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# Treatment of Acne & Rosacea: My Preference

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# Conflict of Interest



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# 肺風粉刺、風刺、面上黑子、面瘡、面皰、婦人 麵粉皰、面瘡、痤瘡

- 內經《素問·生氣通天論》：「汗出見濕，乃生痤癬」，  
「勞汗當風，寒薄為皰，鬱乃痤」
- 隋朝巢元方《諸病源候論》面皰候「面皰者，謂面上有風熱氣生皰，頭如米大，亦如穀大，白色者是也。養生方云：醉不可露臥，令人面發瘡皰。又云：飲酒熱未解，以冷水洗面，令人面發瘡，輕者皰皰。」
- 明朝《普濟方》面粉皰「夫面皰者。是粉刺也。面上有皰如米粒。此由膚腠受於風邪。搏於津脈之氣。因虛而作。亦雲敷之胡散入虛肌。使之然也。」
- 明朝陳實功《外科正宗·肺風粉刺酒渣鼻》「肺風、粉刺、酒皰鼻，三名同種」、「肺風屬肺熱，粉刺、酒渣鼻、酒刺屬脾經，此四名同類，皆由血熱鬱滯不散。又有好飲者，胃中糟粕之味，薰蒸肺臟而成。」
- 清朝乾隆《御纂醫宗金鑒》 肺風粉刺

# Treatment of Acne in Traditional Chinese Medicine

## Systemic

- 枇杷清肺飲、枇杷葉丸、黃芩清肺飲、防風散、清上防風湯、加味瀉心湯…
- 加味逍遙散、荊芥連翹湯、十味敗毒散…

## Topical

- 顛倒散…

## Discussion

- D.D. Acne, rosacea, folliculitis/furuncle/carbuncle, granulomas

# Acne Pathogenesis

- Acne is a human disease
- Cardinal factors
  - Comedogenesis
  - Seborrhoea
  - *Propionibacterium acnes*
  - Inflammation
- Is acne primarily an infectious or inflammatory disease?
- Histology: Acne begins with comedone

# Treatment of Acne: Strategy

- Patients

- Age
- Gender
- Acne pattern and severity
- Wishes & Expectations

- Medication

- Efficacy
- Side effects
- Resistance
- Costs

- Physician

- Profit

# Treatment Failure of Acne

- Compliance and adherence of patients
  - Expectation
  - Impatience
  - Peer pressure and commercials
- Explanation and reassurance of physicians

# Treatment of Acne Comedonica

- Topical treatment

- Tretinoin Cream, 0.025%, 0.05%, and 0.1%
- Adapalene 1%/Benzoyl peroxide 2.5%
- Adapalene 1%
- $\geq 12$  weeks
- Mostly unacceptable for women
- Intensive skin care with moisturizers

- Systemic treatment

- Oral Isotretinoin, 0.1-0.3 mg/kg body weight



# Treatment of Acne Papulopustulosa

Topical treatment: No antibiotic monotherapy

- Facial cleansing: Benzoyl peroxide 4% emulsion
- Triclosan 1-2% does not work
- Combination with different active ingredients
  - Clindamycin 1%/Benzoyl peroxide 5%
  - Clindamycin 1%/Tretinoin 0.025%
  - Clindamycin 1% + Benzoyl peroxide 10%
  - Adapalene 1% ± Benzoyl peroxide 2.5%
  - Isotretinoin 0.05%/Erythromycin 2%
  - Erythromycin 4%/Zinc 1.2%
  - Erythromycin 3%/Benzoyl peroxide 5%
  - Metronidazole 1%/2%
  - Azelaic acid 15-20%
  - Erythromycin 2%/4%?
  - Dapsone 7.5% gel?

# Treatment of Acne Papulopustulosa

## Systemic treatment (combined with topical non-antibiotics)

- Antibiotics
  - Doxycycline 100-200 mg/D
  - Minocycline 50-100 mg/D
  - Azithromycin 250 mg/D (or 500 mg/D, x3 times a week) during pregnancy or breastfeeding
- Combined oral contraceptives
  - Ethinyl estradiol 20 µg/30 µg/35 µg + chlormandionone cyproterone, or drospirenone
- Oral isotretinoin
  - 0.1-0.3 mg/kg/D, for severe acne or acne tarda

# Treatment of Acne Papulopustulosa

- Alternative or supplementary treatment
  - Dapsone 50-100 mg/D, contraindicated to antibiotics or isotretinoin
  - Spironolactone 50-100 mg/D, women with virilization
  - Metformin 500-1500 mg/D, obese patients
  - Zinc 30-60 mg/D?

# Treatment of Acne Nodulosa/Conglobata

- Systemic treatment
  - Oral isotretinoin 0.3 mg/kg/D x 6-12 months ± oral prednisolone (x 2-4 weeks, tapering from 1 mg/kg/D)
  - Alternative
    - Dapsone
    - Azithromycin
- Topical treatment
  - Potent steroids
  - Prevention of *S. aureus* superinfection

# Treatment of Acne Fulminans

- Standard treatment
  - Oral isotretinoin + oral prednisolone
- Cf. SAPHO syndrome, PAPA syndrome
- Alternative treatment
  - Dapsone + oral prednisolone
  - Cyclosporine + oral prednisolone
- Anecdotal treatment
  - TNF $\alpha$  inhibitors?
  - IL-1 $\beta$  blockers?

# Treatment of Acne Tarda

- Oral antibiotics: less effective
- Exclusion of PCO syndrome and insulin resistance
- Treatment of choice
  - Oral isotretinoin ± combined oral contraceptives
- Reluctance and risks of adult women to use oral contraceptives
  - Venous thromboembolism, breast cancer...
  - Melasma in Asian women

*Ju Q et al. Clin Dermatol 2017;35:130-7*

# Use of Oral Isotretinoin: Tips & Traps

- Daily dose:  $\leq 0.3$  mg/kg/D
- Cumulative dose: 120-150 mg/kg for long-term remission?
  - In one session without interruption?
- Ignorant side effects
  - Ocular
    - Contraindication for pilots due to ocular side effects
    - Meibomian gland dysfunction
    - Corneal thickness/opacity, visual acuity, retinopathy/night blindness
  - Thyroid function
  - Growth: Side effects in high-risk pediatric neuroblastoma
  - Pseudotumor cerebri

*Hobbie WL et al. Pediatr Blood Cancer 2011;56:474-6; Karadag AS et al. Dermatology 2015;230:354-9; Uyar B et al. Indian J Dermatol Venereol Leprol 2016;82:587-8; Yildirim N et al. J Dermatolog Treat 2017;28:141-4*

# Combined Oral Contraceptives for Acne Treatment

## ● Efficacy

- COC > Birth control vaginal ring > Mini (progestin only) pills > IUD with progesterone
- NuvaRing®: Etonogestrel 11.7 mg/Ethinyl estradiol 2.7 mg for 3 weeks (etonogestrel 120 µg /ethinyl estradiol 15 µg /D)
- Cerazette®: Desogestrel 75 µg/D
- Mirena® Levonorgestrel 52 mg for 5 years (20 µg/D)

## ● Evidence

- Generally weak
- Cyproterone acetate 2 mg/ ethinyl estradiol 35 µg
- Chlormandinone acetate 2 mg/ ethinyl estradiol 30 µg
- Drospirenone 3 mg / ethinyl estradiol 20 µg



# Combined Oral Contraceptives: Risk of Venous Thromboembolism

- Adjusted odds ratio in current exposure vs. no exposure in the previous year
- To any combined oral contraceptive 2.97 (2.78-3.17, 95% CI)
- To levonorgestrel (2.38, 2.18-2.59), norethisterone (2.56, 2.15-3.06), norgestimate (2.53, 2.17-2.96)
- To cyproterone (4.27, 3.57-5.11), drospirenone (4.12, 3.43-4.96), desogestrel (4.28, 3.66-5.01), gestodene (3.64, 3.00-4.43)
- Annual incidence in Caucasian childbearing women: 10-18 per 10,000
- The number of extra cases per year per 10,000 treated women levonorgestrel (6), norgestimate (6), desogestrel (14), cyproterone (14)

*Vinogradova Y et al. BMJ 2015;350:h2135;  
Heit JA, Nat Rev Cardiol 2015;12:464-74*

# Nutritional Treatment of Acne?

- Avoidance
  - Low fat, low caloric, low glycemic, low insulinogenic foods?
- Enhancement
  - Green tea/tea polyphenols?
  - omega-3 fatty acid 2,000 mg/  $\gamma$ -linoleic acid 400 mg/D
  - ...

*Jung JY et al. Acta Derm Venereol 2014;94:521-5; Melnik BC. Clin Cosmet Investig Dermatol 2015;8:371-88; Saric S et al. Antioxidants (Basel) 2016;6 pii: E2; Lu PH et al. Complement Ther Med 2016;25:159-63*

# Treatment of Acne Scar and Pigmentation

- Evidence based?
- Long-term comparison results?
- Identification of scar susceptible patients?
- Ethnic and genetic difference?
- Prevention by early intervention with oral isotretinoin?

# Isotretinoin and Timing of Procedural Interventions

- Current recommendation
  - Elective surgery 6-12 months after isotretinoin exposure
  - Isotretinoin increased local level of TGF- $\beta$ 1
- Challenge
  - Insufficient evidence for delay of manual dermabrasion, superficial chemical peels, cutaneous surgery, laser hair removal, and fractional ablative and nonablative laser procedures
  - Mechanical dermabrasion and fully ablative laser are not recommended
- Discussion
  - Setting: Daily high-dose treatment in early times
  - Depth of injury

*Spring LK et al. JAMA Dermatol 2017;153:802-9; Tolkachjov SN et al. J Am Acad Dermatol 2017;77:159-61; Leivo T et al. Skin Pharmacol Appl Skin Physiol 2000;13:150-6*



# Rosacea Pathogenesis

- Unclear, polygenic multifactorial
- Pathogenic factors
  - Vasodilatation
  - Inflammation
  - Demodex mites
  - Sebaceous hyperplasia
  - ...

# Rosacea Begins with Facial Erythema

## Regulation of cutaneous circulation

### ● Adrenoceptors

- $\alpha_{1A}$ -,  $\alpha_{1D}$ -,  $\alpha_{2A/D}$ -, and  $\alpha_{2B}$ -receptor subtypes: vasoconstriction
- $\beta_2$ -receptor: vasodilation
- Activation by circulating norepinephrine

### ● Neurotransmitters

- Vasoconstriction: norepinephrine, neuropeptide Y
- Active vasodilatation: unclear
  - Cholinergic innervation: acetylcholine?
  - Other potential mediators: NO, substance P, histamines, prostaglandins

# Rosacea Treatment: Strategy

- Stage adjusted and adapted
- Rosacea classification and staging
  - Rosacea subtypes, progressive and overlapping
  - ROSCO panel?
  - Ethnic and genetic difference?
  - D.D. Primary demodicosis



# Primary Demodicosis without Facial Erythema



*Chen W, Plewig G. Br J Dermatol 2014;170:1219-25*

# Treatment of Rosacea Erythema

## ● Topical treatment

- Brimonidine tartrate 5% gel (Mirvaso ®),  $\alpha_{2A}$ -adrenoceptor agonist
- Oxymetazoline hydrochloride 1% cream (Rhofade ®),  $\alpha_{1A}$ -adrenoceptor agonist
- Continual or episodic use?
- Rebound phenomenon
- Tachyphylaxis

## ● Systemic treatment

- Clonidine (Moxonidine?),  $\alpha_{2A}$ -adrenoceptor agonist
- Carvedilol, nonselective  $\beta$  blocker on  $\alpha_1$ -,  $\beta_1$ - und  $\beta_2$ -adrenoceptors

# Rebound Erythema After Topical Brimonidine Treatment



*Ilkovitch D et al. J Am Acad Dermatol 2014;70:e109-10*

# Treatment of Rosacea Erythema

- Alternative treatment
  - Laser treatment?
  - Botox treatment?
  - Evidence and long-term efficacy?
- Persistent erythema
  - Oral isotretinoin?
- Can early treatment prevent the progression of rosacea?

# Persistent Erythema in Rosacea with Secondary Demodicosis



# Treatment of Rosacea Papulopustulosa

- Topical treatment

- Azelaic acid 20% cream/15% gel
- Metronidazole 0.75%, 1%, 2% cream
- Ivermectin 1% cream
- Erythromycin 2%/4% cream

- Systemic treatment

- Doxycycline 50-100 mg/D
- Minocycline 50-100 mg/D
- Erythromycin 500 mg TID
- Azithromycin 250 mg/D
- Isotretinoin 0.1-0.3 mg/kg/D

# Treatment of Rosacea Phyma

- Laser treatment
- Surgical treatment
- Can early use of oral isotretinoin prevent the formation of phyma?

# Treatment of Rosacea Fulminans

- Standard treatment
  - Oral isotretinoin + systemic glucocorticoids
- Alternative treatment
  - Dapsone
  - Azithromycin



# Rosacea Fulminans in Pregnancy

32-year-old, primigravida, 16. gestational week



# Treatment of Childhood Rosacea

- The same principle, but less evidence based
- Special variant: Idiopathic facial aseptic granuloma (IFAG)?
  - Rosacea nodulosa/conglobata?
  - Oral erythromycin or doxycycline + topical metronidazole cream
  - Long-term follow-up failed

*Boralevi F et al. Br J Dermatol 2007;156:705-8*

# Childhood Rosacea



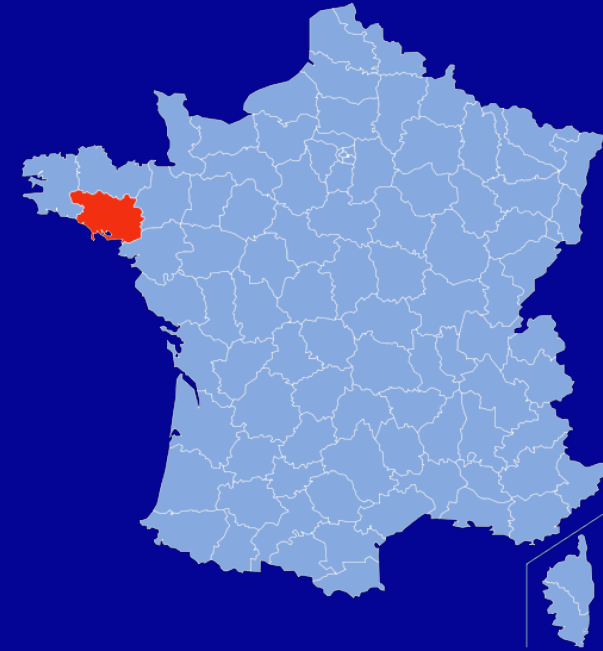
# Idiopathic Facial Aseptic Granuloma (IFAG)



*Martinez-Diaz GJ et al. Dermatol  
Online J 2010;16:9*

# Morbihan Disease

- Degos R, Civatte J, Beuve-Méry. Nouveau cas d'œdème érythémateux faciale chronique. Bull Soc Franc Derm Syph 1973;80:257
- Connelly MG, Winkelmann RK. Solid facial edema as a complication of acne vulgaris. Arch Dermatol 1985;121:87-90
- Jungfer B, Jansen T, Przybilla B, Plewig G. Solid persistent facial edema of acne: successful treatment with isotretinoin and ketotifen. Dermatology 1993;187:34-7



# Morbihan Disease



# Treatment of Morbihan Disease

- Oral isotretinoin
  - High dose 0.5-0.7 mg/kg/D
  - Moderate dose 0.3-0.5 mg/kg/D + Ketotifen 1 mg/D
- Doxycycline or Minocycline
- Thalidomide?
- Clofazimine?

*Hölzle E et al. Hautarzt 1995;46:796-8; Okubo A et al. J Dermatol 2017;44:713-6; Smith LA et al. Arch Dermatol 2012;148:1395-8*

# Conclusions

- Topical cocktail therapy
- Oral antibiotics plus topical retinoids
- Oral isotretinoin
  - The most effective treatment for acne and rosacea in different subtypes
  - Trends: Daily low-dose for 1-2 years
  - Serious concern in Asia due to inadequate contraception
  - Hesitation to use combined oral contraceptives
- Early and unselective use of oral isotretinoin
  - Avoidance in children esp. before puberty
  - Avoidance in pilots, soldiers and professional drivers



Thank you very much!

