Recent Advances in the Treatment of Pediatric Skin Conditions

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Overview
- Update on management of infantile hemangiomas
- Atopic dermatitis: highlights from the guidelines, the importance of maintenance, and new medications in the pipeline
- Molluscum!

UPDATE ON THE PROPRANOLOL REVOLUTION

Propranolol for infantile hemangiomas: game changer
- Consistent, rapid therapeutic effect
  - Improvement in nearly all patients in large series
  - Significant benefit (volume, elevation, redness) demonstrated in randomized controlled studies
- Can shorten the course of involution
  - Improvement described in patients 18 months to 5+ years of age
  - Effectiveness beyond the proliferative phase not observed for other IH treatments

Sans et al Pediatrics 2009
Manunza et al Br J Derm 2010
Hogeling et al Pediatrics 2011

Indications for propranolol treatment of IH
- Severe/recalcitrant ulceration
- Threatened vital functions
  - Vision
  - Airway
- Risk of permanent disfigurement
  - Large, rapidly growing lesions, esp. on face
  - High-risk sites, e.g. nasal tip, columna, or crossing vermilion border of lip

Systematic Review of Propranolol for IH
- 41 studies, 1,264 patients
- Propranolol therapy
  - Initiated at mean age of 6.6 months (range, 3 days–10 y)
  - Mean 2.1 mg/kg/day dose x mean of 6.4 months
  - 96% response rate
  - 17% with rebound upon d/c, esp. if at age <1 y
- Adverse effects
  - Sleep changes (11%), respiratory symptoms (3%)
  - <0.5% symptomatic hypotension, bradycardia, or hypoglycemia
  - Recent case-control study: no developmental or growth impairment in 4-year-olds (n=82) treated as infants with propranolol x >6 months

Marqueling et al Pedi Derm 2013
Moyakine et al JAAD 2016
**Initial RCT of propranolol for IH**

- 40 children, ages 9 wk–4 y (median 10 mo)
- Propranolol 2 mg/kg/d vs placebo x 6 mo

**International RCT of propranolol for IH**

- 456 patients, ages 1-5 months (proliferative phase)
- Propranolol 1 or 3 mg/kg/d x 3 or 6 mo vs placebo
- Improvement after 5 weeks in:
  - 88% with 3 mg/kg propranolol
  - 5% with placebo (p<.001)
- Complete or nearly complete resolution in:
  - 60% with 3 mg/kg/day x 6 mos
  - 38% with 1 mg/kg/day x 6 mos
  - 4% with placebo (p<.001)
- Overall tolerated well
  - No dose-dependence except for bronchial hyperreactivity and diarrhea

**FDA-approved pediatric formulation of propranolol for IH**

- FDA approval in March 2014
- 4.28 mg/mL solution (vs 4 mg/mL ‘standard’ propranolol)
  - Alcohol- and paraben-free; contains saccharin
- Initiation of treatment at age 5 weeks (gestationally corrected) to 5 months
  - vs prior consensus recs for inpatient initiation (with more rapid dose escalation) if <8 weeks age or comorbidities
- Contraindications include:
  - Corrected age <5 weeks or weight <2 kg
  - Asthma or history of bronchospasm
  - HR <80 bpm, BP <50/30, >1st degree heart block, decompensated heart failure

**Propranolol for IH: counseling for parents**

- Preventing hypoglycemia
  - Feed during or shortly after administration
  - Hold medication if vomiting or decreased oral intake
- Educate re: signs of potential side effects
  - Hypoglycemia:
    - early: sweating, shakiness, fussiness, irregular/fast HR
    - late: poor feeding, lethargy, low body temperature, seizures, loss of consciousness
  - Hypotension: bradycardia, cold or pale/blue/purple extremities, lethargy

*May be masked with β-blockade*
What is done in practice?

- **Propranolol in the Treatment of Complicated Hemangiomas (PITCH) taskforce**
  - 1096 patients from 39 centers in 8 European countries, 2013-14
  - Mean age at initiation = 4 months (range, <1 month to 7 years)
  - 93% focal, 6% segmental, 1% multifocal

- **Baseline cardiac evaluation**
  - ECG in 89%
  - Echocardiography in 68%
  - Cardiologist consult in 55%

PITCH study cont.

- **Dosing**
  - Started at 1 mg/kg/d in 47%, <1 mg/kg/d in 19%, 2 mg/kg/d in 26%
  - Target 2 mg/kg/d in 86%, <2 mg/kg/d in 5%, >2 mg/kg/d in 11%

- **Treatment course**
  - Mean duration, 8 months; median age at d/c = 13 months
  - Rebound growth in 15% of focal, 32% of segmental (despite longer mean course)

- **Adverse events**
  - Most often sleep disturbance (8%), cold extremities (5%), wheezing (3%), diarrhea (2%)
  - Infrequent symptomatic hypotension (1.5%) or hypoglycemia (0.7%)
  - No difference in frequency with or without baseline evaluation
  - 2.4-fold increased risk if >2 mg/kg/d; 50% decreased risk if started on lower dose than target

Propranolol for PHACE patients

- **Retrospective series of 32 PHACE patients treated with propranolol**
  - 1 with onset of mild hemiparesis
  - 3 with worsening ulceration/tissue necrosis

- **7 patients at ‘high risk for stroke’**
  - MRI showing severe narrowing/nonvisualization of major cerebral/cervical arteries without collaterals, ± cardiovascular anomalies

- **Caution if vascular compromise**
  - Neurology, neuroradiology, & cardiology consultation
  - Slower dose escalation, more monitoring

Propranolol for IH: how long?

- **Typically treat for 6−12+ months**
  - Longer if younger at initiation (e.g. until age 9-15+ mo)

- **At end of treatment, taper over ≥2 weeks**

- **Recurrences can occur, esp. if d/c at <9-12 mo age**
  - Onset days to months after cessation
  - More common if deep component and/or segmental, female

- **LUMBAR syndrome**
  - Lower body hemangioma (large/segmental/ulcerated), lipomas and other cutaneous anomalies (eg ‘tags’)
  - Urogenital anomalies
  - Myelopathy (spinal dysraphism)
  - Bone deformities (eg limb underdevelopment)
  - Neurocutaneous malformations and renal anomalies
  - Renal anomalies

- **Evaluation**
  - Ultrasound of abdomen, pelvis & (if <3 mos/lumbar) spine
  - MRI of spine if midline lumbar hemangioma or lipoma
  - MRA/MRV if extensive limb involvement

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Topical β-blockers for hemangiomas

- Topical timolol 0.5% gel-forming solution
  - Benefit described for superficial hemangiomas, especially on eyelids
- Potential for systemic effects, esp. if used on mucosa or ulcerated skin
  - If 100% absorbed, 1 drop ~ equivalent to ~4 mg oral propranolol
  - 1 drop (0.05 ml) of timolol 0.5% = 0.25 mg
  - Timolol dose should be <0.25 mg/kg/day
- Use caution if premature/postmenstrual age <44 weeks or weight <2500 g
  - Symptomatic bradycardia reported

Topical timolol for superficial IH

- 0.5% ophthalmologic solution BID

Topical timolol for superficial IH

- Retrospective, nonrandomized, single-blind study
- Non-vision-threatening periocular IH; mean age ~4 mo
- After 2-mo study period, >50% improvement in:
  - 8/13 (62%) pts tx with timolol 0.25% gel BID
  - 0/10 (0%) pts who were observed (p=.001)

Topical timolol for superficial IH

- Randomized controlled trial
  - n = 41, mean age 2.1 months (range, 1-6 months)
  - 0.5% ophthalmologic gel vs placebo, 1 drop BID
  - Treatment group vs placebo
    - Greater reduction in volume by 8-16 weeks, especially if baseline <100 mm³ (p <.003)
    - 47% vs 6% with no redness by 24 weeks (p <.003)
    - No sig differences in BP, HR

ATOPIC DERMATITIS: THE IMPORTANCE OF MAINTENANCE

AAD guidelines on topical therapies for AD: summary of A/I recommendations

- Use of moisturizers
- Use of topical corticosteroids
  - Including proactively for maintenance
- Use of topical calcineurin inhibitors
  - Including as steroid-sparing agents, proactively for maintenance, and off-label in children <2 years of age
- Do not routinely use topical antistaphylococcal antibiotics*
  - Don’t help
  - Can lead to allergic contact dermatitis, bacterial resistance

*Exception of bleach baths + intranasal mupirocin
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  - Including proactively for maintenance
- Use of topical calcineurin inhibitors
  - Including as steroid-sparing agents, proactively for maintenance, and off-label in children <2 years of age
- Do not routinely use oral nonsedating antihistamines in the absence of other conditions such as urticaria or allergic rhinoconjunctivitis

Eichenfield et al. JAAD 2014
Sidbury et al. JAAD 2014

Proactive maintenance therapy

- If frequent, repeated outbreaks in the same areas
- Apply to the usual sites of AD when clear
  - Mid-potency topical corticosteroid (e.g. fluticasone) 1-2 days/week (e.g. Sundays + Thursdays)
  - Topical calcineurin inhibitor (TCI) 2-3 days/week
  - Topical corticosteroid/TCI rotational therapy

Nakahara T et al. J Dermatol 2004
Kubota et al. JAAD 2009
Thaci et al. JEADV 2010
Bangert et al. Dermatology 2011

New evidence supporting proactive maintenance in AD

- Residual subclinical inflammation is present at previous sites
  - Histologic evidence of epidermal barrier dysfunction, lymphocytic infiltration, and proinflammatory cytokine milieu
- Proactive maintenance upon ‘induction of remission’ reduces rates of flares, increases time to first relapse and number of flare-free days
  - Strength A, level of evidence I
- Pooled relative risks of flares in metaanalysis
  - With fluticasone 2 days/week: 0.46 [95% CI, .38-.55]
  - With tacrolimus 2-3 days/week: 0.78 [95% CI, .60-1.00]
- Twice weekly fluticasone for up to 40 weeks had no skin side effects, no adrenal suppression in two 16-week trials

Sidbury et al. JAAD 2014

TCI phobia: safety conclusions

- Systemic exposure is minimal regardless of age, extent/severity of dermatitis and duration of treatment
  - Rare exception in patients with Netherton syndrome
- No evidence of systemic immunosuppression
  - Normal DTH & response to vaccinations
  - No increase in systemic infections
  - Decreased S. aureus colonization and no consistent increases in viral skin infections
- No evidence of an increased risk for malignancy in children
  - Association with/confusion between AD & CTCL (primarily in adults)

Siegfried et al. BMC Ped 2016
Eichenfield et al. JAAD 2014
Legendre et al. JAAD 2015
Sigurgeirsson et al. Pediatrics 2015

TCIs in infants

- AAD recommendation for off-label use of pimecrolimus and tacrolimus 0.03% in children <2 years of age, including infants
  - Strength A, level of evidence I
- Multiple clinical trials in this age group demonstrate safety and efficacy, including recent 5-year RCT in >2400 infants 3-11 months of age

Lugge et al. Ped All Immunol 2015
Eichenfield et al. JAAD 2014
Can moisturizers prevent AD?

- Randomized controlled trials in neonates with a parent/sib with AD/atopy
- Oil, cream/gel or ointment moisturizer applied daily to entire body (total n=124) → 50% relative risk reduction vs moisturizer-free controls at 6 months (p=0.017)
- Emulsion-type moisturizer applied daily (total n=118) → 32% risk reduction vs controls at 32 weeks (p=0.012)

Simpson et al J All Clin Immunol 2014
Horimukai et al J All Clin Immunol 2014

Dupilumab for atopic dermatitis

- Human monoclonal Ab against IL-4 receptor α subunit
  - Blocks IL-4 and IL-13 signaling important to Th2-mediated inflammation
- RCT in 109 adults with moderate-severe AD
  - EASI decrease of 50% & 75% after 12 weeks:
    - Dupilumab 85% & 60%
    - Placebo 35% & 15% (p <0.001)
  - Adverse events similar with drug and placebo; mild-moderate nasopharyngitis, headache
  - More skin infections with placebo (24%) than drug (5%)


Crisaborole ointment for AD

- Inhibitor of phosphodiesterase 4 (PDE4)
  - PDE4 degrades cAMP and leads to cytokine release
- RCT in 1522 patients (age ≥2 y) with mild-moderate AD, applied BID x 4 weeks
  - Clear/almost clear with ≥2-grade improvement:
    - Crisaborole 31-33%
    - Vehicle control 18-25% (p <0.04-0.001)

Paller et al JAAD 2016

Topical tofacitinib for AD

- Janus kinase (JAK) inhibitor
  - Blocks JAK-STAT pathway of cytokine signaling, including IL-4
- RCT in 69 adults with mild-moderate AD, applied BID x 4 weeks
  - Clear/almost clear with ≥2-grade improvement:
    - Tofacitinib 68%
    - Vehicle control 13% (p <0.001)

Bissonnette et al Br J Derm 2016

Update on molluscum & its treatment

- Epidemiology
  - Affects ~15-20% of children by 10-15 years of age
- Natural history
  - Mean duration ~12 months (range, several months to 4 years)
  - 30% last >18 months, ~15% last >2 years
- Imiquimod for molluscum?
  - 2 large, industry-sponsored, unpublished "failed" randomized controlled trials in 2006 showed lack of efficacy

Update on molluscum treatment: cantharidin

- Used by >90% of pediatric dermatologists
- Retrospective study of 405 children treated with cantharidin
  - Almost 10,000 lesions over >1000 visits
  - 86% of parents were satisfied and/or would use again
  - Pain in 7%, significant blistering in 2.9%
- Small prospective randomized controlled study
  - 29 children randomized to receive cantharidin vs placebo
  - Application Q1-2 weeks, max 5 visits over 4-11 weeks
  - Complete clearance in 2 of 13 vs 1 of 16 children
  - Critique:
    - Underpowered
    - Short interval – usually Q3-8 weeks, 2-3+ treatments
    - Placebo group had longer duration of MC, fewer patients with dry skin

Retrospective study of 405 children treated with cantharidin

- Mean age 5.5 y (range, 7 mos-17 y)
- Atopic dermatitis (in 37%) assoc. with higher # of MC lesions
- Molluscum dermatitis in 39%
  - 51% if AD vs 32% if no AD
  - # of MC lesions ↑ over next 3 months in 33% not treated vs 23% treated with topical steroid, vs 18% if no dermatitis
- Inflamed MC lesions in 22%
  - Often mimicked furunculosis or cellulitis
  - # of MC lesions ↑ over next 3 months in 5%, vs 18% if no inflamed lesions (p < .03)

Molluscum: ‘the bump that rashes’

- Retrospective study of 696 patients with molluscum
  - Mean age 5.5 y (range, 7 mos-17 y)
  - Atopic dermatitis (in 37%) assoc. with higher # of MC lesions
- Molluscum dermatitis in 39%
  - 51% if AD vs 32% if no AD
  - # of MC lesions ↑ over next 3 months in 33% not treated vs 23% treated with topical steroid, vs 18% if no dermatitis
- Inflamed MC lesions in 22%
  - Often mimicked furunculosis or cellulitis
  - # of MC lesions ↑ over next 3 months in 5%, vs 18% if no inflamed lesions (p < .03)

Coloet al Ped Derm 2009; Dosal et al Ped Derm 2014; Moye et al Ped Derm 2014; Osier & Eichenfield Ped Derm 2015

Gianotti-Crosti syndrome-like/"id" reaction to molluscum

- 34 patients (5%) in our series
- Pruritic eruption of monomorphous, erythematous papules/papulovesicles separate from MC lesions
  - Extensor arms & legs (94%) > face, trunk
  - Occasionally initially unilateral on trunk, like unilateral laterothoracic exanthem
  - Responded to mid potency topical CS
- Associated with inflamed MC in 65%
- Often heralded resolution of MC
  - Median duration ≤5 weeks after onset

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'BOTE' sign: a helpful acronym

- Beginning
- Of
- The
- End

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Butala et al Pediatrics 2013

Butala et al Pediatrics 2013