



Antibiotico Resistenza

5 novembre 2016, Ferrara

Batteri e cute: una convivenza difficile

Vincenzo Bettoli

Ac - Fe



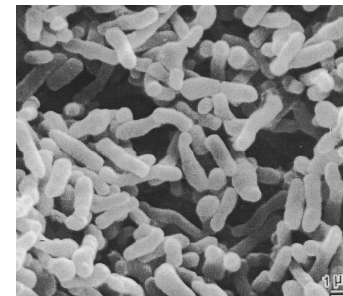
HS - Fe





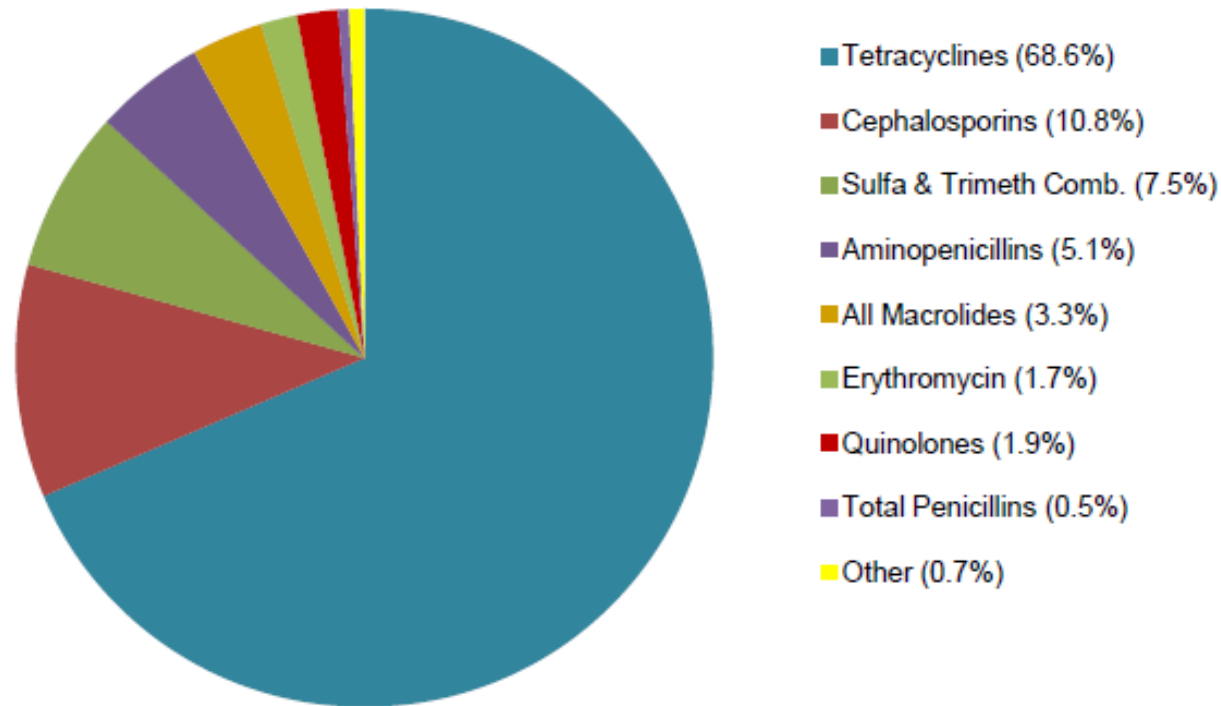
Batteri patogeni: *S.aureus*, *Str.pyogenes*
Infezioni di cute e tessuti molli

Batteri commensali: *P.acnes*
Acne



Prescription of Antibiotics in Dermatology

Oral Antibiotics Dispensed in Dermatology,* 2009

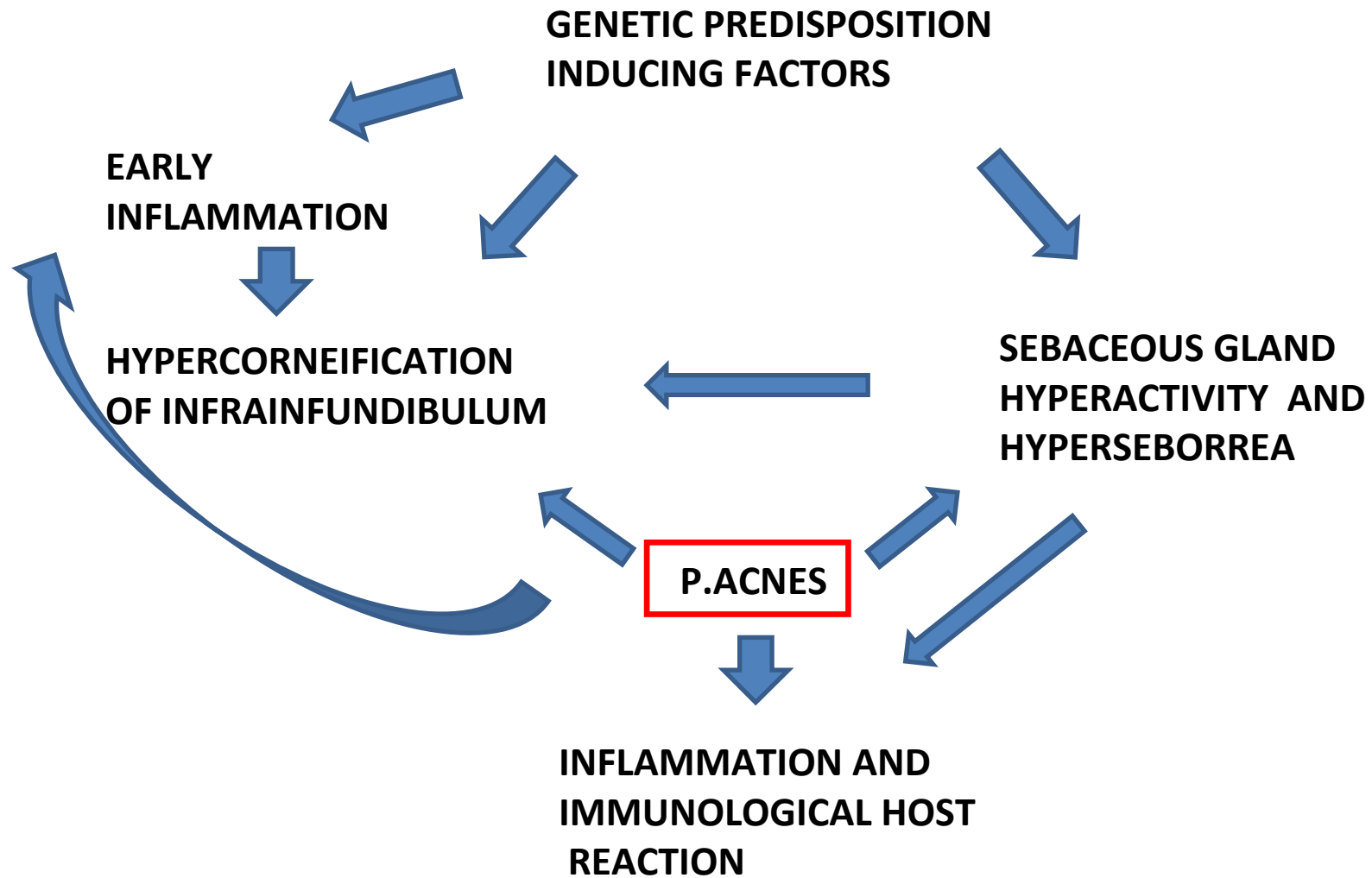


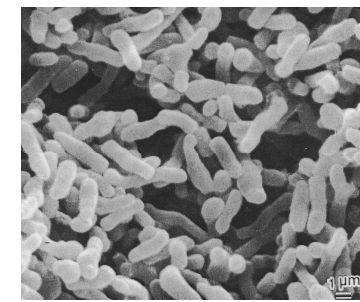
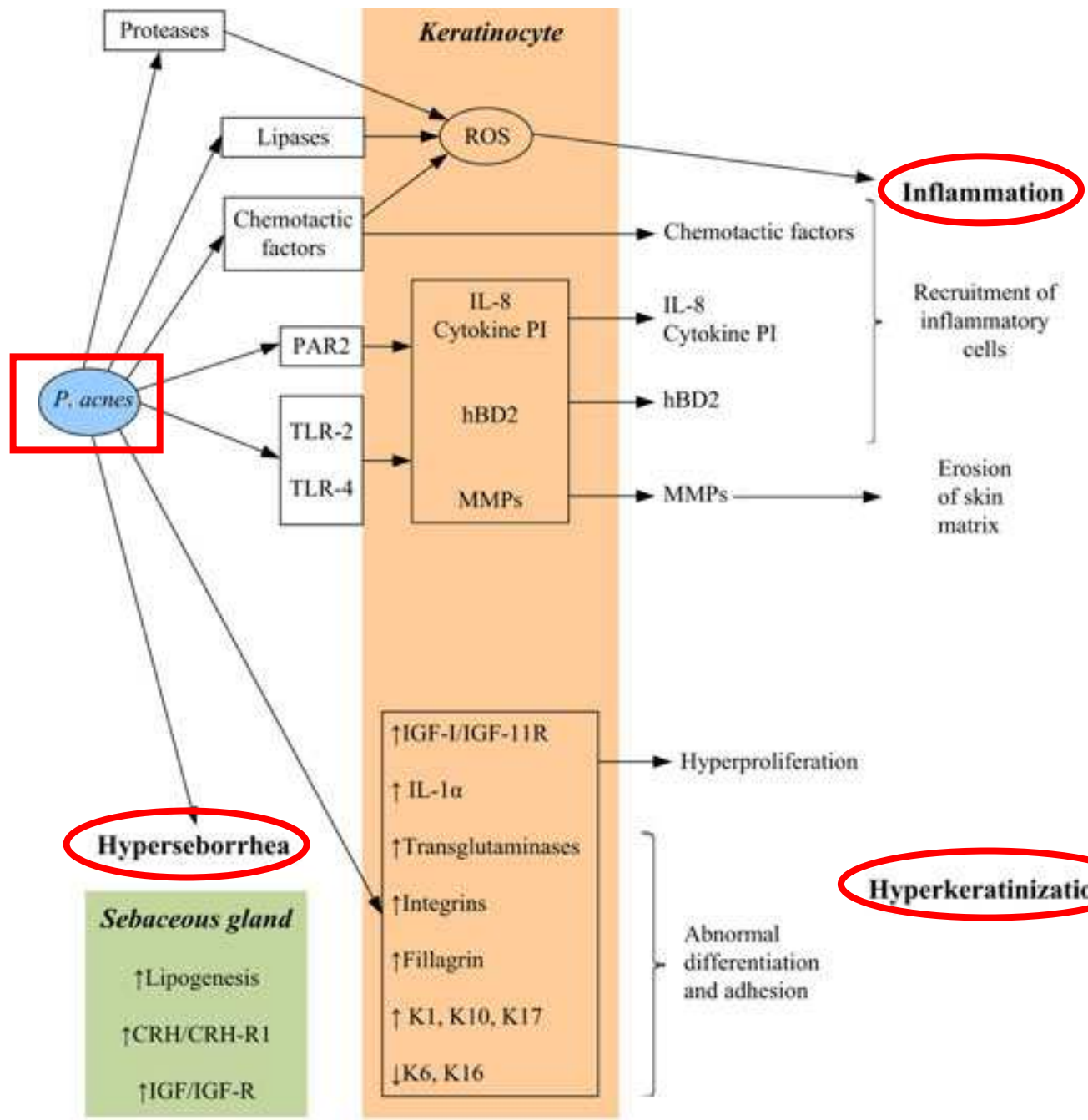


**Perché i Dermatologi - Acneologi
sono interessati agli antibiotici ?**



ACNE PATHOGENESIS





**Beylot et al.
JEADV 2013**



P.acnes

- **Sierotipi induttori di infiammazione**
- **Sierotipi inerti**



ANTIBIOTICS IN ACNE

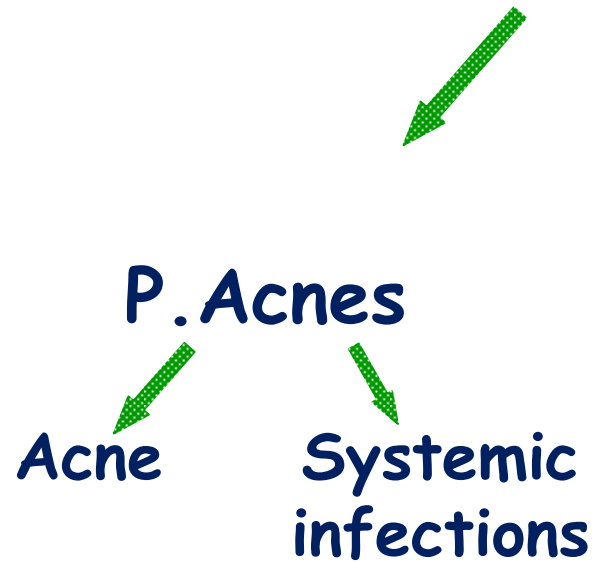
Topical antibiotics:

- act locally
- have effects on bacteria close to the area of application
- "edge effect"
- systemic absorption is rarely significant

Systemic antibiotics: - act systemically with different penetrance according to the tissue distribution



ANTIBIOTICS IN ACNE

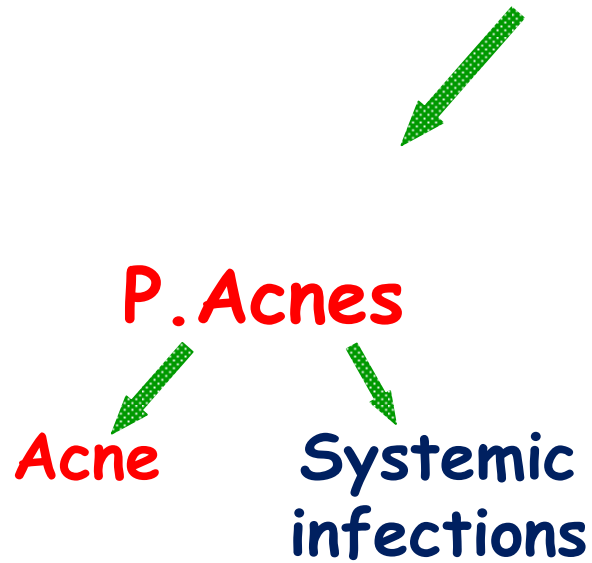


Other bacteria:

- Staf. (aureus, epidermidis)
- Str. (pyog, pneum, virid)
- GI tract
- Urinary tract
- Gram neg (big folds)



ANTIBIOTICS IN ACNE



Other bacteria:

- Staf. (aureus, epidermidis)
- Str. (pyog, pneum, virid)
- GI tract
- Urinary tract
- Gram neg (big folds)

Antibiotic-resistance of P.acnes

Global phenomenon

Worldwide, prevalence of ATB res from 20% in 1978 to 62% in 1996

Frequently cross-resistance between erythromycin and clindamycin e

Country	Clindamycin	Erythromycin	Oxytetracycline	Doxycycline
Spain	91	91	5	---
United States	79	81	63	57
Greece	75	75	7	---
Egypt	65	48	18	6
Italy	58	58	0	---
United Kingdom	55.5	55.5	26.4	---
Hong Kong	53.5	20.9	16.3	16.3
Singapore	>50	>50	>11.5	>11.5
Iran	50	52	35	---
Sweden	45	45	15	---
Hungary	45	45	0	---
Northern Mexico	36	46	14	20
Japan	4	4	2	2
France	---	75.1	9.5	9.5
Chile	7.5	12.5	---	---
Colombia	15	35	8	9
South Korea	30	26.7	---	---



1. Rosen T;JDD 2011;10:724-33.
2. . Luk NM, et al. JEADV 2013;27:31-6-
3. Abdel Fattah NS et al , JEADV 2012. –
4. Leyden JJ et al. Journal clinical aesthetic dermatology 2011;4:40-7.
5. Schafer F,et al . Int J Dermatol 2013;52:418-25 -
6. Mendoza N, et al. Int J Dermatol 2013;52:688-92.
7. Moon SH, et al . J of dermatology 2012;39:833-7.



Systematic review of antibiotic resistance in acne: an increasing topical and oral threat



Timothy R Walsh, John Efthimiou, Brigitte Dréno

Topical and oral antibiotics are routinely used to treat acne. However, antibiotic resistance is increasing, with many countries reporting that more than 50% of *Propionibacterium acnes* strains are resistant to topical macrolides, making them less effective. We reviewed the current scientific literature to enable proposal of recommendations for antibiotic use in acne treatment. References were identified through PubMed searches for articles published from January, 1954, to March 7, 2015, using four multiword searches. Ideally, benzoyl peroxide in combination with a topical retinoid should be used instead of a topical antibiotic to minimise the impact of resistance. Oral antibiotics still have a role in the treatment of moderate-to-severe acne, but only with a topical retinoid, benzoyl peroxide, or their combination, and ideally for no longer than 3 months. To limit resistance, it is recommended that benzoyl peroxide should always be added when long-term oral antibiotic use is deemed necessary. The benefit-to-risk ratio of long-term antibiotic use should be carefully considered and, in particular, use alone avoided where possible. There is a need to treat acne with effective alternatives to antibiotics to reduce the likelihood of resistance.

Lancet Infect Dis 2016; 16: e22-32

Published Online
February 4, 2016
[http://dx.doi.org/10.1016/S1473-3099\(15\)00527-7](http://dx.doi.org/10.1016/S1473-3099(15)00527-7)

Department of Medical Microbiology and Infectious Diseases, Heath Hospital, Cardiff, UK (Prof T R Walsh DSc); Independent Medical Consultancy, Oxford, UK (J Efthimiou MD); and Department of Dermatology,

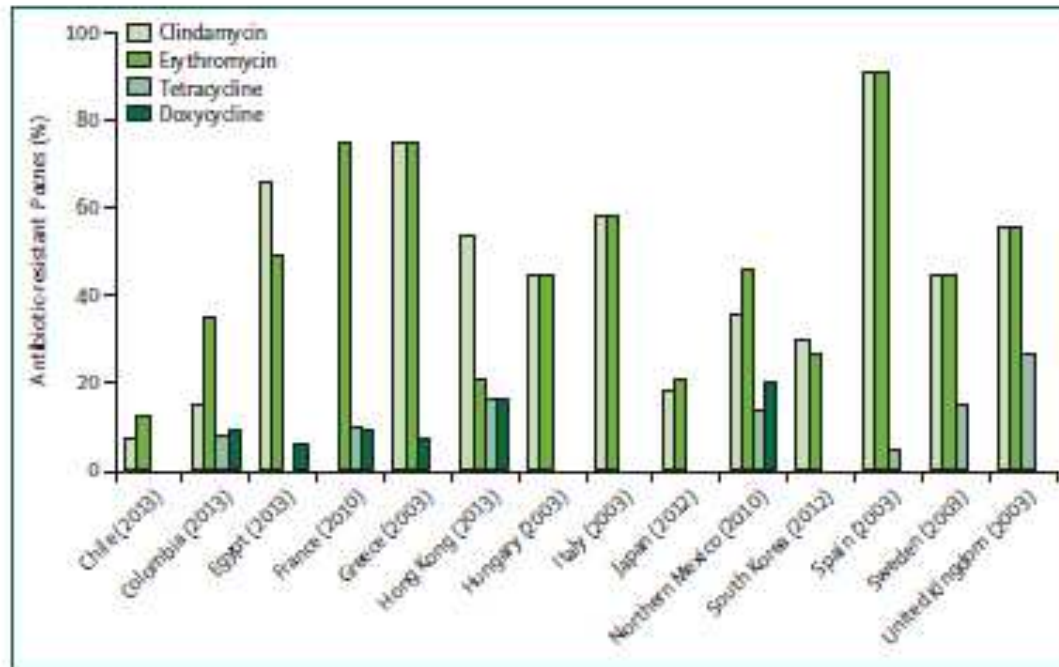


Figure 3: Topical and oral antibiotic-resistant *Propionibacterium acnes* isolated from acne patients in different countries^{8, 9, 10, 11}

Sardana et al. Pilot Study of Antibiotic resistance in P.acnes strains: A Comparison Among Treatment Modalities Including Antibiotics, BPO, Isotretinoin. Indian J Dermatol 2016 ;61(1):45

•Of the 52 P.acnes strains isolated (80 pts) resistance was observed to:

- AZI (100%), ERY (98%), CL (90%),
- DOX (44%), and TETs (31%), MINO (1.9%)
- LEVO (9.6%).

Isotretinoin/BPO had the least number of resistant strains.

•**CONCLUSIONS:** High resistance was seen to macrolides-lincosamides (AZI and CL) while MINO and LEVO resistance was low.



Clinical relevance of *P. acnes* ATB Resistance

Correlation between the carriage of resistant strains of *P. acnes* and reduced therapeutic outcome

Positive

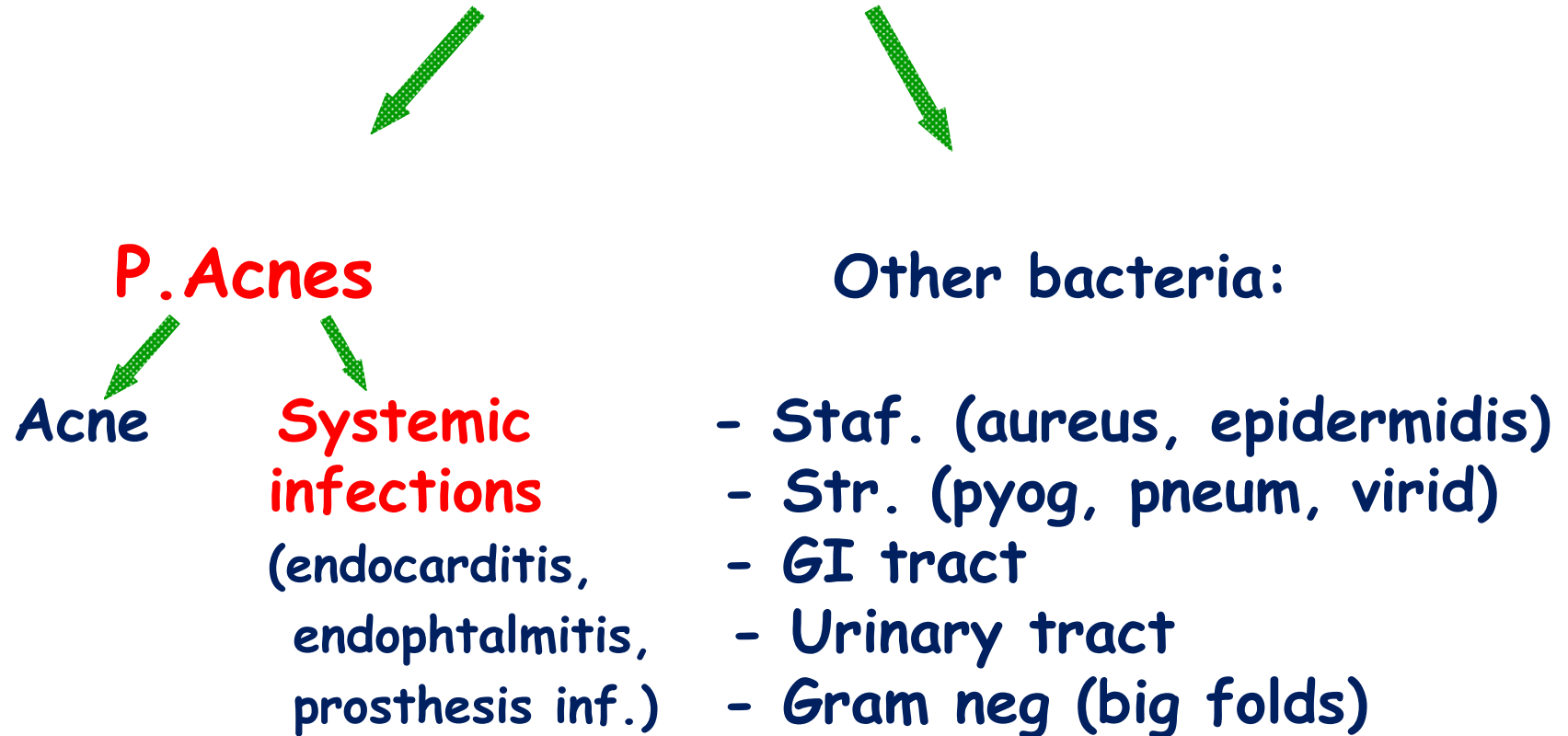
Leyden et al. 1983
Eady et al. 1989
Ozolins et al. 2003

Negative

Oprica 2007



ANTIBIOTICS IN ACNE





P.acnes and Acute Systemic Infections

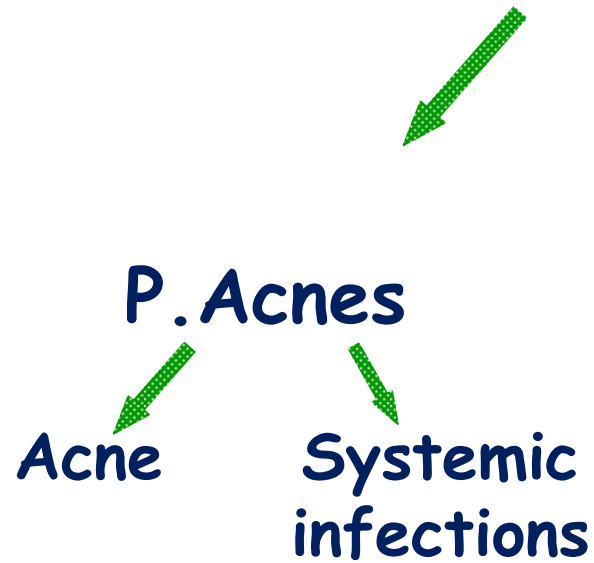
- *Propionibacteria* are very susceptible to β -lactams, such as penicillin

- None of the agents we use to treat acne would be candidates for therapeutic use in acute deep *P.acnes* infections

- Antibiotic-resistant *P.acnes* secondary to acne treatment puts neither patients nor the community at risk of ATB-resistant *propionibacterial* infections



ANTIBIOTICS IN ACNE



Other bacteria:

- **Staf.** (aureus, epidermidis)
- **Str.** (pyog, pneum, virid)
- **GI tract**
- **Urinary tract**
- **Gram neg** (big folds)



**Gli antibiotici utilizzati nell'acne hanno
effetti sul microbioma ?**



BACTERIAL MODIFICATIONS INDUCED BY ATB












Author	carriage	patients	results
Delost 2015	<i>S. Aureus</i> - nose	263	<i>S. Aureus</i> Atb 15.7 > 6.3 Res no diff ↓
Ozuguz 2015	<i>S. Aureus</i> - nose	20	<i>S. Aureus</i> Atb 0 > 25% ↑
Toyne 2012	<i>S. aureus</i> nose	116	<i>S. aureus</i> (tetra, ery, clinda) ↓
Fanelli 2011	<i>S. aureus</i> nose + throat	83 43% colon	<i>S. aureus</i> Tetra < colon = resistance ↓
Levy 2003	<i>S. aureus</i> <i>S. pyogenes</i> oropharynx	105 42 atb 63 no atb	<i>S. pyogenes</i> Atb > colon + res ↑ <i>S. aureus</i> Atb = no Atb ↔
Mills 1998	<i>S. aureus</i> nose	208	<i>S. aureus</i> Ery > colon > resist (4 wks) ↑
Vowels 1996	<i>S. aureus</i> nose, forehead	225	<i>S. Aureus</i> Ery ↔
Marples 1969	<i>S. aureus</i> nose	31	<i>S. aureus</i> user 14%, no 35%, no acne 32% ↓



BACTERIAL MODIFICATIONS INDUCED BY ATB












Author	carriage	patients	results
Delost 2015	<i>S. Aureus</i> - nose	263	<i>S. Aureus</i> Atb 15.7 > 6.3 Res no diff 
Ozuguz 2015	<i>S. Aureus</i> - nose	20	<i>S. Aureus</i> Atb 0 > 25% 
Toyne 2012	<i>S. aureus</i> nose	116	<i>S. aureus</i> (tetra, ery, clinda) 
Fanelli 2011	<i>S. aureus</i> nose + throat	83 43% colon	<i>S. aureus</i> Tetra < colon = resistance 
Levy 2003	<i>S. aureus</i> <i>S. pyogenes</i> oropharynx	105 42 atb 63 no atb	<i>S. pyogenes</i> Atb > colon + res  <i>S. aureus</i> Atb = no Atb 
Mills 1998	<i>S. aureus</i> nose	208	<i>S. aureus</i> Ery > colon > resist (4 wks) 
Vowels 1996	<i>S. aureus</i> nose, forehead	225	<i>S. Aureus</i> Ery 
Marples 1969	<i>S. aureus</i> nose	31	<i>S. aureus</i> user 14%, no 35%, no acne 32% 



BACTERIAL MODIFICATIONS INDUCED BY ATB



Author	carriage	patients	results
Delost 2015	<i>S. Aureus</i> - nose	263	<i>S. Aureus</i> Atb 15.7 > 6.3 Res no diff 
Ozuguz 2015	<i>S. Aureus</i> - nose	20	<i>S. Aureus</i> Atb 0 > 25% 
Toyne 2012	<i>S. aureus</i> nose	116	<i>S. aureus</i> (tetra, ery, clinda) 
Fanelli 2011	<i>S. aureus</i> nose + throat	83 43% colon	<i>S. aureus</i> Tetra < colon = resistance 
Levy 2003	<i>S. aureus</i> <i>S. pyogenes</i> oropharynx	105 42 atb 63 no atb	<i>S. pyogenes</i> Atb > colon + res  <i>S. aureus</i> Atb = no Atb 
Mills 1998	<i>S. aureus</i> nose	208	<i>S. aureus</i> Ery > colon > resist (4 wks) 
Vowels 1996	<i>S. aureus</i> nose, forehead	225	<i>S. Aureus</i> Ery 
Marples 1969	<i>S. aureus</i> nose	31	<i>S. aureus</i> user 14%, no 35%, no acne 32% 



Toyne H, et al. Propionibacterium acnes resistance and antibiotic use in patients attending Australian general practice. Australasian Journal of Dermatology 2012

1997-8 99 pts P.acnes + 86 (res 11)

2007 116 pts P.acnes + 94 (res 9)

No difference in prevalence of P.acnes atb res after 10 years

2007

Sa+ nose reduced with atb (9/116 oral, 0/116 topical, 33% no atb)

Sa+ nose increased after stopping atb



Toyne H, et al. Propionibacterium acnes resistance and antibiotic use in patients attending Australian general practice. Australasian Journal of Dermatology 2012

5/30 Sa res clinda and ery 1/30 MRSA (but none of these pts had res P.acnes)
No demonstration of simultaneous resistance of Sa and P.acnes

Marked decline in the percentage of resistant P.acnes by time in days since ceasing

Antibiotics: day 0 15 res,
 day 1-120 5 res,
 day > 120 0 res.

Demonstration that resistance is reversible



Gli antibiotici utilizzati ell'acne hanno effetto sul microbioma ?



Sì



Questi effetti sono clinicamente rilevanti ?



I pazienti acneici trattati sono affetti da patologie infettive più frequentemente di altri ?



INDUCTION OF INFECTIONS BY ATBs FOR ACNE

Author	treatment	patients	infections
Margolis 2005	Top / syst ATBs (tetra, ery, clin) 71.7%	database 118.496	ATB users odds URTI 2.15 vs non users (???)
Adams 1985	Tetra / Ery (bowel flora)	26	Tetra > resistance Ery no resistance No G.I. infections



Margolis DJ, et al. Antibiotic treatment of acne maybe associated with upper respiratory tract infections. Arch Dermatol 2005

Objective: determine if long-term use of atb (at least 6 weeks) in acne increases URTI or urinary tract infections (UTI)

Results: 118.496 patients - 71.7% users (tetra, ery, clinda) 28.3% not users

Within the first year of observation:

URTI: 15.4% of acne patients at least 1 URTI

Odds of URTI among users 2.15 times greater than in not users

UTI: no association was noted



Margolis DJ, et al. Antibiotic treatment of acne maybe associated with upper respiratory tract infections. Arch Dermatol 2005

Comments: 10% of URTI are due to a bacterial source

Atb used in acne are no longer frequently used in bacterial URTIs

"The true clinical importance of our findings requires further investigation"

The plausability of the association as causal inference not established

The risk of these infections and benefits in acne must be balanced

Incidence of URTI in the 12 months preceding the study is missing

Editorial: what are the implications of this study for clinicians ?

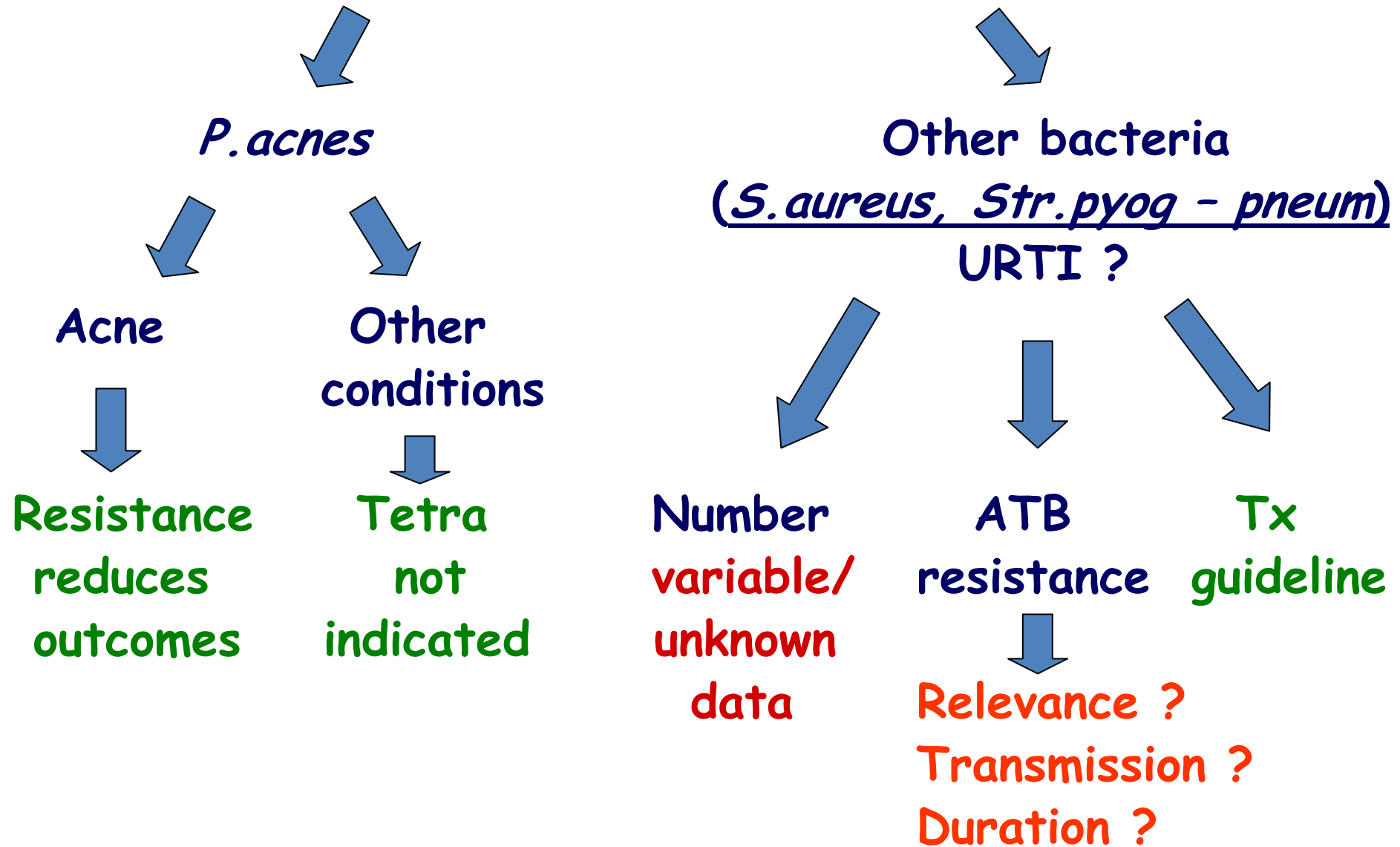
The findings do not yet justify a change in current practice !!!



**I dati disponibili mostrano una rilevanza clinica
non significativa**



ANTIBIOTICS and ACNE





REVIEW

Advances in the prevention, management, and treatment of community-acquired pneumonia [version 1; referees: 2 approved]

Mathias W. Pletz¹, Gernot G. Rohde², Tobias Welte³, Martin Kolditz⁴, Sebastian Ott⁵

Antibiotic treatment

Most major guidelines suggest an empiric treatment stratified according to severity of disease^{79,80}. Outpatients are treated orally with penicillins, macrolides, tetracyclines, or fluoroquinolones with anti-pneumococcal activity (i.e. moxifloxacin or levofloxacin).

severity precluded from the macrolide combination. This supports the obligated empiric beta-lactam/macrolide combination treatment for at least all CAP patients admitted to the ICU, a strategy suggested by most major guidelines^{80,81,91}.



Status Report from the Scientific Panel on Antibiotic Use in Dermatology of the American Acne and Rosacea Society

Part 3: Current Perspectives on Skin and Soft Tissue Infections with Emphasis on Methicillin-resistant *Staphylococcus aureus*, Commonly Encountered Scenarios when Antibiotic Use May Not Be Needed, and Concluding Remarks on Rational Use of Antibiotics in Dermatology

¹JAMES Q. DEL ROSSO, DO; ²TED ROSEN, MD; ³DIANE THIBOUTOT, MD; ⁴GUY F. WEBSTER, MD;
⁵RICHARD L. GALLO, MD, PhD; ⁶JAMES J. LEYDEN, MD; ⁷CLAY WALKER, PhD;
⁸GEORGE ZHANEL, PhD; ⁹LAWRENCE EICHENFIELD, MD

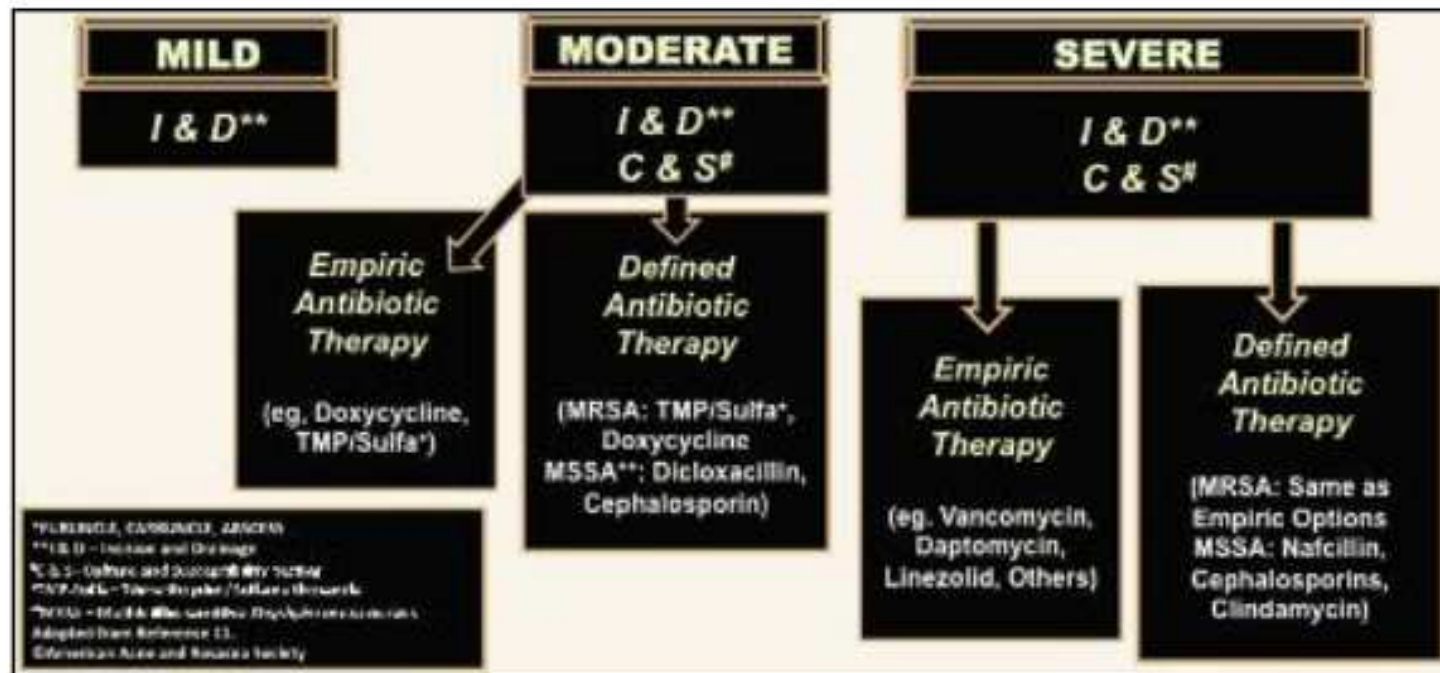


Figure 2. Management of PURULENT skin and soft tissue infections*



Status Report from the Scientific Panel on Antibiotic Use in Dermatology of the American Acne and Rosacea Society

Part 3: Current Perspectives on Skin and Soft Tissue Infections with Emphasis on Methicillin-resistant *Staphylococcus aureus*, Commonly Encountered Scenarios when Antibiotic Use May Not Be Needed, and Concluding Remarks on Rational Use of Antibiotics in Dermatology

*JAMES Q. DEL ROSSO, DO; *TED ROSEN, MD; *DIANE THIBOUTOT, MD; *GUY F. WEBSTER, MD;
*RICHARD L. GALLO, MD, PhD; *JAMES J. LEYDEN, MD; *CLAY WALKER, PhD;
*GEORGE ZHANEL, PhD; *LAWRENCE EICHENFIELD, MD

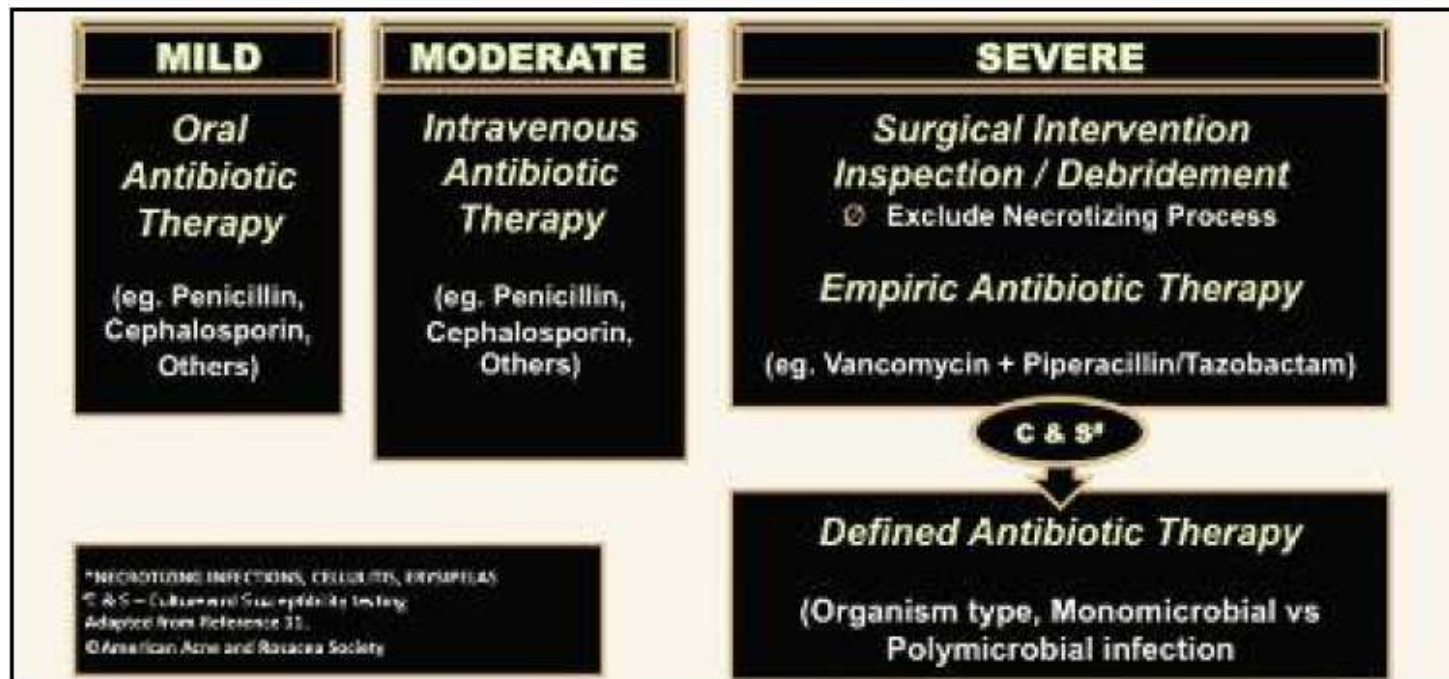


Figure 3. Management of NONPURULENT skin and soft tissue infections*



Antibiotico-Resistenza e Acne: La Posizione di Dermatologi Italiani (Risultati di una Consensus Conference)

Bettoli V, Antonioli P*, Barbareschi M, Bellosta M, Di Pietro A,
Drago L**, Libanore M***, Pelfini C, Pravettoni C, Rossi R**,
Skroza N, Veraldi S, Virgili A.

In rappresentanza di ADOI, SIDeMaST, AIDA, ISPLAD, IAB, DDI



ARTICOLI SPECIALI - SPECIAL ARTICLES

Acne, terapia antibiotica e antibiotico-resistenza: la posizione dei dermatologi italiani

Acne, antibiotic therapy and antibiotic-resistance: the position of Italian dermatologists

Vincenzo BETTOLI ^{1*}, Paola ANTONIOLI ², Mauro BARBARESCHI ³, Mario BELLOSTA ⁴,
Silvia M. CAMMARATA ⁵, Antonio DI PIETRO ⁶, Lorenzo DRAGO ⁷, Marco LIBANORE ⁸, Carlo PELFINI ⁹,
Sandra PETRAGLIA ⁵, Cecilia PRAVETTONI ¹⁰, Rita ROSSI ¹¹, Nevena SKROZA ¹², Giulia TONI ¹,
Stefano VERALDI ¹³, Stefania ZAULI ¹, Annarosa VIRGILI ¹

The occurrence of bacterial antibiotic resistance is a physiological event and it is increasingly important concern all over the world, which has alarmed the Authorities for Health. Acne is an inflammatory disease that develops within the pilo-sebaceous follicles. Several factors intervene in the development of the disease. Among the others, there is P. acnes, a Gram positive, anaerobic-optional bacterium which can induce inflammatory processes that may lead to the development of acne lesions. Among the different therapeutic options for acne, antibiotics play a relevant role. Analyzing the details of the practical aspects which correlate antibiotic therapy and acne and the problem of antibiotic resistance, four points must be considered separately: 1) the relationship between P. acnes and acne; 2) the systemic infections induced by P. acnes; 3) the relationship among antibiotic drugs, P. acnes and other bacteria different from P. acnes, along with the modification of bacterial environment and induction of resistance; 4) the relationship among antibiotics in acne, antibiotic resistance and possible increased risk of bacterial infections (not by P. acnes). Considering the available data on this topic, the possible side effects related to the drugs that may substitute antibiotics and the benefits provided by antibiotics in acne, it is believed that their use is indicated and reasonable provided that specific prescription rules must be followed.



Il testo della Consensus è pubblicato nel sito dell'AIFA (ricerca > antibiotico resistenza acne)

Acne, terapia antibiotica e antibiotico-resistenza: la posizione dei dermatologi italiani condivisa dall'AIFA



11/01/2011

L'acne è una patologia molto diffusa tra gli adolescenti. L'uso degli antibiotici topici o sistemici è frequente e probabilmente non sempre giustificato. Le più recenti ricerche confermano infatti che l'acne è una patologia infiammatoria legata all'alterazione della produzione di sebo e l'intervento del batterio p.acnes è un fenomeno secondario.


Nell'ottica della promozione di un uso ragionato degli antibiotici, a cui l'AIFA dedica da anni iniziative specifiche di comunicazione e sensibilizzazione, l'Agenzia condivide e rende disponibile sul portale istituzionale la posizione dei dermatologi italiani sul controllo della terapia antibiotica nei soggetti con acne.

Il documento, che analizza gli aspetti pratici che correlano la terapia antibiotica a questa patologia dermatologica e raccomanda alcune norme prescrittive alla luce della più recente letteratura scientifica e delle linee guida internazionali, è firmato da rappresentanti dell'Associazione Dermatologi Ospedalieri Italiani (ADOI), della Società Italiana di Dermatologia e Malattie a Trasmissione Sessuale (SIDeMaST), dell'Associazione Italiana Dermatologi Ambulatoriali (AIDA), della Società Italiana di Dermatologia Plastica (ISPLAD), dell'Italian Acne Board (IAB), delle Donne Dermatologhe Italiane (DDI) e dell'AIFA.

Leggere in allegato il documento



Allegati

 [Acne, terapia antibiotica e antibiotico-resistenza: la posizione dei dermatologi italiani](#)

ACNE, TERAPIA ANTIBIOTICA E ANTIBIOTICO-RESISTENZA: LA POSIZIONE DEI DERMATOLOGI ITALIANI

Lo sviluppo di resistenza dei batteri agli antibiotici è un problema che nasce parallelamente all'utilizzo degli antibiotici stessi. In tutti i paesi del mondo, da vari anni, si osserva un suo preoccupante crescendo. Il numero di infezioni batteriche causa di decesso o di rilevante e prolungata inabilità, come conseguenza dello sviluppo di resistenza batterica agli antibiotici, ha raggiunto livelli tali da allarmare le autorità sanitarie a livello internazionale. Basti pensare come la WHO, nel marzo 2015, ha reso pubblico il draft del "global actionplan on antimicrobial resistance" (1), da cui chiaramente si evince la necessità che tutti i paesi sviluppino in tempi rapidi actionplans in linea con quello della WHO. I batteri, sottoposti alla pressione selettiva esercitata dagli antibiotici, rispondono sviluppando modalità di resistenza che riducono, in modo più o meno marcato, l'efficacia terapeutica dell'antibiotico stesso. Sviluppare resistenza ad un antibiotico è, per il batterio, una reazione naturale di sopravvivenza e di adattamento ad una situazione ambientale mutata per la presenza del farmaco: si tratta quindi di un processo fisiologico e prevedibile.



Strategies for preventing antibiotic resistance (1)

- 1) Evitare l'antibiotico, sia topico che sistemico, come monoterapia
- 2) Combinare un retinoide topico, base della terapia dell'acne, con l'antimicrobico
- 3) Associare il BPO per il suo effetto antimicrobico e per la capacità di non favorire antibiotico-resistenza
- 4) Utilizzare l'antibiotico per una durata preferibilmente non superiore ai 3 mesi



Strategies for preventing antibiotic resistance (2)

- 5) Preferibile evitare l'uso combinato di antibiotico topico e sistemico
- 6) **Valutare l'andamento clinico dopo 6-8 settimane di terapia.** In caso di assenza di risposta clinica sospendere l'antibiotico e passare ad un altro trattamento. Nel caso in cui si fosse già ottenuta la scomparsa dell'acne si consiglia il passaggio alla terapia di mantenimento
- 7) Come terapia di mantenimento considerare il retinoide topico ed associare il BPO quando si ritenga necessario. Da evitare l'antibiotico.



Ac - Fe







CONCLUSIONS

- **ATBs used in acne may influence** human commensal bacterial environment
- **Apparently no significant increase** of bacterial infectious diseases