

European Federation of Pharmaceutical Industries and Associations

Development of Drugs for Skin Infections

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EFPIA - Skin Infection comments



Skin Infections

- Significant recent debate:
 - Acceptable forms: A focus on fever & cellulitis; abscess alone suggested as not acceptable
 - Endpoint and endpoint timing: A focus on resolution of cellulitis at approximately 72h
- EFPIA find these debates helpful, but
 - Need to avoid final rules that lead to study of nonrepresentative populations
 - Need to recognize that early endpoints are already incorporated into traditional endpoints



Is fever required at enrollment?

- Requiring fever at enrollment will lead to a nonrepresentative study population
 - Only 13% of 322 adults with infection requiring hospital care had T > 38°C at admission

Jenkins Clin Infect Dis 2010; 51:895-903

- Instead, sponsors should document severity of infection (or potential to become severe)
 - Fever is one option, but also can use evidence of systemic inflammatory response (SIRS) or high-risk comorbidities



What can be studied? (1 of 4)

• Antibiotic effect in abscess:

Table 3. Clinical cure rates for major abscesses.

	Treatment		
Outcome	Other ^a	Sulfonamide	Penicillin
Overall, proportion of patients cured	254/336	60/69	282/293
Percentage of patients cured (95% CI)	76 (71–80)	87 (80–94)	96% (94–98)
Effect size, % (95% Cl)		11 (0–23)	21 (14–27)
Lower limit of effect size, ^b %			14

NOTE. CI, confidence interval. This table is available in its entirety in the online version of the journal.

^a "Other" refers to nonantimicrobial therapies, including topical creams (eg, magnesium sulfate, glycerin, etc.), blood transfusion, injection of anti-streptococcal serum into lesions, X-ray or ultraviolet therapy, or bacteriophage therapy.

^b Lower limit of effect size is calculated by subtracting the upper bound of the 95% CI of cure with no antibiotic therapy (68%) from the lower bound of the 95% CI of cure with penicillin (96%).

Spellberg et al. Clin Infect Dis 49:383-91, 2009. Major abscess differentiates from uncomplicated abscess (e.g., furuncles)

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What can be studied (2 of 4)?

- Modern study of <u>uncomplicated</u> abscess*
 - Multi-center, I&D followed by TMP-SMX vs. placebo
 - Endpoints were failure at d7, new lesions at day 30

TMP-SMXPlacebo95% Cl (range)D7 (failure):17% (15/88)26% (27/102)-9% (+2 to -21%)D30 (recur):9% (4/46)28% (14/50)-19% (-4 to -34%)

- This sets lower bound on effect size for <u>complicated</u> abscess
- Spellberg commentary (Ann Emerg Med, 2011, in press)
 - Reviews 7 studies in toto
 - "cannot exclude a 5-10% improvement in end-of-therapy cure with antibiotics for <u>uncomplicated</u> abscesses"
 - 10-20% excess recurrence rate without antibiotics
 - Two further NIH-sponsored studies are underway

*Schmitz 2010 Ann Emerg Med 56:283-7



What can be studied? (3 of 4)

- Requiring cellulitis of a minimum size may limit enrollment to non-representative subset
 - 75 cm² (8.9 x 8.9 cm) has been proposed as a goal
 - This may exceed size of some body parts (hand, feet), especially on women & children
- Size is not the only measure of severity
 - Of 322 adults requiring hospital care
 - Only 20% had predominant cellulitis
 - Of 8 with MRSA bacteremia, cellulitis: 2, abscess: 6

Jenkins Clin Infect Dis 2010; 51:895-903



What can be studied? (4 of 4)

- Comments by others:
 - ... insistence that only patients with cellulitis be enrolled in future clinical trials of SSTIs will make completion of enrollment of such studies very difficult and will leave clinicians in the unacceptable position of not knowing the efficacy of new antibacterial agents for complicated abscesses and wound and ulcer infections".

Spellberg (Clin Infect Dis 2010; 51:904-6)

- Conclusions: We suggest that sponsors should
 - Limit percentage with just abscess
 - Size should be adequate for clear response but can also be judged proportionate to body region
 - Document severity or comorbidity



How & when is response measured?

- Early reduction of lesion size has been discussed
 - Early response should be a good antibiotic effect measure
 - Implicitly required in prior trials: response needed by 3-4d
 - Proposals to use as 1° endpoint at day 3-4 have been made
- But, overall clinical response (TOC) is patient's goal
 - Late response at a fixed time point such as day 10 or 14 makes most clinical sense
 - Should capture response of both signs & symptoms
 - Although signs are biomarkers, they appear with the infection and are tightly linked to progression & resolution
- Suggestion: If an early measure is 1^o endpoint, a late measure must also be documented. A late TOC measure requiring early success is also logical.



Non-inferiority margin (1 of 2)

- The effect size of antibiotics is very large
 - Erysipelas-related mortality, 1880-1960



Spellberg et al. Clin Infect Dis 49:383-91, 2009

Major abscess: 6% mortality

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Non-inferiority margin (2 of 2)

- Effect size estimates are large
 - Cellulitis/erysipelas: 29%
 - Wounds and ulcers: 42%
 - Major abscess: 14%
 - Hierarchy evident ("dose-response"): PCN > Sulfa > Other* Spellberg (Clin Infect Dis 2010; 51:904-6)
- These effect sizes could easily be larger
 - Effect sizes based on difference in 95% confidence bounds
 - Point estimates for all forms of skin infection exceed 20%
- Margin can be based on clinical reasoning
- Margins below 10% are not feasible

*PCN = Penicillin; Other = Non-antimicrobial therapies, including topical creams (e.g., magnesium sulfate, glycerin, etc.), blood transfusion, injection of anti-streptococcal serum into lesions, X-ray or ultraviolet therapy, or bacteriophage therapy.



A famous & instructive story

- 4 y.o. girl in excellent health suddenly developed facial skin infection
- Spread relentlessly, fever to 104°F
- Could not sleep because her face and neck so swollen she could not swallow her own secretions
- Began gasping for breath

Herrell & Smith, Proc Staff Meetings Mayo Clinic 18:65-76, 1943.



On arrival to the hospital



"Moribund" (on the verge of death)

Blood cultures were positive.

As the authors note: "An infection of this type complicated by septiciemia is almost universally fatal."

Penicillin therapy was begun.



On arrival to the hospital

After 14

days of

penicillin



Totally fine... and lived a long life

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"Moribund" (on the verge of death)



On arrival to the hospital

Is this 75 cm²?

For this, needs to have diameter = 10 cm. Per standard growth tables*, the average mandibular body for a 4-year-old girl is $5.5 \pm 0.3 \text{ cm}$.

She would not meet a 75 cm² rule.

Size is not the only critical factor.

After 14 days of penicillin





"Moribund" (on the verge of death)

Totally fine... and lived a long life



Skin: Summary

EFPIA suggest that studies should be

- Representative: Must capture typical patients
 - Abscess should be included but as a limited percentage
 - Sponsors should document size, severity, & comorbidity
- Informative: traditional test of cure endpoints are relevant and can incorporate early response
- Valid: Effect size is large
 - Margin <u>></u> 10% based on clinical reasoning
- Feasible: 10% margins yield feasible programs
 - E.g., ceftaroline and telavancin