  Had smoother skin

90%  Showed a reduction in red, inflammatory acne

85%  Agree it is gentle on skin
Hidradenitis Suppurativa
The burden of HS disease

HS lesions
- Nodules and cysts
- Tunnels
- Pain
- Suppuration
- Scarring

Comorbidities

Psychological
- Anxiety
- Depression
- Impairment of QOL
- Sexual dysfunction

Metabolic
- Obesity
- Metabolic syndrome
- Atherosclerosis

Pathogenic factors for HS
- Hormones
- Microbiome
- Cigarettes
- Obesity
- Stress
- Genetics

Disease associations

Rheumatology
- Spondyloarthropathy
- Inflammatory arthritis
- SAPHO
- Pyoderma gangrenosum

Gastroenterology
- Inflammatory bowel disease
- Pilonidal sinus

Endocrinology
- PCOS

Hoffman et al., SCMS, 2017, submitted

Slides courtesy of M. Lowes MBBS, PhD
Proposed pathogenic model of HS

- Follicular occlusion
  - Cyst formation
- Recurrent acute inflammatory nodules
- Chronic cutaneous suppurative inflammation & tunnels
- Systemic inflammation

- Piloapocrine unit abnormalities
- Activation of cutaneous innate immune system
- Failure to turn off inflammation
- Recruitment of systemic immune system

Gammasecretase mutation
- Apocrine gland variation
  - "Missing" sweat proteins
- Infundibular anatomy & fn
- Risk factors for HS

Microbial activation
- Inflammosome activation
- Toll-like receptors (TLRs), AMPs
- Keratinocyte responses
- Cytokines: TNF, IL-1, IL-17

Biofilms in dermal tunnels
- Exhausted monocytes
- Lesional Th17 & Th1 (IFN-γ)
- Circulating Th17 & Th22 cells
- Loss of negative regulators

Acute phase reactants
- Immuno globulins
- Elevated cytokines
- Comorbid: obesity & stress
- Disease associations

IL-6?
• I – Axillary mammary
  • predom ♀; approx 50%
  • Not usually a/w other follicular subtypes

• II – Follicular type
  • ♀ + ♂; Fam Hx+
  • Cysts, comedones, acne, pilonidal sinus + folliculitis
  • 96% - breast + axilla; 50% chest/ears/back and/or legs

• III – Gluteal
  • Less likely to be obese or fam hx
  • Majority lack breast/ax involvement

• IV – Gamma secretase mutations (LOF)
  • Affects NOTCH signalling – epidermal cell + hair follicle diff, hair follicle + seb gland maintenance

Chris J Sayed, MD
Ultrasound In-Depth Characterization and Staging of Hidradenitis Suppurativa

XIMENA WORTSMAN, MD,* CLAUDIA MORENO, MD,† ROSAMY SOTO, MD,‡ JAVIER ARELLANO, MD,† CARLO PEZO, MD,† AND JACOBO WORTSMAN, MD†
TABLE 1. Sonographic Scoring of Hidradenitis Suppurativa (SOS-HS)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Single fluid collection and/or dermal changes* affecting a single body segment (either one side or bilateral), without fistulous tracts.</td>
</tr>
<tr>
<td>II</td>
<td>Two to four fluid collections and/or a single fistulous tract with dermal changes, affecting up to two body segments (either one side or bilateral).</td>
</tr>
<tr>
<td>III</td>
<td>Five or more fluid collections and/or two or more fistulous tracts with dermal changes, and/or involvement of three or more body segments (either one side or bilateral).</td>
</tr>
</tbody>
</table>

Extracted from Wortsman et al (11).

*Dermal changes include hypoechoic or anechoic pseudocystic nodules, widening of the hair follicles, and/or alterations in the dermal thickness or echogenicity.
239 patients with dx HS and had swabs for m/c/s
Patient characteristics and documentation of AB use at time of culture documented in **227 (54% on ABs)**
Use of multiple ABs in 21%
**Top clinda** – 63% had clinda-resistant SA (vs 17%)
**Oral cipro** – 100% had cipro-resistant MRSA (vs 10%)

- Oral TMP/SMX – 44% vs 13% grew proteus + 88% TMP/SMX-resistant proteus (vs 0%)
- No significant anti-microbial resistance patterns noted with use of tetracyclines or oral clindamycin
- ? More judicious use of ABs indicated
- Avoid use of cipro and TMP/SMX w/o specific indications
Prospective multi-centre study of triamcinolone 10mg/ml into inflamed lesions a/w HS flares

Volume injected depended on size of lesion and decided by treating clinician

Redness, odema + suppuration evaluated on 5 point scale; lesions also divided by size (>2cm excluded)

Daily VAS scores by patient

36 patient included (3 patients DNA follow-up and excluded)

Mean injection vol 0.75ml (0.2 – 2ml)
Table I.
Median, mode, and physician-assessed parameters at day 0 (preinjection) and at follow-up

<table>
<thead>
<tr>
<th>Physician-assessed parameters</th>
<th>Day 0</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness (mode)</td>
<td>2 (2)</td>
<td>1 (1)*</td>
</tr>
<tr>
<td>Suppuration (mode)</td>
<td>2 (2)</td>
<td>1 (1)*</td>
</tr>
<tr>
<td>Size (mode)</td>
<td>3 (3)</td>
<td>1 (1)*</td>
</tr>
<tr>
<td>Edema (mode)</td>
<td>2 (2)</td>
<td>1 (1)*</td>
</tr>
</tbody>
</table>

* $P = .001$. 

Fig 1.
Mean visual analog scale (VAS) scores and SD for days 0 through 7. *Days with a significant difference from the day before.
Adalimumab

• Adalimumab – no new safety concerns

• Consolidated improvement –
  • Disease waxes + wanes over long time in response to treatment
  • ↓ loss of efficacy compared to psoriasis

• Flares off treatment

• Licenced in paediatric cases
Experience with ustekinumab for the treatment of moderate to severe hidradenitis suppurativa.

Prospective open label uncontrolled design
17 patients; HS II/III
Treatment phase 28 weeks + 12 week f/u
mSS + DLQI + VAS + Skin-dex 29 Q
Post-hoc analysis using HiSCR
ITT analysis + LOCF

mSS ↓ x 50% in 35%
Week 40 – 8/17 (47%) achieved HiSCR 50
Moderate to marked improvement in primary outcomes in 82%
Limitations: high drop out rate; multiple outcome measurements
Need intensified dosing regimen
Other Systemic agents/Biologics

• Infliximab 7.5mg/kg q6weekly
• Infliximab is effective –
  • suboptimal scoring systems used
  • under powered
  • 5mg/kg every 8 weeks dosing

• Clinical trials → Apremilast, IL17 MAb, IL1αMAb
Personalized treatment in HS

Lifestyle treatments
(25% placebo responses in RCTs)

Measure serum cytokines
CRP, Hb

Personalized Treatment
Anti-TNF
Anti-IL-1
Anti-IL-23/12

Treat aggressively
to prevent progression

? Anti-IL-17
? Anti-IL-6
IL-6 predicts response in HS

- Prospective pilot study moderate-severe HS (n=13)
- Infliximab treatment 5mg/ml weeks 0, 2, 6, 14

Table II. Characteristics of nonresponding patients compared with responders at week 14

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonresponders, n = 4</th>
<th>Responders, n = 9</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>2/2 (50%)</td>
<td>2/7 (23%)</td>
<td>.53</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td>43 ± 14</td>
<td>33 ± 11</td>
<td>.20</td>
</tr>
<tr>
<td>DLQI</td>
<td>18 (11-30)</td>
<td>10 (4-20)</td>
<td>.14</td>
</tr>
<tr>
<td>VAS</td>
<td>80 (50-100)</td>
<td>30 (0-70)</td>
<td>.09</td>
</tr>
<tr>
<td>TNF-α</td>
<td>1.2 (0-8.9)</td>
<td>1.3 (0.7-3)</td>
<td>.70</td>
</tr>
<tr>
<td>IL-1/β</td>
<td>2 (1-4)</td>
<td>2 (1-3)</td>
<td>.77</td>
</tr>
<tr>
<td>IL-6</td>
<td>23 (6-367)</td>
<td>4 (1-7)</td>
<td>.0168</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>25.95 (7.3-31.1)</td>
<td>15.00 (7.7-17.7)</td>
<td>.0112</td>
</tr>
<tr>
<td>IFX trough level</td>
<td>8.245 (0.063-16)</td>
<td>6.042 (5.2-17.2)</td>
<td>.844</td>
</tr>
<tr>
<td>Antibodies against IFX</td>
<td>1/4 (25%)</td>
<td>0/9 (0%)</td>
<td>.31</td>
</tr>
</tbody>
</table>

- Low baseline IL-6 was predictive of clinical response
- Correlation between CRP and IL-6 (r=0.79, p=0.005)

Montaudie et al, JAAD, 2016
Surgical Management

- I&D
- Cyrosurgery
- Cryo-canulation
- Destructive: Electrosurgical, Laser/Nd-Yag
- Excision w/ or w/o repair
  - ↓ recurrences w/ 2º IH
- Unroofing
  - ↓ recurrence
  - Good comfort + healing
  - STEEP technique (RecRs not defined)
- CO2 Laser excision + marsupialization
Pyoderma Gangrenosum
• PG + Levamisole
  • 8 patient series [Jeong et al JAAD 2016]
  • 100% had at least 1 APL AB
  • 87.5% P-ANCA+
  • Rx with cocaine abstinence + wound care

• Extra-cutaneous PG
  • Rare; skin lesions first
  • Lung most common < 40 cases
    • Variety of presentations
  • Liver, bone, spleen, airway
STOP GAP trial

- Two-arm, observer-blind, parallel-group, RCT comparing CycA (4mg/kg/d) vs pred (0.75mg/kg/day) [Omerod et al BMJ 2015]

- 112 pts in 39 centers over 4 years

- 1\textsuperscript{st} outcome: velocity of healing at 6 wks

- No statistical difference in outcomes

- More serious AE in prednisolone group
Anti-IL1 therapy

• Canakinumab: selective anti-IL-1b AB  [Kolios et al BJD 2015]
  • 5 adult pts w/ steroid-resistant PG
  • 150mg SC wk 0, optional 2\textsuperscript{nd} dose wk 2, wk 8
  • 4/5 pts with PG responded (↓ target lesion size, DLQI + PGA)
  • 3/5 CR at wk 16

• Anakinra: IL-1RA
  • Reports of use in PG and Sweet’s
  • Beware of pathergy!!
Other options

• Topical dapsone
  • Reports in peristomal PG

• Timolol gel + collagenase oint
  • Case reports
  • Timolol (β2-AR antag) – enhanced keratinocyte migration + promotion of wound healing + ?↓ neutrophil recruitment
  • Collagenase oint – MPs Collagenase I + II → enzymatic debridement to enhance wound healing

• VAC dressing/NPWTx
  • No controlled trials
  • May cause pathergy
  • Consider use in non-inflammatory stable PG wounds
  • Frequent monitoring advised
  • +/- STSG
  • Recommend pretreat with CS, dapsone, infliximab, pentoxyphylline [Pichler et al JEADV Feb 17]
  • Lower setting