# Justification of Non-Inferiority Margin for the Treatment of Complicated Skin and Skin Structure Infections

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## Background

Skin and skin structure infections are common and encompass a wide variety of disease presentations and severity. Complicated skin and skin structure infections (cSSSI) include infected ulcers, burns, and major abscesses and infections of deeper soft tissues. Infections such as necrotizing fasciitis, secondarily infected atopic dermatitis or eczema, ecthyma gangrenosum in neutropenic patients or infections involving prosthetic materials (e.g., catheter tunnel infections) are usually not included in the primary clinical studies supporting the approval of a new agent.[1] The majority of skin infections are caused by Gram positive organisms such as *Staphylococcus aureus*, *Streptococcus pyogenes, and Streptococcus agalactiae*. All recent registrational trials for the indication of cSSSI have been non-inferiority trials with a non-inferiority margin of 10-15%. Treatment guidelines recommend antibacterial agents for the treatment of skin and soft-tissue infections, the choice of antibacterials is based on the nature and severity of infection and susceptibility patterns. [2]

FDA issued draft guidance on the use of active-controlled non-inferiority studies for approval of anti-bacterial agents in October, 2007, to articulate FDA's thinking regarding appropriate clinical study designs to evaluate antibacterial drugs (Appendix). This document outlines the steps taken by the Agency to estimate the treatment effect of antibacterials in the treatment of cSSSI and to justify an appropriate non-inferiority (NI) margin.

The first step in determining an appropriate NI margin is reliable estimation of the treatment effect of the active comparator (i.e., effect of the active comparator over placebo, referred to as M1, based on placebo-controlled studies). In the absence of data from placebo-controlled studies, this determination is often based on data available from treated versus untreated disease. To protect from drawing false conclusions from an NI study, it is important to discount (or reduce) the magnitude of the treatment effect based on previous data to account for trial-to-trial variability, untestable constancy assumptions, and for other uncertainties. The second step involves clinical judgment regarding how much of the estimated treatment effect (M1) should be preserved in determining a clinically acceptable NI margin, referred to as M2.

As no data from placebo-controlled studies in cSSSI are available, results from comparative clinical trials of treated versus standard-of-care, and from observational studies in patients treated with antibacterial agents or with no specific therapy were reviewed to estimate the treatment effect of antibacterials in cSSSI. Direct extrapolation of treatment effect from historical studies to contemporary cSSSI trials is problematic. The historical studies do not meet the standards of present clinical trials in terms of randomization and blinding. Additionally, differences in patient populations and microbiologic characteristics of the causative micro-organisms make direct comparisons difficult. Several of the historical studies specifically addressed patients with bacteremia or severe streptococcal infections often in the setting of war wounds. Such patients are generally excluded from clinical trials and hence direct applicability of those data to determining an NI margin is limited.

Based on review of the data discussed in the following sections, the Agency believes that non-inferiority trials are acceptable for the indication of cSSSI, provided that appropriate patient populations are enrolled and acceptable endpoints are assessed.

**Approach in determining the NI margin:** The following steps were followed by the Agency in justifying an appropriate non-inferiority margin for cSSSI:

1. Estimate historical evidence for sensitivity to drug effect in cSSSI
2. Evaluate constancy of the treatment effect: Validity of the assumption that current treatment effect of the active control is similar to the effect seen in historical studies
3. Review other supportive evidence for antibacterial treatment effect in skin and skin structure infections
    - Treatment effect in uncomplicated skin and skin structure infections (uSSSI) such as impetigo and skin abscesses
    - Dose-ranging studies
    - Use of prophylactic antibacterials to prevent wound infections
    - Outcomes in patients who received discordant therapy based on *in vitro* susceptibility results
4. Review of contemporary cSSSI trials
5. Review of contemporary uSSSI trials
6. Estimation of NI margin

**Historical evidence for sensitivity to drug effect (HESDE) in cSSSI**

**1. Placebo-controlled trials in cSSSI:**

No placebo controlled studies were identified, likely due to the reduction in mortality observed since the introduction of sulfonamides and penicillins compared to observed mortality in natural history studies from the pre-antibiotic era.

**2. Treated vs. standard of care**

Two studies were identified that compared outcomes in patients treated with sulfonamides to those treated with ultra-violet (UV) light. Both studies were conducted by the same authors under very similar conditions. These studies are summarized below:

1. Snodgrass WR and Anderson T (BMJ 1937) [3]: Cases of erysipelas were studied from middle of May 1936-middle February 1937 in Ruchill Hospital Glasgow. All groups were treated under similar conditions. The wards and nursing staff were common to both groups. Each case was reviewed daily. Duration of disease before admission to hospital, age of the patient, severity of the infection, and associated diseases were similar in the two groups. The authors report that these factors were evaluated by a statistician who felt that weighting either line of treatment by any of these factors was not needed. The

authors note that 49 cases were "severe" and that in 5 cases in the prontosil group, the condition was so severe that a fatal result would not have been unexpected. One patient in the UV group showed uncontrolled spread with high fever for 6 days and was in a typhoid state when prontosil was used and the patient's recovery was completely unexpected.
Methods: The first 161 cases were allocated to 3 groups in order of admission: Group 1-UV light only, Group 2 Prontosil only and Group 3 UV light plus prontosil. The second 151 cases were divided into 3 groups, the first two were same as above and the third was treated with scarlet fever antitoxin. Six cases were removed from the series as the diagnosis was questionable. The number of cases per group was as follows: UV light alone-104, Prontosil alone-106, UV light+Prontosil-54, and antitoxin alone-48.

Treatments: Treatments were given during the acute stage only, and was not maintained after the subsidence of the local lesion and cessation of fever and toxemia. No other local treatment was given to any case. UV light was administered at a distance of 12" and was given for 8 minutes in females and 10 minutes in males, once daily. Treatment was repeated at 24 hr intervals if considered necessary. Average number of exposures was 2.6. Prontosil was administered orally as 1, 2, or 3 tablets of 0.3 g each every 4 hours; 10 patients received intramuscular (IM) prontosil, six of whom also received oral therapy. The average dose was 5 g (range 1.2-15 grams).

Results: Patients who died [n=15, 5 each in the UV group and prontosil group (1 had failed UV light), 1 in UV+Prontosil group and the 4 in anti-toxin group] were excluded, so the total number of cases in the series was 297.The fatal cases were not directly related to worsening erysipelas. However, some were bacteremic/ had other foci of streptococcal infection such as meningitis and empyema. In some there was no clear cause of death as post-mortem was not performed.

The following two tables summarize the results of this study for two endpoints, cessation of spread of lesion and resolution of fever. The authors had also provided results for resolution of toxemia. As the definition of toxemia (prostration, headache, state of the tongue, insomnia, vomiting, abdominal distension, and delirium) was subjective, the results are not included here.

The proportion of cases that showed no spread of the lesion after the end of the first day was 58/98 (59%) in the UV group and 84/102 (82%) in the prontosil group. After two days in the hospital, the lesion continued to spread in only 2% (2/102) of all prontosil cases compared to 23/98 (23%) for the UV group. The number and percentage of patients who had resolution of the spread of the lesion by day of treatment in the UV light and prontosil groups are summarized in the following table:

**Table 1: Cessation of spread of lesion**

| Treatment | 0 days N (%) | 1 day N (%) | 2 days N (%) | 3 days N (%) | 4 days N (%) | 5 days and more N (%) | Total |
|---|---|---|---|---|---|---|---|
| UV light | 32 (32.7) | 26 (26.5) | 17 (17.3) | 11 (11.2) | 5 (5.1) | 7 (7.1) | 98 |
| Prontosil | 48 (47) | 36 (35.3) | 16 (15.7) | 1 (1) | 1 (1) | 0 | 102 |

After 48 hrs of treatment, 43/89 (48%) of patients in the UV group were afebrile compared to 70/72 (76%) in the prontosil group. As some patients did not have pyrexia at admission they were excluded from the denominators. The number and percentage of patients who had resolution of fever by day of treatment in the UV light and prontosil groups are summarized in the table 2:

**Table 2: Resolution of primary pyrexia**

| Treatment | 1 day N (%) | 2 days N (%) | 3 days N (%) | 4 days N (%) | 5 days and more N (%) | Total with Fever |
|---|---|---|---|---|---|---|
| UV light | 16 (18) | 27 (30.3) | 12 (13.5) | 11 (12.4) | 23 (25.8) | 89 |
| Prontosil | 37 (40.2) | 33 (35.9) | 14 (15.2) | 2 (2.2) | 6 (6.5) | 92 |

Treatment difference between the prontosil group and the UV group for the endpoints of cessation of spread of lesion and resolution of pyrexia 48 hours after institution of treatment are provided in the following table:

**Table 3: Assessment at 48 hrs**

| **Endpoint** | **Prontosil** | **Ultra-violet** | **Treatment difference (95% CI)** |
|---|---|---|---|
| Cessation of spread of lesion | 100/102 (98.0%) | 75/98 (76.5%) | 21.5% (11.7%, 31.3%) |
| Resolution of pyrexia | 70/92 (76.1%) | 43/89 (48.3%) | 27.8% (13.1%, 42.4%) |

2. Snodgrass and Anderson (BMJ 1937) [4]: As the previous study had demonstrated benefit of prontosil in the treatment of erysipelas and there was evidence that prontosil was converted in the body to sulphanilamide, Snodgrass and Anderson conducted the

second study with the following objectives: To evaluate the benefits of sulphanilamide in the treatment of erysipelas, to investigate the effects of a larger and more prolonged dosage and to investigate the effect of varying dosage of sulphanilamide during the first 12 hours.

Methods: All cases from middle of February to middle of August 1937 were included. The cases were assigned to two treatment groups in the order of their admission. There was a total of 270 cases, 135 in each group; 12 cases originally in the UV light group were subsequently treated with sulphanilamide. Other than the specific treatments assigned, the two groups were comparable. The wards to which they were admitted and the nursing staff was common to all cases. No other local treatment was given. Duration of illness before admission to hospital, age of the patient, severity of infection, and associated diseases were similar in the two groups.

Treatments: UV light was administered at a distance of 12" and was given for 8 minutes in females and 10 minutes in males, once daily. Treatment was repeated at 24 hr intervals if considered necessary. Average number of exposures was 1.4.

Sulphanilamide was given orally in a powder form as 1, 2, or 3 gram doses at 4 hourly intervals and was continued until temperature became normal. The average duration of this treatment was 2. 5 days and the average dose was 14.64 grams. Thereafter 0.75 grams was given three times a day until patient left the hospital. The average stay in the hospital was 14.4 days.

Results: Five deaths in the sulphanilamide group and one death in the UV light group were excluded from the analyses. In addition 12 patients who failed UV light and were switched to sulphanilamide (9 of whom recovered) were also excluded from the analyses. So, the total number of cases in the sulphanilamide group was 130 and in the UV light group was 122. In the sulphanilamide group 11 patients (8.1%) developed septic complications directly attributable to erysipelas compared to 28 patients (20.7%) in the UV light group.

The following two tables summarize the results of this study for two endpoints, cessation of spread of lesion and resolution of fever. The authors have also provided results for resolution of toxemia. As the assessment of toxemia was subjective, the results are not included here.

The proportion of cases which showed no spread of lesion after the end of the first day was 126/130 (96.9%) in the sulphanilamide group and 72/122 (59%) in the UV light group. After two days in the hospital, the lesions continued to spread in 1/130 (0.8%) of sulphanilamide treated cases and in 33/122 (27%) of the UV light treated patients.

The number and percentage of patients who had resolution of the spread of the lesion by day of treatment are summarized in the following table:

**Table 4: Cessation of spread of lesion**

| Treatment | 0 days N (%) | 1 day N (%) | 2 days N (%) | 3 days N (%) | 4 days N (%) | 5 days and more N (%) | Total |
|---|---|---|---|---|---|---|---|
| Sulphanilamide | 78 (60) | 48 (36.9) | 3 (2.3) | 1 (0.8) | - | - | 130 |
| UV light | 48 (39.3) | 24 (19.7) | 17 (14) | 12 (10) | 14 (11.5) | 7 (5.7) | 122 |

After 48 hrs of treatment, 53/112 (47.3%) patients in the UV light group were afebrile compared to 94/125 (75.2%) in the sulphanilamide group. Pyrexia continued for more than three days in 12/125 (9.6%) sulphanilamide treated cases compared to 45/112 (40%) in the UV light treated group. As some patients did not have pyrexia at admission they were excluded from the denominators. The number and percentage of patients who had resolution of fever by day of treatment are summarized in the following table:

**Table 5: Duration of primary pyrexia**

| Treatment | 0 days N (%) | 1 day N (%) | 2 days N (%) | 3 days N (%) | 4 days N (%) | 5 days and more N (%) |
|---|---|---|---|---|---|---|
| Sulphanilamide | 5 | 48 (38.4) | 46 (36.8) | 19 (15.2) | 9 (7.2) | 3 (2.4) |
| UV light | 10 | 28 (25) | 25 (22.3) | 14 (12.5) | 10 (8.9) | 35 (28.7) |

Treatment difference between the sulphanilamide group and the UV group for the endpoints of cessation of spread of lesion and resolution of pyrexia 48 hours after institution of treatment are provided in the following table:

**Table 6: Assessment at 48 hrs**

| **Endpoint** | **Sulphanilamide** | **Ultra-violet** | **Treatment difference (95% CI)** |
|---|---|---|---|
| Cessation of spread of lesion | 129/130 (99.2%) | 89/122 (73.0%) | 26.3% (17.5%, 35.1%) |
| Resolution of pyrexia | 94/125 (75.2%) | 53/112 (47.3%) | 27.9% (15.1%, 40.7%) |

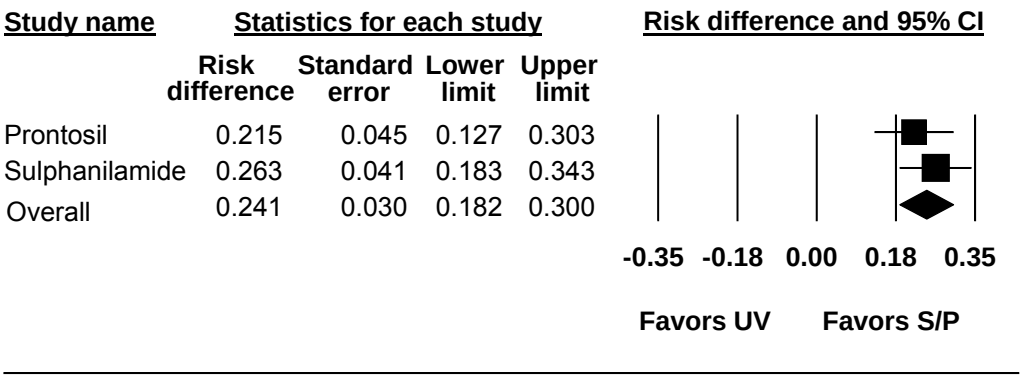
For the two endpoints of cessation of spread of lesion and proportion with apyrexia, a meta-analysis using a random-effects model was performed. The results are shown below:

Meta-analysis for cessation of spread of lesion

Figure 1 shows the results of a DerSimonian and Laird random effects meta-analysis for the endpoint of cessation of spread of lesion at 48 hours for the two studies described

above. The meta-analysis reveals that the overall antibacterial treatment effect with sulfonamides for the clinical endpoints of cessation of spread of lesion was 24.1% (95% CI, 18.2%, 30.0%).

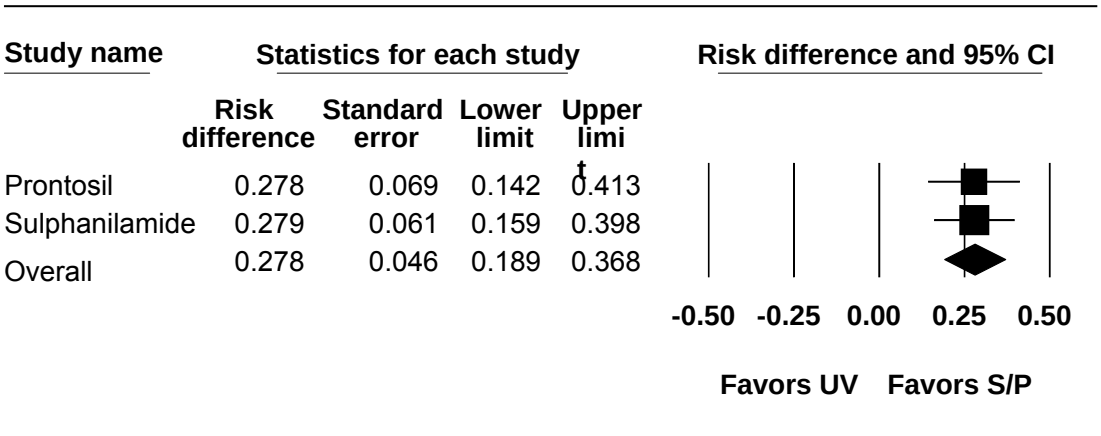
**Figure 1: Meta-analysis for cessation of spread of lesion at 48 hours**




Meta-analysis for resolution of pyrexia

Figure 2 shows the results of a DerSimonian and Laird random effects meta-analysis for resolution of fever at 48 hours as an endpoint in the two studies described above. The meta-analysis reveals that the antibacterial treatment effect for sulfonamides for the clinical endpoint of resolution of fever was 27.8% (95% CI, 18.9%, 36.8%).

**Figure 2: Meta-analysis for resolution of pyrexia at 48 hours**




The results of the two random effects meta-analyses in patients with erysipelas demonstrate that there is a statistically significant difference for the clinical endpoints of cessation of lesion spread and resolution of fever at 48 hours with the use of sulfonamides compared to UV light. The treatment effect of sulfonamides compared to

UV light in erysipelas for the endpoints of cessation of spread of lesion and/or the resolution of pyrexia was estimated to be 18% based on the lower bound of the 95% confidence intervals for the two meta-analyses discussed above. Using the lower bound of the 95% confidence interval is a conservative estimate of the antibacterial treatment effect and discounts for some of the uncertainties and the associated variability in the estimate of treatment effect.

**Other studies in erysipelas**

Several historical studies were identified that compared UV light therapy to other topical therapies. [5-9] Most of these studies showed that patients treated with UV light had better outcomes in terms of resolution of local signs and fever. It was not possible to quantify the treatment effect of UV light over other local therapies from these studies because the proportion of patients who had complete resolution of signs and symptoms at a fixed time point was not reported. Only the average time to resolution was reported, which can be influenced by outliers. Results of some of the larger series are summarized here. These data support the assumption that the placebo cure rate estimated from patients with erysipelas who were treated with UV light is likely to be an overestimate of the true placebo effect.

1. Ude WH and Platou ES [7]. JAMA July 5, 1930: Four hundred and two cases of erysipelas treated in the department of contagious diseases at the Minneapolis General Hospital during the years 1922-1929 were summarized in this report. Data from a follow up publication with 68 additional cases of erysipelas treated with UV light are included in the last column[8]. Mortality, average time to resolution of symptoms and to resolution of fever was lower in UV light treated patients.

**Table 7: Outcomes for different modalities of treatment in erysipelas**

| | Mg sulfate and glycerin pack | X-ray | UV light | Antitoxin | X-ray and Antitoxin | UV light and Antitoxin | UV light¶ |
|---|---|---|---|---|---|---|---|
| Years studied* | 1922, 1923, 1925 | 1926-1928 | 1928-1929 | 1927-1929 | 1926-1928 | 1928-1929 | 1928-1930 |
| N | 151 | 113 | 79 | 12 | 26 | 21 | 147 |
| Deaths | 30 (19.9%) | 15 (13.3%) | 6 (7.6%) | 0 | 4 (15.4%) | 5 (23.8%) | 11 (7.5%) |
| Deaths due to erysipelas | 27 (17.9%) | 14 (12.4%) | 5 (6.3%) | 0 | 4 (15.4%) | 5 (23.8%) | 10 (7%) |
| No. of patients < 1 yr old | 10 | 7 | 3 | 0 | 2 | 4 | 5 |
| % of deaths < 1 yr old | 70 | 86 | 33 | 0 | 50 | 50 | 40 |
| Average time to normal temp. (days) | 6.25 | 3.8 | 3.3 | 4.5 | 5.9 | 4.1 | 3.7 |
| Average time to normal symptoms (days) | 8.65 | 5.3 | 4.5 | 5.5 | 7.4 | 6.4 | 4.0 |

* The year 1924 was omitted due to the smallpox epidemic ¶ includes data from the follow up publication

2. Sutherland DS and Fay FM. The Medical Officer November 2, 1935[9].

A series of 90 cases of varying age and severity who were treated with UV light are described in this report. The majority of cases were elderly and debilitated and several were complicated by other conditions. All cases were treated in one ward reserved for acute cases of erysipelas. In 60% of cases, only one treatment was given. The authors note that 6-12 hrs after exposure, the erysipelas lesion was surrounded by erythema and usually in 48 hrs both the erythema and erythematous swelling subsided and usually pain was also completely relieved. The irradiated area desquamated later. Patients treated with UV light had better outcomes compared to those treated with other local therapies as summarized in the following table:

**Table 8: Comparison of outcomes in erysipelas patients treated with UV light**

| | UV light (n=90) | Other methods (n=90) |
|---|---|---|
| Average age of patients | 40 years | 38 years |
| Deaths | 6 (6.6%) | 9 (10%) |
| Average duration of pyrexia | 60 hrs | 108 hrs |
| Average stay in hospital | 18 days | 28 days |
| No. of relapses | 12 | 10 |

Others: ichthyol, glycerine, iodine, magnesium sulfate, anti-streptococcal serum

### 3. Natural history studies

Most of these studies describe patients with various types of skin infections, several of whom were bacteremic or had severe disease such as necrotizing gangrene. In clinical trials, the proportion of patents with bacteremia is usually very low and patients with necrotizing gangrene are usually excluded. So, these studies are not directly relevant to the majority of patients enrolled in present day clinical trials. Also, most of these studies used mortality as an endpoint, while in contemporary clinical trials clinical outcome is the primary endpoint. However, these studies still provide evidence that untreated disease is often fatal and that in survivors is associated with significant morbidity. In the following section, these studies will be described briefly.

1. Meleney FL, Archives of Surgery, 1924[10]: This case series of 20 patients with hemolytic streptococcus gangrene provides one of the earliest descriptions of the clinical outcomes in untreated streptococcal gangrene. Seven patients were bacteremic. Four patients (20%) died (three were bacteremic) and the remainder had a very prolonged recovery. Most were preceded by a minor trauma, while in a few there was no obvious portal of entry. The author notes that within 24 hours, the local lesion enlarged significantly and was often accompanied by systemic symptoms and prostration. By the $4^{th}$-$5^{th}$ day, the area became frankly gangrenous and by day 7-10, the line of demarcation became sharply defined, dead skin separated and eventually healing set in. However, in the more severe cases, the process continued to advance and the patient became progressively more ill. Wound care consisted of incision and drainage, use of soaks and

Dakins solution. Re-epithelialization took much longer and often grafting was done on an average by the fiftieth day.
2. Skinner and Keefer, Archives of Internal Medicine 1941[11] : This report described 122 cases of *S. aureus* bacteremia at Boston city Hospital. Only 22 patients recovered (fatality rate 82%). The portal of entry was skin (57), respiratory tract (30), bone (11), genitourinary tract (11), other/unknown (13). Of the 57 cases of skin infections, 30 had boils and carbuncles, 14 had infected wounds, and 14 had other lesions.

Of the 75 patients who received only general care, 63 (84%) died, while 33/42 (78.5%) who received general care plus sulfonamides died. In all 22 cases that recovered, the infection was localized into superficial abscesses with no deep infections. It is unclear as to how many of these patients were treated with sulfonamides. In 31 patients, the infection localized and an abscess formed that was amenable to surgical treatment. In this group, mortality was 29%.

3. Keefer CS, Ingelfinger FJ, Spink WW 1937[12]: This is a series of 246 cases of hemolytic streptococcal bacteremia; 61 had cellulitis/erysipelas. The overall mortality was 72%, with the highest (49/61, 80%) mortality in those with cellulitis and erysipelas irrespective of age.

### 4. Uncontrolled studies

A series of articles have been published describing the clinical response seen in patients with various types of surgical infections, including skin and soft tissue infections who were treated with penicillins or sulfonamides. Most of these studies were uncontrolled and are only discussed briefly. The study by Florey conducted in patients with hand infections is described in greater detail as the types infections studied are fairly representative of the types of infections seen in patients enrolled in current cSSSI trials. Also, as the surgical procedures were standardized between the two groups, it is likely that treatment effect seen with penicillin represents an antibacterial effect beyond that achieved by the surgical procedure alone.

**Studies that evaluated use of penicillin**
1. Florey et al. Lancet 1944[13]

This was a study of local application of penicillin driven primarily by the limited availability of penicillin. Hand infections were chosen as they were common, caused permanent disability and considerable loss of working time. In this comparative study of 212 cases of acute hand infections, half were treated with current methods and the other half by local penicillin application in addition to the usual surgical procedures. The authors state that "*the great majority of control cases remained septic for over a week and nearly 3/4$^{ths}$ were infected till their wounds healed. In penicillin treated cases, sepsis by clinical and bacteriologic criteria was eliminated within a week, pus was scanty, and relief of pain and improvement in general condition was striking*."

Alternate cases were treated with penicillin. Observations were made at operation and daily in the acute phase and twice a week after that. Patients were followed for up to 6 months after surgery. The same team operated on both the penicillin treated and control patients. Post-operative care of outpatients in both series was provided by one investigator. Control patients received various local applications and some received sulfonamides by mouth.

Treatments:
Controls: Wounds were packed with paraffin gauze at operation and later with eusol preparations. As wounds became superficial, topical sulfonamide or gentian violet was sometimes applied.

Penicillin: At operation, the wounds were powdered with the calcium salt of penicillin and packed with gauze soaked in penicillin paste. Treatment was usually given for a week.

Other treatments: Oral sulfonamides were used in the more severe control cases and in 3 of the penicillin cases.

**Table 9: Summary of cases based on site of infection**

| Site of infection | Control | Penicillin-treated |
|---|---|---|
| Paronychia | 26 | 26 |
| Pulp infection | 27 | 28 |
| Web-space infection | 9 | 9 |
| Tendon sheath infection | 11 | 11 |
| Miscellaneous abscesses | 12 | 12 |
| Septic lacerations | 5 | 6 |
| Miscellaneous lesions | 12 | 18 |
| Total | 102 | 110 |

These reflect numbers treated, follow up was not available for all patients so numbers in the descriptions may differ

Group A Streptococci and *S. aureus* were the most common organisms identified. Others included micrococci, other hemolytic streptococci, and coliforms. The initial infecting organisms were as follows:

**Table 10: Initial infecting organisms**

| Group | *S. aureus* | *S. pyogenes* | Both | Other hem strep | Micrococci | Coliforms | Total |
|---|---|---|---|---|---|---|---|
| Controls | 74 | 6 | 21 | 0 | 1 | 0 | 102 |
| Penicillin | 66 | 13 | 27 | 1 | 2 | 1 | 110 |

Following is a summary of the cases by infection type:

**Paronychia:**
There were 21 controls and 22 cases of paronychia. Duration of symptoms was 1 day- 6 weeks. Infections were due to *S. aureus* or *S. pyogenes*. There was little evidence of pus in both groups, hence drying was considered an adequate criterion to assess efficacy. The mean days to drying in the penicillin group was 15.5 ± 8.2 days and in the control group was 7.7 ±3.2 days (difference 7.8±2.6).

**Simple pulp infections:**
This group was confined to deep infections of the soft tissues of the pulp, all subcutaneous abscesses were excluded. Six penicillin cases and 4 controls had osteitis and were excluded from the analysis.

**Table 11: Outcomes in patients with simple pulp infections**

| | Days to disappearance of pus (21 controls, 22 cases) Mean±SD | Dry (23 controls, 22 controls) Mean±SD | Epithelialised (19 controls, 20 cases) Mean±SD | Full movement (22 controls, 19 cases) Mean±SD |
|---|---|---|---|---|
| Control | 14.2 ± 12.8 | 20.7 ± 13.0 | 29.7 ± 13.5 | 25.7 ± 19.5 |
| Penicillin mean±SD | 1.4 ± 2.7 | 10.8 ± 4.8 | 21.7 ± 8.7 | 11.7 ± 4.3 |
| Difference mean±SD | 12.8 ± 2.9 | 9.9 ± 2.9 | 8.0 ± 3.7 | 14.0 ± 4.3 |

In addition to the difference in days to resolution of signs and symptoms noted above, there was difference in between the two groups in duration of pain and throbbing.

**Web-space infections:**
One control case received oral sulphathiazole after surgery. There was one case of thenar infection in each group and one control and 3 penicillin cases had two spaces affected. As shown in table 12, penicillin-treated patients had better outcomes.

**Table 12: Outcomes in patients with web-space infections**

| | Days to disappearance of pus (9 controls, 9 cases) Mean±SD | Full movement (9 controls, 9 cases) Mean±SD | Healed (9 controls, 9 cases) Mean±SD |
|---|---|---|---|
| Control | 15.7 ± 16.0 | 24.7 ± 17.3 | 34.2 ± 20.3 |
| Penicillin | 3.6 ± 3.3 | 10.4 ± 8.3 | 18.8 ± 6.5 |
| Difference | 12.1 ± 5.3 | 14.3 ± 2.1 | 15.4 ± 7.1 |

**Tendon-sheath infection:**
Patients with tenosynovitis that occurred as a complication in other groups and cases of suspected tendon-sheath infection that did not have evidence at operation of increased fluid or perforation of sheath by a septic sinus were excluded. Severity was judged based

on type of fluid in sheath (clear, turbid, or frankly purulent), condition of tendons and extension into other spaces. Six penicillin cases and 4 controls were severe. Five controls received oral sulphonamide, 4 post operatively and one pre-operatively. One penicillin treated patient who had lymphangiitis and lymphadenitis received sulphanilamide for two days before surgery.

The authors note that pus was copious in all controls and slough was a prominent feature while in the penicillin group it was always scanty. They also note that these patients were ill, had fever, loss of appetite, pain and often sleeplessness and if sepsis persisted, pallor and weight loss were obvious. Penicillin patients were fit enough to be asking to go home in the second week and apart from the painful dressings they appeared to recover rapidly and to suffer little pain. Clinical outcomes in the two groups are summarized in the following table:

**Table 13: Outcomes in patients with tendon-sheath infections**

| | Disappearance of pus (10 controls, 11 cases) Mean±SD | Disappearance of fever (10 controls, 11 cases) Mean±SD | Healing (11 controls, 10 cases) Mean±SD |
|---|---|---|---|
| Control | 40.4 ± 21.4 | 12.0 ± 8.8 | 58.9 ± 30.3 |
| Penicillin | 5.9 ± 5.8 | 3.7 ± 2.6 | 34.1 ± 18.6 |
| Difference | 34.8 ± 7.0 | 8.3 ± 4.0 | 24.8 ± 10.9 |

**Abscesses:** This series included well formed circumscribed abscesses, in various parts such as hand, forearm, axilla, groin, back of neck. Three-quarters of each series had received expectant treatment and in some resolution was already taking place. The authors stated that the value of drug was not likely to be great in this group of patients. Three patients received penicillin injection into abscess cavity. Healing time and, in some cases, cessation of pus was similar in the two groups. However, the amount of pus formed was much less in the penicillin group.

**Table 14: Outcomes in patients with abscesses**

| | Days to disappearance of pus (12 controls, 12 cases) Mean±SD | Dry (12 controls, 12 cases) Mean±SD |
|---|---|---|
| Control | 9.6 ± 7.8 | 23.6 ± 10.3 |
| Penicillin | 3.4 ± 1.8 | 20.8 ± 10.9 |
| Difference | 6.2 ± 2.8 | 2.8 ±0.17 |

**Septic lacerations of hand:**
As clinically, the cases and controls were different, the authors did not compare clinical outcomes and only compared microbiologic outcomes. All cases were open suppurating wounds which involved more than one tissue.

2. Lyons C. JAMA 1943 [14]. In this series, both intravenous and intramuscular penicillin were used. Limited local treatment was also used. Overall, 49/57 (86%) of patients were

improved. It appears that patients with abscesses had a higher cure rate compared to those with wound infections. The numbers of patients with the different types of skin infections were however very small. The following table summarizes the results seen in patients with skin and skin structure infections:

**Table 15: Outcomes in patients with skin and skin structure infections**

| Diagnosis | Number | Improved | Died | No effect |
|---|---|---|---|---|
| Abscesses | 12 | 11 | 0 | 1 |
| Burns | 2 | 1 | 1 | 0 |
| Skin and subcutaneous tissue | 12 | 11 | 0 | 1 |
| Wound infections | 21 | 17 | 0 | 4 |
| Cellulitis | 5 | 5 | 0 | 0 |
| Erysipelas | 1 | 1 | 0 | 0 |
| Wound infections | 2 | 1 | 0 | 1 |
| Pyoderma | 1 | 1 | 0 | 0 |
| Cellulitis | 1 | 1 | 0 | 0 |
| Total | 57 | 49 | 1 | 7 |

3. Garrod LP. BMJ 1943 [15]: This is an abstract of a report published by the War Office entitled "A preliminary report to the war office and the medical research council on investigations concerning the use of penicillin in war wounds carried out under the direction of Prof HW Florey and Brig. Hugh Cairns".

A total of 171 cases of recent soft- tissue wounds treated with penicillin were described. Most wounds were 3-12 days old, majority were infected, some were purulent and most were clinically dirty. All underwent immediate closure and penicillin was administered through tubes inserted at operation twice daily for 4 days. In some cases, penicillin powder was used. Results were as follows: 104/171 (60.8%) had complete union, 60/171 (35%) had subtotal union, i.e. healing by granulation and 7/171 (4%) failed.

4. Keefer CS et al. JAMA 1943 [16]: This report summarizes 500 cases of various types of infections treated with penicillin. Penicillin was administered IV, IM or locally. The amount of penicillin and frequency of administration varied. There were 91 patients with *S. aureus* bacteremia; 34/91 (37%) died. Of the patients with bacteremia, 10 had infections of the skin and subcutaneous tissues and all recovered. Of the 137 cases with local staphylococcal infections without bacteremia, 109 (80%) recovered or improved, 11 (8%) died, and in 17 (12%) there was no effect. Among the 23 patients with cSSSI in the non-bacteremic group, 19 greatly improved or recovered completely and 4 failed (1 had an abscess of the thigh, treated locally, 1 had extensive psoriasis with local staphylococcal infection, and one each had chronic sinus/ulcer).

5. Lockwood JS et al. Annals of Surgery 1944[17]: This is a summary of 440 medical and surgical cases treated with penicillin. Of the 57 cases of staphylococcic bacteremia, two thirds survived. The source of bacteremia was not specified in the cases. Only a few cases

of boils/carbuncles were treated because of the likelihood of spontaneous recovery and shortage of penicillin supply. The author noted that checking the spread of cellulitis and localization of the suppurative focus usually occurred 2-3 days after commencing systemic therapy.
6. Meleney FL. Annals of Surgery 1946[18]: This report summarizes 744 cases of surgical infections including cases of skin infections treated with systemic or topical penicillin (438 systemic alone, 142 local alone, 164 both systemic and local). Outcomes were classified as follows:

Excellent- Cases responding abruptly/ definitely within first 72 hours of treatment
Good- Cases clearly showing the benefit of the drug but over a longer period of time, perhaps a week or ten days.
Questionable- Cases which might have done just as well without the drug as a result of the surgical procedure or some other associated treatment.
No effect- Cases in which infection was not altered in any way but ran its natural course.

Overall results were favorable in ~65% of penicillin treated cases and unfavorable in 35% as shown in the following table:

**Table 16: Outcomes in patients with all types of surgical infections**

| Total number | Favorable | | | Unfavorable | | |
|---|---|---|---|---|---|---|
| | Excellent | Good | Combined | Questionable | No effect | Combined |
| 744 | 14.8 % | 49.9 % | 64.7 % | 17.8 % | 17.6 % | 35.4 % |

In the following table, the outcomes by diagnosis for 340 patients with skin and skin structure infections are presented. Cure rates varied by the infection type with the highest cure rates in patients with cellulitis and furuncles and the lowest rates in those with ulcers/ infected burn.

**Table 17: Outcomes in patients by type of skin and skin structure infection**

| Diagnosis | Total cases (n) | Favorable % | Unfavorable % |
|---|---|---|---|
| Furuncle | 26 | 92.3 | 7.7 |
| Cellulitis | 36 | 91.7 | 8.3 |
| Carbuncle | 28 | 82.2 | 17.9 |
| Superficial abscess | 32 | 81.3 | 18.8 |
| Deep abscess | 58 | 68.9 | 31.0 |
| Infected soft part wound | 37 | 64.8 | 35.1 |
| Infected operative wound | 70 | 61.3 | 38.6 |
| Ulcer of the skin | 22 | 50.0 | 50.0 |
| Infected burn | 31 | 45.2 | 54.8 |

**Studies that evaluated use of other antibacterials**

1. Long and Bliss. JAMA 1937 [19]: This is a summary of 19 cases treated with para-amino-benzene-sulfonamide and its derivatives. Cases were treated with parenteral (iv/sc) and oral therapy. Of the 7 cases of SSSI, all 5 with erysipelas recovered. Fever returned to normal in 24-60 hours and lesions disappeared rapidly. One patient was bacteremic with beta hemolytic streptococcus. In the one patient with chronic impetigo (3.5 months) who had resisted all therapy lesions improved after drug administration and culture was negative for beta hemolytic streptococcus in 4 days. The seventh patient had cellulitis, bacteremia due to beta hemolytic streptococcus and septicemia and died 9 hrs after first injection.

2. Keefer CS. NEJM 1938 [20]. In this report, nine cases of hemolytic streptococcal infection with bacteremia and 8 cases of localized infection without bacteremia were described. Of the 9 patients with bacteremia three had SSTI (2 cellulitis, one post-operative wound infection) and all of them survived. Of the eight cases of localized infection without bacteremia, 7 with puerperal sepsis and 1 with cellulitis were described; there were no deaths.

3. Kirby WMM. NEJM 1960[21]. In the 1950s, the role of vancomycin in the treatment of staphylococcal infections was evaluated. Several of these patients were bacteremic and some of them had localized staphylococcal infections. Kirby et al. evaluated vancomycin in 33 patients from 1957-1959. All patients except one had bacteremia. Overall, 20/33 (61%) patients were cured, 6 improved but died of underlying diseases and 7 were failures. Of the 20 patients with skin infections, 11 were cured and 4 had improved.

## 5. Historical evidence for sensitivity to drug effect (HESDE) in uSSSI

The placebo cure rates in impetigo were estimated from studies that compared topical/systemic therapy to placebo. Placebo success rates in simple cutaneous abscesses were assessed from studies that compared incision and drainage plus systemic antibacterials to incision and drainage alone.

### Impetigo
### Studies assessing topical therapy

1. Phase 3 clinical trial of Altabax (retapamulin ointment, 1%)[22]: Retapamulin is a topical antimicrobial, approved for the treatment of impetigo. This study was used to estimate the placebo success rate because it was conducted in a contemporary patient population. This was a randomized, double-blind, multi-center, placebo-controlled Phase 3 study in adult and pediatric subjects ≥ 9 months of age with impetigo. Topical retapamulin 1% BID was compared to placebo BID for 5 days in 210 (139 retapamulin and 71 placebo) adult and pediatric patients with a clinical diagnosis of primary bullous or non-bullous

impetigo. Patients with a bacterial skin infection that due to depth or severity could not be treated by a topical antibiotic were excluded.

The primary endpoint was clinical response at the end of therapy (EOT) visit on Day 7. Clinical success was defined as the absence of lesions that had been treated, or if the treated lesions were dry, without crusts, and with or without erythema compared to baseline, or there was improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy was required. Success rates in the ITT population at the EOT visit were 119/139 (85.6%) for retapamulin and 37/71 (52.1%) for placebo. The treatment difference between the retapamulin and placebo group was 33.5% (95% CI, 20.5%-46.5%).

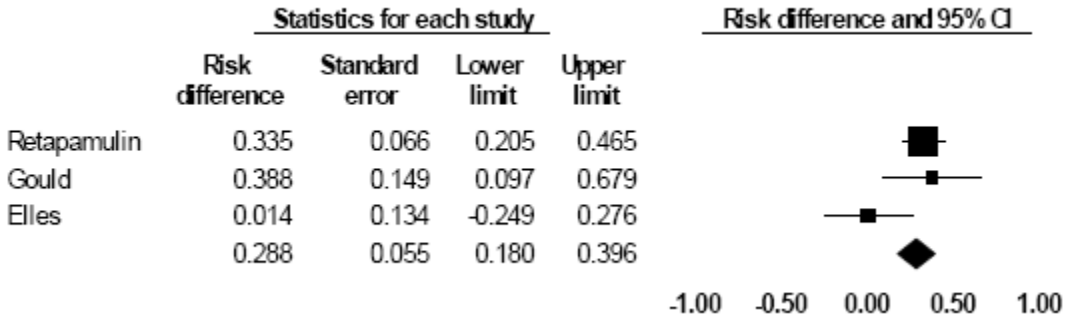
2. Eells LD. Arch Dermatol 1986 [23]: This was a randomized, double-blind, vehicle-controlled study comparing 2% mupirocin to vehicle (polyethylene glycol) in the treatment of impetigo/ecthyma. Fifty-two patients were enrolled and 27% of patients were subsequently not evaluable. Treatment was administered three times per day for 8±1 days. One patient in the vehicle group who had ecthyma was excluded from the ITT analysis. The ITT results for clinical success (Cure + Improvement) at the EOT visit were 17/26 (65.4%) in the mupirocin group and 16/25 (64.0%) in the vehicle group. It should be noted that 27% of the patients were unevaluable. The treatment difference between the mupirocin and vehicle group was 1.4% (-28.8%, 31.6%).

3. Gould PW. N Z Med J 1986 [24]: This was a randomized, double-blind, placebo-controlled study comparing mupirocin and placebo. One hundred seven (107) patients (54 mupirocin and 53 placebo) with acute primary skin infections, infected dermatoses, or infected traumatic lesions who had not received topical or systemic antibiotics during the preceding 3 days were enrolled in the study. The clinical success (Cure + Improvement) in the subgroup of patients with impetigo in the ITT population at the EOT visit were 12/17 (70.6%) in the mupirocin group and 7/22 (31.8%) in the placebo group. The treatment difference between the mupirocin and placebo group was 38.8% (4.4%, 73.1%).

4. Koning 2004 [25]: In a Cochrane review of interventions for impetigo, topical antibiotics showed better cure rates than placebo (pooled odds ratio (OR) 6.49, 95% CI, 3.93 to 10.73), and neither of the two topical antibiotic was superior to the other (pooled OR of mupirocin versus fusidic acid 1.76, 95% CI 0.69 to 2.16).

Meta-analysis of topical studies
Using a fixed effects meta-analysis of the three topical antibacterial studies in impetigo described above, the antibacterial treatment difference compared to placebo in the ITT population was 28.8% (95% CI, 18.0%, 39.6%).

**Figure 3: Meta-analysis of topical studies for uSSSI**




## Studies assessing systemic therapy

1. Burnett JW. NEJM 1962[26]: Eighty-nine outpatients with yellowish crusted skin lesions were studied from Jan-June 1961. They were randomly assigned to one of four groups- erythromycin propionate and wet dressings, erythromycin without wet dressings, placebo, or wet dressings. Of the 89 cases, 60 had impetigo and 29 had other skin infections (all had very purulent edematous, yellow exudates and had antecedent dermatologic conditions that had become secondarily infected). Patients were seen 3-4 days after starting therapy and at intervals of 3-4 days. There were no dropouts. When continual treatment did not occur, treatment was declared a failure and patients were given an alternate antibiotic. The gram stain was positive in 97.8% of patients, 75 (84.2%) had a positive culture for *S. aureus, S. pyogenes*, or both.

In the erythromycin group, the cure rate was 86.4% (38/44) and in the no-antibiotic group the cure rate was 24.4% (11/45). The treatment difference between the two groups was 61.9% (95% CI 43.5%, 80.3%). The average time to healing in the antibiotic group was 10 days and in the controls was 25 days.

2. Eaglstein WH. Arch Dermatol 1977[27]: Hospitalized patients with dermatitis considered secondarily infected based on wet, oozing, weeping appearance and crusts were included in this study. They were afebrile, had normal WBC and negative blood cultures. Patients were randomly assigned to cloxacillin 250 mg qid or placebo capsules for 7 days. All patients received tap water compresses. Each clinical feature was graded on a scale of 0-3.

Twenty-eight patients were studied over the three year period, 14 in each treatment group. The mean pre-treatment values for the clinical characteristics were similar in the two groups. The groups were also similar with respect to age, sex, race, and type of dermatitis. On the 6$^{th}$ day, the cloxacillin-treated group had significantly less redness, weeping, and crusting and by the 7$^{th}$ day, there was more re-epithelialization in the antibiotic-treated group.

Bower M. Med J Aust 1984 [28]: Children > 4 months of age attending an outpatient clinic were enrolled in the trial if they presented for treatment of sores only, had a skin lesion which had surrounding cellulitis, or was exuding pus, or was greater than 3 cm in

diameter, or had more than 5 sores greater than 2 cm in size, and had no medical treatment for six days. Children were randomly assigned to receive either penicillin or placebo. In the penicillin group they received i.m. procaine penicillin on day 0 and day 2. In the placebo group, they received one dose of pigbel vaccine on day 0 and a dose of triple antigen on day 2.

There were a total of 227 children in the study, 114 in the penicillin group and 113 in the placebo group. Of the 227 children, 70 (30%) had infected sores, 58 (26%) had infected scabies, 44 (19%) had infected cuts, 30 (13%) had tropical ulcers and the remainder had boils, burns or a bite. Effect of treatment was only assessed in the 68 children who had three visits (30 in the penicillin group and 38 in the placebo group). A scoring system was used to assess response and the overall cure rates were significantly higher in those treated with penicillin.

The following table summarizes the treatment effect seen in studies of uSSSI:

**Table 18: Clinical Success in the ITT Population for Impetigo Studies**

| Study | Administration Route | Antibacterial Agent | Success Rate n/N (%) | | Treatment Difference (Antibacterial – Vehicle) (95% CI) |
|---|---|---|---|---|---|
| | | | Antibacterial | Vehicle | |
| Retapamulin | topical | retapamulin | 119/139 (85.6%) | 37/71 (52.1%) | 33.5% (20.5%, 46.5%) |
| Gould | topical | mupirocin | 12/17 (70.6%) | 7/22 (31.8%) | 38.8% (4.4%, 73.1%) |
| Eells | Topical | mupirocin | 17/26 (65.4%) | 16/25 (64.0%) | 1.4% (-28.8%, 31.6%) |
| Burnett | PO | erythromycin | 38/44 (86.4%) | 11/45 (24.4%) | 61.9% (43.5%, 80.3%) |

## Abscesses

The utility and clinical benefit of adjunctive antimicrobial therapy following primary incision and drainage of abscesses has been questioned. Based on the following randomized, double-blind, placebo-controlled studies there is evidence to suggest that antimicrobial therapy following primary incision and drainage of abscess provides no additional benefit, over incision and drainage alone.

1. Llera JL. Annals of Emergency Medicine 1985[29]: Adults with cutaneous abscesses treated in a single ER with primary incision and drainage were randomized to receive cephradine or placebo QID for 7 days. Although 81 patients were randomized, follow-up and results were reported for 50 (62%) patients; 27 treated with cephradine and 23 with placebo. Follow-up results at 7 days (either in person or by telephone) indicated clinical improvement in 26/27 patients receiving cephadrine and 22/23 patients receiving placebo (both 96%).

2. Rajendran PM. Antimicrob Agents Chemother 2007[30]: A randomized, double-blind study of 166 subjects with surgically drainable, non-recurrent abscesses was conducted in an outpatient clinic where patients were at high risk for MRSA infection. Approximately 80% of abscesses were < 5 cm in size. After primary incision and drainage, patients were randomized to receive cephalexin 500 mg or placebo QID for 7 days. There was no difference in clinical cure rate between patients receiving cephalexin 69/82 (84.1%)

versus placebo 76/84 (90.5%); 42/82 patients treated with cephalexin had MRSA with 2 failures and 43/84 patients treated with placebo had MRSA with 4 treatment failures.

3. Lee MC. Pediatr Infect Dis J 2004[31]: This was a prospective observational study in which children presenting to a single ER or acute care center with a skin abscess caused by MRSA were identified by microbiological culture results. Information regarding patient characteristics and nature of infection, along with initial and subsequent antimicrobial therapy following incision and drainage was obtained. Clinical improvement was noted in most instances despite ineffective antimicrobial therapy. However, patients with infection site of > 5 cm were more likely to fail management with incision and drainage if given inappropriate antimicrobial therapy.

**Supportive evidence for treatment effect in cSSSI**

1. **Dose ranging studies:**

Dose-ranging studies for the treatment of cSSSI were reviewed to assess if clinical cure rates with the lower dose could be used as an estimate of the placebo cure rates in patients with cSSSI. [32, 33]
Both studies were open-label randomized controlled studies. The placebo cure rates could not be estimated from these two dose-ranging studies for the following reasons:

- In one study there was a difference in the assessment time between the two groups
- In the other study, a small difference (<10%) in clinical success rates between the high (approved dose) and low dose groups suggests that the low dose may have been effective and therefore does not provide a reasonable estimate for the placebo success rate. The following table summarizes these two studies:

**Table 19: Dose-ranging studies in cSSSI**

| Author/Year | n | Treatments | Response | Comments |
|---|---|---|---|---|
| Seltzer et al. CID 2003 | 62 | 2 doses of dalbavancin 1100 mg or 1 gram followed by 500 mg 1 week later vs. standard of care | ITT: 60% in single dose group, 91% in 2-dose group, 76% in comparator<br>CE: 64% in single dose group, 92% in 2-dose group, 76% in comparator | Small number of patients/group. Follow up period in the 1 –dose group occurred sooner (day 24) than that in 2-dose group (day 34) |
| Postier et al. Clin Therap 2004 | 160 | Tigecycline 25 mg BID vs. 50 mg BID | ?CE: 67% (53.3-79.3) in the low dose and 74% (60.3-85) in the high dose | Likely low dose was also effective |

## 2. Studies of prophylaxis:

Prophylactic administration of antimicrobial therapy has demonstrated the ability to reduce the rate of infections in certain circumstances and provide supportive evidence for treatment effect with antibacterials in SSTI. However, since infection rates were low and the studies were of limited size, it was difficult to quantify the magnitude of the treatment benefit.

1. Maddox JS. J Am Acad Dermatol 1985 [34]: Use of prophylactic topical therapy for skin infections was assessed at a day care center during the known seasonal peak for streptococcal pyoderma. Fifty nine children 2-5 years of age were treated with either an antibiotic or placebo ointment (treatment was blinded to observers, but randomization process not stated). Children were observed daily, with ointment applied to minor breaks in the skin or bites. Skin infections developed in 4/27 (15%) treated with bacitracin and 15/32 (47%) of patients receiving placebo.

2. Dire DJ. Acad Emerg Med1995 [35]: This was a single center, randomized, double-blind, placebo-controlled study of topical antimicrobial therapy in prevention of infection in patients with uncomplicated soft-tissue wounds presenting to the ER within 12 hours of injury and necessitating suturing. Patients with puncture wounds, immunosuppression, underlying fractures, neurovascular compromise, or who had used antibiotics within the past 7 days were excluded. Patients were randomized to one of four topical treatments; antibiotic-free carrier ointment (petrolatum control - PTR), bacitracin zinc ointment (BAC), neomycin sulfate, bacitracin zinc, and polymixin B sulfate combination (NEO), or silver sulfadiazine (SIL). Use of BAC, NEO, or SIL for uncomplicated, repaired lacerations resulted in lower infection rates compared to the control group that received petrolatum.

Four hundred sixty five patients were enrolled. Data for 39 patients was excluded due to protocol violations (primarily no follow-up). Infection prevention rates (per protocol) were reported for those patients who followed up. The overall wound infection rate was 9.9% (42/426). The infection rates for each treatment group were as follows: BAC 6/109 (5.5%), NEO 5/110 (4.5%), SIL 12/99 (12.1%), and PTR 19/108 (17.6%).

## 3. Discordant therapy:

Studies in which administered antimicrobial therapy is shown to be inactive against the pathogen isolated have served as surrogates for placebo-controlled studies or untreated infection. These studies are retrospective in nature and have limited utility in establishing treatment effect due to inclusion of a variety of bacterial organisms, small sample size, inadequate endpoint definition, failure to include co-morbidities, and consideration of spontaneous resolution of minor infections. However, they provide indirect evidence for treatment effect with antibacterials in skin infections.

**Contemporary cSSSI trials**

In most contemporary cSSSI trials, entry criteria include lesions that involve deeper soft tissue or require surgical intervention such as surgical/traumatic wound infection, major abscesses, cellulitis, and infected ulcers. Severity is often defined based on the presence of the following: fever, presence of purulent drainage, localized warmth, tenderness, elevated WBC etc. Often patients in these studies have underlying comorbidities such as diabetes mellitus and peripheral vascular disease. Most recent clinical trials have evaluated parenteral antibacterial therapy, most often administered in an inpatient setting, though some patients have been treated as outpatients provided they meet certain pre-specified criteria. Patients with uSSSI such as simple abscesses, impetigo, furuncles, folliculitis, and secondarily infected dermatoses are excluded from these studies.

Concomitant therapy in the form of surgical interventions and local wound care measures are usually permitted. The exact number and nature of surgical procedures allowed has varied among the studies. Some studies have differentiated bedside surgical interventions from those performed in the operating room. Similarly, the nature and extent of local therapies allowed has also varied among studies. Patients who undergo amputation such that the focus of infection is removed are usually considered failures.

Outcome is typically assessed at a fixed time point relative to completion of study therapy. The test of cure visit generally occurs 7-14 days after end of therapy. Patients are classified as either cure or failure based on resolution or improvement of signs and symptoms and the need for further antibacterial therapy.

All recent registrational trials have been non-inferiority trials and have used an NI margin of 10-15%. The active comparators in these studies have included vancomycin, linezolid, and semi-synthetic penicillins. Some studies have allowed for initiation of therapy with vancomycin with an option to switch to semi-synthetic penicillins if MSSA was identified. Similarly some studies have allowed for oral switch after a period of parenteral therapy. Additionally, some studies have allowed for concomitant aztreonam for gram-negative coverage and metronidazole for anaerobic coverage.

**Active comparator success rates in cSSSI**

To examine the effect of antibacterials that could be used as active comparators, studies from recent NDA submissions were identified. Recent studies were used because of concerns about constancy of the treatment effect related to potential differences in baseline patient and pathogen characteristics. Table 20 displays the results for clinical studies from recent NDA submissions.

**Table 20: Clinical Success Rates at TOC for Contemporary cSSSI Studies (ITT)**

| Drug / Study | Comparator | Test Drug Clinical Success Rate n/N (%) | Comparator Clinical Success Rate n/N (%) |
|---|---|---|---|
| Tigecycline Study 300 | vancomycin + aztreonam | 217/295 (73.6) | 217/288 (75.4) |
| Tigecycline Study 305 | vancomycin + aztreonam | 231/275 (84.0) | 235/271(86.7) |
| Daptomycin Study 9801 | vancomycin or SSP | 165/264 (62.5) | 162/266 (60.9) |
| Daptomycin Study 9901 | vancomycin or SSP | 217/270 (80.4) | 235/292 (80.5) |
| Linezolid Study 55 | SSP | 278/400 (65.5) | 274/419 (65.4) |
| Meropenem Study 3591IL/009 | imipenem-cilastatin | 295/510 (57.8) | 321/527 (60.9) |
| Moxifloxacin Study 100273 | piperacillin / tazobactam | 148/273 (54.2) | 157/274 (57.3) |
| Moxifloxacin Study 10279 | amoxicillin/clavulanate | 295/406 (72.6) | 297/397 (74.8) |

SSP: semi-synthetic penicillin

As shown in the above table, the cure rates varied between studies. The relatively low clinical success rates seen in moxifloxacin Study 100273, may be explained by the large proportion of patients who had inconclusive results at the TOC assessment (moxifloxacin: 30%; piperacillin/tazobactam: 26%). Most of these patients were missing a TOC assessment (moxifloxacin: 22%; pipercillin/tazobactam: 20%). Note, this level of inconclusive data was not seen in the other moxifloxacin study, Study 10279, where the proportion of indeterminate findings was small (moxifloxacin 1%; amoxicillin /clavulanate 1%). For meropenem Study 3591IL/0079, the relatively low rates for clinical success may be explained by the large number of patients who discontinued study treatment due to failing enrollment criteria [meropenem: 79/510 (16%); imipenem-cilastatin: 60/527 (11%)].

**Treatment Efficacy of Linezolid versus Vancomycin**

To examine whether there is evidence that linezolid is more effective than vancomycin for the treatment of cSSSI, the following studies were identified that compared linezolid to vancomycin in the treatment of cSSSI.

Weigelt J. Antimicrob Agents Chemother 2005[36]: Study 128 was a Phase IV randomized, open-label, multi-center trial comparing linezolid to vancomycin in the treatment of cSSSI; 1180 patients were randomized and received either IV or oral linezolid 600 mg every 12 hours or IV vancomycin 1 gm every 12 hours. Vancomycin patients with documented MSSA were to be switched to a semi-synthetic penicillin (oxacillin, nafcillin, flucloxacillin, or dicloxacillin). The minimal treatment period was 4 days, and the treatment duration was intended to be 7 to 14 days but not longer than 21 days.

The primary endpoint was clinical response at the Test-of Cure visit (7 days after End-of-Therapy) in the ITT population. The ITT results presented in the paper excluded 226 (107 linezolid, 119 vancomycin) patients who had indeterminate outcomes. Because this analysis is not protected by randomization and is susceptible to selection bias, we present the authors' sensitivity analysis where all indeterminates were considered failures. In this analysis, the clinical response rates were 75.3% (439/583) for the linezolid group and 70.2% (402/573) for the vancomycin group. The observed treatment difference was 5.1% with a corresponding 95% CI of (0%, 10.3%). As this was an open label study it has the potential to seriously bias the results. Thus, it can be inferred that linezolid is at worst similar to vancomycin. This study does not however provide evidence that a larger NI margin can be justified when linezolid is used as a comparator rather than vancomycin.

Stevens DL. Clin Infect Dis 2002[37]: This was a randomized, open-label, multicenter trial that compared linezolid IV/PO to vancomycin IV for the treatment of methicillin-resistant *Staphylococcus* species (MRSS) infections; 468 patients, thirteen years or older, were randomized with 460 patients receiving study medication. Patients enrolled had the following primary sources of MRSS infections: skin and soft tissue infections, pneumonia, urinary tract infections, right sided endocarditis, and bacteremia. Patients with skin and soft tissue infections made up 50% (230/460) of the population. In this subgroup, the cure rates in the ITT population were 52.4% (64/122) for the linezolid group and 50.0% (54/108) for the vancomycin group. The estimated treatment difference (linezolid – vancomycin) was 2.5% with a 95% CI of (-11.4%, 16.3%). These results should be interpreted with caution as they represent subgroup analyses and are prone to multiplicity issues.

Sharpe JN. Am J Surg. 2005 [38]: This was a randomized, open-label, single-center study that compared oral linezolid (600 mg every 12 h) with vancomycin IV (1 g every 12 h) in patients with lower-extremity cSSSI caused by MRSA. Treatment was administered for 7-21 days and assessment of clinical response was performed ten days after end of therapy.

One hundred seventeen patients were enrolled and sixty were randomized in 1:1 ratio to study drug (30 linezolid, 30 vancomycin). Fifty-seven patients were excluded if they had known penicillin allergies that would prevent the use of cefazolin, were hypersensitive to linezolid or vancomycin formulations, or had received other investigational medications. Some of the exclusion criteria included: secondary skin infection; recurrent infection at the same site within 2 months; an infected, irremovable device; osteomyelitis; endocarditis; meningitis; septic arthritis; necrotizing fasciitis; gas gangrene; uSSSI; medical conditions causing prolonged inflammation; acute infections not caused by MRSA or caused by a gram-negative pathogen; long-term hospitalization resulting from concomitant morbidities; pregnancy; or lactation.

Reported clinical response (cure + improvement) rates were 97% in the linezolid group and 43% in the vancomycin group. The statistical test for the difference in cure rates between groups has a reported p-value of 0.015. However, neither the population nor the

denominator was reported in the calculation of these percentage rates. If we assume all randomized patients were in the analysis population the reported p-value cannot be reproduced. This study had several limitations: it was a small, open-label, single-center study, patients could have received upto 48 hours of effective therapy prior to enrollment, the study report does not provide any information on the frequency of such antibiotic use or the types of prior therapies used in the two treatment groups, and finally, a large proportion of enrolled patients were not randomized.

The following table summarizes results from two studies that compared linezolid with vancomycin:

**Table 21: Clinical Response in cSSSI Studies comparing Linezolid and Vancomycin (ITT population)**

| Study | Linezolid n/N (%) | Vancomycin n/N (%) |
|---|---|---|
| Weigelt | 439/583 (75.3) | 402/573 (70.2) |
| Stevens (cSSSI subgroup) | 64/122 (52.4) | 54/108 (50.0) |

**Active comparator rates in uSSSI**

Four recent studies that were used to support the indication of uSSSI were reviewed. All four studies were randomized, active controlled, non-inferiority studies. The types of infections seen in these studies included cellulitis, folliculitis, impetigo, simple abscesses, and furunculosis. About 10-20% of patients enrolled had abscesses. The timing of the test of cure visits varied between studies (7-14, 10-21 days after end of therapy). The primary analysis populations also varied between studies. The following table summarizes cure rates in the ITT population seen in these studies:

**Table 22: Clinical Success Rates at TOC for Contemporary uSSSI Studies (ITT)**

| Test Drug | Comparator | Test Drug Clinical Success Rate n/N (%) | Comparator Clinical Success Rate n/N (%) |
|---|---|---|---|
| Cefditoren | Cefadroxil | 215/278 (77%) | 207/273 (76%) |
| Cefditoren | Cefuroxime | 215/291 (74%) | 225/283 (80%) |
| Linezolid | Clarithromycin | 293/341 (85.9%) | 269/322 (83.5%) |
| Linezolid[#] | Cefadroxil | 205/248 (82.7) | 193/251 (76.9) |

# Pediatric patients

**Constancy of treatment effect**

The conclusion that HESDE can be used to choose an M1 can be reached based on the assumption that the current clinical trials are sufficiently similar to the historical studies with respect to all important study design and conduct features that might influence the effect size of the active control. The design features of interest include the characteristics of the patient population, disease definition, disease severity, definitions and ascertainment of study endpoints, dose of active control, entry criteria, age, comorbidities, and analytic approaches.

From the historical studies, it is evident that antibacterial therapy, primarily sulfonamides or penicillins had a remarkable effect on the resolution of signs and symptoms of skin infections. In the comparative studies of sulfonamides and ultra-violet light (Snodgrass 1937, 1938) there was a clear benefit of treatment with sulfonamides for both resolution of fever and cessation of spread of lesion. Data from uncontrolled studies of penicillins and sulfonamides have shown that patients treated with antibacterials appeared to have quicker resolution of pus and faster return to normal function (Florey 1944, Meleney 1946). Additional supportive evidence is provided by natural history studies of untreated *S. aureus* and *S. pyogenes* bacteremia where the mortality was ~70% (Keefer 1937, Skinner and Keefer 1941). Although several of these patients had severe skin and soft tissue infections, the antibacterial treatment effect derived from these studies is likely to be higher than that seen in cSSSI trials, as very few patients in cSSSI trials are bacteremic. Also, in these natural history studies, the endpoint reported was mortality and not clinical outcome as assessed in clinical trials.

In the absence of placebo-controlled studies in patients with cSSSI, evidence of antibacterial treatment effect was indirectly derived from these historical data. In cSSSI, as currently defined, it is safe to assume that the treatment effect will at least be the same if not greater than that seen in the studies of erysipelas.

Although erysipelas is not always a severe disease, it can nevertheless be associated with mortality in the more severe cases especially at the extremes of age. In a paper by Hosford in 1938 [39], he states "*since the introduction of sulphanilamide as a remedy in streptococcal infections, we have a drug of utmost value in the general treatment of erysipelas".* He also states that " *In most cases it has a profound, sometimes dramatic effect: the temperature drops to normal in 48 hrs or less, the rash fades, and the patient feels better. Although left untreated, it will run its own course and disappear, the treatment is planned to shorten the course of the disease and add to the comfort of the patient".* So, there seems to be no uncertainty in a treatment effect with sulfonamides in erysipelas with respect to resolution of signs and symptoms.

There are some limitations to these historical data. The assessments for treatment effect in the Snodgrass studies were made 48 hours after instituting treatment, while in clinical trials, assessment of cure is usually made 7-14 days after completing therapy. However, the endpoint assessed was cessation of spread of lesion and not resolution the lesion. Hence the treatment effect seen at 48 hours for cessation of spread is still applicable to an endpoint evaluating resolution of signs and symptoms at a later time point. Secondly, the very high success rate in terms of cessation of spread of lesion may not be directly applicable to all types of cSSSI. As erysipelas is a superficial cellulitis with prominent lymphatic involvement, it has a characteristic raised border that is very well demarcated. The lack of spread of the lesion is thus easier to define. In other forms of cSSSI, such as deep abscesses, wound infections or cellulitis this may be harder to discern. In the series of patients describing the effects of penicillin therapy in surgical infections (Lyons 1943, Meleney 1946), the cure rates certainly differed depending on the type of infection with higher cure rates in patients with cellulitis and lower rates in those with wound infections,

ulcers or other types of infections. As no untreated controls were used in these studies, it is not possible to directly estimate a treatment effect compared to placebo by infection type.

*S. aureus* and *S. pyogenes* were the main microorganisms isolated from patients with skin infections in historical studies and they continue to be the most common microorganisms identified in present trials. However, there are differences in the microbiological characteristics of organisms when comparing studies from the earlier part of the 20$^{th}$ century to the present especially with regard to antimicrobial susceptibility. There has been an increasing prevalence of MRSA, especially community-acquired MRSA in skin and soft tissue infections in recent years.

One other area of difference between patient populations in historical studies and contemporary trials is the presence of co-morbidities and availability of supportive care. Patients in contemporary trials tend to often have co-morbidities such as obesity, diabetes mellitus and renal impairment which can impact on the nature of cSSSI and also on the cure rates. However, ancillary care including wound management and other supportive care is more advanced in the present day trials compared to historical studies.

The only contemporary placebo-controlled studies identified in patients with skin and soft tissue infections were the studies conducted in patients with impetigo or superficial skin abscesses. A clear treatment effect over placebo was seen in the study comparing retapamulin to placebo in the treatment of impetigo. Although there are differences in the clinical characteristics, need for surgical intervention(s) and outcomes in patients with cSSSI compared to patients with impetigo there are similarities in that both types of infections involve the skin and the most common micro-organisms in these two infections are *S. aureus* and *S. pyogenes*. It is thus reasonable to assume that in patients with cSSSI, the treatment effect should at least be the same if not greater than that seen in studies of impetigo.

Despite these uncertainties, it is still reasonable to assume that there is a significant treatment effect with antibacterials in cSSSI and that the treatment effect seen in historical studies is applicable to contemporary clinical trials. Some of the uncertainties can be addressed by discounting the treatment effect (M1).

**Estimate of Treatment Effect**

Based on a meta-analysis of the studies of sulfonamides in the treatment of erysipelas, the treatment effect of sulfonamides over UV light for cessation of lesion spread at 48 hours was 24.1% (95% CI, 18.2%, 30.0%) and for resolution of pyrexia at 48 hours was 27.8% (95% CI, 18.9%, 36.8%). The treatment effect for impetigo from a meta-analysis of placebo-controlled trials of topical therapies was 28.8% with a corresponding 95% CI of (18.0%, 39.6%). Based on a single study of systemic erythromycin for treatment of impetigo and other uncomplicated skin and skin structure infections, the treatment effect was 61.9% (95% CI, 43.5%, 80.3%). Randomized, double-blind, placebo-controlled studies in patients with superficial skin abscesses have shown no treatment effect with

antibacterials beyond the benefit of incision and drainage. The direct applicability of this information to larger/deeper abscesses seen in cSSSI trials is unclear. Hence, there is greater uncertainty in treatment effect for this type of infection included under the indication of cSSSI.

There are concerns about the internal consistency of the treatment effect and the fact that evidence came from studies based on very limited data. It is possible that these estimates and conclusions could change based on the availability of more information on the placebo and/or control effect in the future. It is important that the magnitude of the estimated treatment effect based on HESDE accounts for all possible sources of uncertainties. One of the strategies employed in choosing an M1 for an NI trial is by way of 'discounting ' or reducing the effect of the active control to account for these uncertainties. The treatment effect (M1) of 18% using the lower bound of the 95% CI discounts for uncertainties and the associated variability in the estimate and should be considered keeping the following points in mind:

- No placebo controlled studies were identified in patients with cSSSI

- The two erysipelas studies (Snodgrass 1937, 1938), used to estimate treatment effect (M1) showed that patients treated with sulfonamides had better outcomes for cessation of spread of lesion and resolution of fever than those treated with UV light. Further evidence for a treatment effect is provided by the fact that in the sulphanilamide group 11 patients (8.1%) developed septic complications directly attributable to erysipelas compared to 28 patients (20.7%) in the UV light group.

- In studies of UV light therapy, it appears that there was a treatment effect for UV light over other local therapies. Hence, the treatment effect of sulfonamides over placebo is likely to be higher.

- Although some cases of erysipelas can be considered as being in the spectrum of uncomplicated skin infections, in historical studies the mortality in untreated erysipelas was 15%, with higher mortality at the extremes of age; patients who were bacteremic had a mortality of 70-90%. In the study of prontosil versus UV light, the authors state that "*in 5 cases in the prontosil group, the condition was so severe that a fatal result would not have been unexpected. One patient in the UV group showed uncontrolled spread with high fever for 6 days and was in the typhoid state when prontosil was used and patient's recovery was completely unexpected",* providing evidence that some of these cases were in fact severe.

- Patients in the erysipelas studies were treated with various dosing regimens of sulfonamides, some of which were inadequate. Treatment effect with current antibacterials is likely to be higher than that seen with Prontosil or other sulfonamides; patients enrolled in current cSSSI trials are generally treated with parenteral antibacterials.

- It is likely that for other forms of cSSSI such as cellulitis and wound infections, the treatment effect is at least the same or greater than that seen with erysipelas or impetigo.

- It is difficult to compare the patient populations from the 1930s with those enrolled in contemporary trials. It is however possible that patients in present studies have more comorbidities that can have an impact on the type and severity of the cSSSI and the outcomes. On the other hand, ancillary care such as wound management is likely to be far superior in current trials and its contribution to overall cure is difficult to discern from that of the treatment effect due to antibacterials.

- The uncontrolled study of topical penicillin by Florey (1944) showed a clear treatment effect for reduction of pus and resolution of signs and symptoms in severe hand infections. Further evidence is provided by the authors' statement that *"the great majority of control cases remained septic for over a week and nearly 3/4$^{ths}$ were infected till their wounds healed. In penicillin treated cases, sepsis by clinical and bacteriologic criteria was eliminated within a week, pus was scanty, and relief of pain and improvement in general condition was striking."* As most of these patients were treated with topical penicillin, the treatment effect with systemic penicillin or with present day antibacterials is only likely to be higher.
- Natural history studies showed that mortality in untreated staphylococcal and streptococcal bacteremia was very high (70-80%).

- Uncontrolled studies of treatment with penicillin or sulfonamide (Lockwood 1944, Keefer 1938) in patients with staphylococcal or streptococcal bacteremia showed reduction in mortality and improvement in signs and symptoms.

- Randomized, double-blind, placebo-controlled studies suggest that antimicrobial therapy following primary incision and drainage of superficial abscess provides no additional benefit. Patients enrolled in studies of cSSSI have deeper/larger abscesses that often require hospitalization. So, whether or not the lack of treatment effect in superficial/small abscesses is applicable to abscesses classified as cSSSI is unknown. In the study by Florey (1944), it does appear that some patients with abscesses were improving with expectant treatment. The treatment effect was also small in these cases compared to other types of infections. Hence, the greatest uncertainty in treatment effect for cSSSI exists for this subgroup of patients.

**Non-inferiority Margin**

With the limitations discussed above, the treatment effect (M1) of antibacterial drugs in cSSSI for a clinical response endpoint of resolution/improvement in signs and symptoms is estimated to be at least 18%, based on studies in erysipelas and impetigo. The timing of assessment in the erysipelas studies was at 48 hours after starting therapy while in the impetigo study it was at the end of 7-10 days of therapy. A fraction of this treatment effect should be preserved in determining a clinically acceptable NI margin. For cSSSI, the magnitude of treatment effect will be at least the same or greater than that seen in the studies of impetigo or erysipelas from which the M1 was derived. Additionally, data from other historical studies have shown a clear benefit of antibacterial treatment for skin infections that were more severe than impetigo and erysipelas. Hence, a 10% NI margin that preserves 44% of M1 can be justified for a clinical response endpoint in cSSSI trials, provided appropriate patient populations are enrolled and appropriate endpoints are evaluated. It will also be important that confounders such as surgical interventions be minimized and balanced across treatment arms.

However, in a uSSSI study, there are more uncertainties in the treatment effect especially if patients with infections such as minor skin abscesses, folliculitis, and furunculosis are enrolled. It will thus be important to enroll patients in an uSSSI study with disease conditions such as erysipelas (cellulitis) or impetigo wherein a treatment effect has been demonstrated and to exclude patients with minor skin abscesses where there is no demonstrable treatment effect for antibacterials beyond that achieved by the incision and drainage procedure alone. Given these uncertainties in treatment effect for uSSSI, a larger fraction of the treatment effect should be preserved compared to that used for a cSSSI study.

**Topics of Discussion**

**cSSSI**

Are non-inferiority trials acceptable for the indication of cSSSI? If so, is a margin of 10% acceptable? Please discuss the appropriate endpoints and timing of assessment. If not, please discuss alternative study designs.

Is the timing of assessments at a fixed time point after completion of therapy appropriate or should these assessments be made sooner when the magnitude of treatment effect is likely to be greater?

Is it acceptable to justify a margin for cSSSI as a group or should it be separated by specific infection type, i.e. cellulitis, wound infections, abscesses etc? Should the number/fraction of infections of any one type be limited?

Should patients with diabetic foot infections be studied in a separate clinical trial or should they be included in cSSSI studies?

Is there evidence to support a different NI margin if linezolid is used as a comparator rather than vancomycin?

**uSSSI**

Are non-inferiority trials acceptable for the indication of uSSSI? If so, what margin is acceptable? Please discuss the appropriate endpoints and timing of assessment. If not, please discuss alternative study designs.

Should uSSSI studies only enroll patients with infections such as impetigo, erysipelas, and cellulitis?

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# Guidance for Industry

# Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval

## *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Edward Cox at 301-796-1300.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**October 2007**
**Clinical Antimicrobial**

# Guidance for Industry

# Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval

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**U.S. Department of Health and Human Services**
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# Guidance for Industry[1]
# Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

## I. INTRODUCTION

The purpose of this guidance is to inform industry of the Food and Drug Administration's (FDA's) current thinking regarding appropriate clinical study designs to evaluate antibacterial drugs, and to ask sponsors to amend ongoing or completed studies accordingly. This guidance is in response to a number of public discussions in recent years regarding the use of active-controlled studies designed to show noninferiority (NI) as a basis for approval of antimicrobial drug products (references to the individual meetings can be found in section II, Background). These discussions have focused primarily on the indications acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and acute bacterial otitis media (ABOM). In addition to the discussions in these three therapeutic areas, the broader question of the role of active-controlled studies designed to show NI to support approval of antimicrobial drugs and the selection of appropriate NI margins (in circumstances where an active-controlled trial designed to show NI is an appropriate trial design) have been issues of recent concern.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Antimicrobial Products, representing the Division of Anti-Infective and Ophthalmologic Products and the Division of Special Pathogen and Transplant Products, in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

## II. BACKGROUND

In October 2003 and September 2006, the Anti-Infective Drugs Advisory Committee (AIDAC) discussed ABS clinical trials, with a focus on the use of NI designs.[2] In September 2006, the AIDAC addressed appropriate use of NI studies for ABS in the context of a specific product.[3] Based on these deliberations and a review of available data, the FDA has not found it possible to define an NI margin for active-controlled NI studies in ABS because a consistent and reliable estimate of the efficacy of active treatment relative to placebo has not been established.

More recently, in a December 2006 joint meeting of the AIDAC and the Drug Safety and Risk Management Advisory Committee, the issue of NI study design was discussed in the context of evaluating the risk-benefit profile of a drug. In this case, ABS, ABECB, and community-acquired pneumonia were the indications under discussion.[4]

Trial designs for the ABOM and ABECB indications and some of the issues with interpretation of trials designed to show NI have been discussed at previous FDA advisory committee meetings; ABOM was discussed on July 11, 2002, and ABECB was part of a broader discussion of NI trial design held on February 19, 2002.[5]

All of these public discussions have contributed to the FDA's evolving understanding of the science of clinical trials and, in particular, the appropriate role of active-controlled studies designed to show NI in the development of antibacterial products. We anticipate that continued discussions on the role of active-controlled trials designed to show NI will provide further advancement in the field with regard to the use of NI studies. The FDA plans to publish more general guidance on the use of NI trials to support approval in all therapeutic areas, and will provide more specific methodological advice. Sponsors also should review the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials*,[6] which provides a general discussion on the selection of control groups, including consideration of conditions under which active-controlled studies designed to show NI can be informative.

In addition, it is essential to note that in any proposed trials, adequate provisions need to be in place so that human subjects will not be exposed to an unreasonable and significant risk of illness or injury (21 CFR 312.42). During protocol development, study designs should be carefully considered to ensure that there are adequate provisions to protect patient safety.

[2] See http://www.fda.gov/ohrms/dockets/ac/cder03.html#Anti-Infective and http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective, respectively.

[3] See http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective.

[4] See http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective.

[5] See http://www.fda.gov/ohrms/dockets/ac/cder02.htm#Anti-Infective.

[6] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

## III. PROVIDING EVIDENCE TO SUPPORT JUSTIFICATION FOR ACTIVE-CONTROLLED STUDIES DESIGNED TO SHOW NONINFERIORITY

### A. Studies Proposed during Protocol Development

We encourage sponsors to carefully consider the basis for demonstrating treatment effect with a particular trial design during protocol development. NI study designs may be appropriate when there is adequate evidence of a defined effect size for the control treatment so that the proposed NI margin can be supported. For an NI study, having an adequately justified NI margin is essential to having an informative study. If NI studies are being considered, a comprehensive synthesis of the evidence that supports the effect size of the active control and the proposed NI margin should be assembled during the period of protocol development and provided to the FDA along with the protocol. We are asking sponsors to provide adequate evidence to support the proposed NI margin for any indication being studied using active-controlled studies designed to show NI (21 CFR 314.126). It is likely, however, that for some indications, such as ABS, ABOM, and ABECB, available data will not support the use of an NI design.[7] We recommend that sponsors consider other study designs (e.g., superiority designs) to provide evidence of effectiveness in these three indications. In some cases, it may be useful to compare time for clinical improvement in addition to overall cure rates.

### B. Ongoing or Completed Studies Intended for Submission to a New Drug Application

Sponsors should re-evaluate all ongoing or completed NI studies that will be submitted to a new drug application for antibacterial indications to ensure there is adequate scientific rationale for the effect size of the active control and the proposed NI margin that is used. This recommendation includes trials that may have been previously reviewed by the Office of Antimicrobial Products under a special protocol assessment (SPA). Because the state of the science has changed, prior commitments from the FDA under an SPA may no longer be valid for some products.

If the sponsor concludes that an NI study design was appropriate for a completed trial or remains appropriate for an ongoing study, the relevant investigational new drug application (IND) should be amended as soon as possible with the scientific evidence and rationale to support the proposed NI margin. If scientific evidence does not support the proposed NI margin, additional studies employing other study designs (e.g., superiority designs) should be considered to provide evidence of effectiveness for the proposed indication. Proposals for additional studies should be submitted to the FDA. See ICH E10 for a discussion on the issues of choice of control group for clinical trials.

Any changes to a sponsor's development program that result from the recommendations in this guidance should be made as early as possible and documented in the sponsor's IND. Sponsors who have questions or who are unsure about the status of their development plans should submit a meeting request to discuss these issues further with the appropriate review division.

[7] Patients enrolled in ABECB studies in new drug applications have, in general, included patients with outpatient, *milder*, or less well-characterized disease.

Alternatively, sponsors should submit a new protocol as part of an SPA, or request a new SPA for a previously reviewed SPA.


**Infectious Diseases Society of America (IDSA)**

# Background Information on

# Antimicrobial Agents for Complicated Skin and Skin Structure Infections:

# Justification of Non-Inferiority Margins in the Absence of Placebo-Controlled Trials

**for the**

**Food and Drug Administration**

**Anti-Infective Drugs Advisory Committee Meeting**

**November 18, 2008**

# Antimicrobial agents for complicated skin and skin structure infections: justification of non-inferiority margins in the absence of placebo-controlled trials

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**Disclosures:**

B. Spellberg has received research support from Astellas, Gilead, Enzon, Novartis, Merck, and Pfizer, serves on the scientific advisory board of Merck, has consulted for Arpida, Basilea, and Cerexa, and owns equity in NovaDigm Therapeutics, Inc. Dr. Spellberg has previously received speaker's honoraria from Astellas and Pfizer.

G. Talbot serves, or has recently served, as a consultant to the following pharmaceutical companies: Actelion, Calixa, Cerexa, Cubist, Ipsat, Nabriva, PTC, Rib-X, Shire, Tetraphase, Theravance, and ViroPharma.

J. Bradley's employer has received research grants from AstraZeneca, Cubist, Johnson & Johnson, and Wyeth, and reimbursement for Dr. Bradley's role in consulting for AstraZeneca, Cubist, Johnson & Johnson, Wyeth, Forest/Cerexa, Pfizer, Schering Plough, and Trius.

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**Abstract**

**Background:** The United States Food and Drug Administration requires clinical trial non-inferiority (NI) margins to be narrow enough to preserve a significant fraction (e.g. 50%) of the established comparator drug's efficacy versus placebo. Lack of placebo-controlled trials (PCT) for many infections complicates NI margin justification, and is a major barrier to approval of new antimicrobial agents. Clarification of NI margins is therefore critical to enable continued antimicrobial development. We sought to define NI margins, in the absence of PCT, for antimicrobial trials in complicated skin and skin structure infections (cSSSI). **Methods:** We systematically reviewed cSSSI literature from 1900-1950 (before widespread penicillin [PCN]-resistance), and defined treatment outcomes and confidence intervals (CI). Antimicrobial efficacy was calculated as: (lower limit CI of success with antimicrobials) – (upper limit CI of success without antimicrobials). **Results:** We identified 90 articles describing > 28,000 patients with cSSSI. For cellulitis/erysipelas, cure rates (95% CI) were 66% (64-68%) for untreated and 98% (96-99%) for PCN-treated patients, and PCN reduced mortality by 10%. Cure rates for wound/ulcer infections were 36% (32-39%) for untreated and 83% (81-85%) for PCN-treated patients. For major abscesses, cure rates were 76% (71-80%) for untreated and 96% (94-98%) for PCN-treated patients; PCN reduced mortality by 6%. **Conclusion:** Systematic review of historical literature enables rational NI margin justification in the absence of PCT, and may facilitate regulatory review of NI trials. To preserve ≥50% of antibiotic efficacy, the suggested NI margins for cSSSI subsets are 14% for cellulitis/erysipelas, 21% for wound/ulcer infections, and 7% for major abscesses.

## Introduction

Clinical trials of an investigational drug may seek to determine if the efficacy of the new drug is superior to that of placebo or to a standard, active comparator drug (so-called "superiority" studies) [1, 2]. Alternatively, such clinical trials may test the hypothesis that the investigational drug is not inferior to an established comparator drug by a pre-specified margin (so-called "non-inferiority" trials).

Over the last several decades, rising antimicrobial resistance has driven a critical need to develop new antimicrobial agents [3]. Ironically, while resistance decreases the efficacy of available antimicrobial agents, it paradoxically increases the difficulty of superiority testing of new antimicrobial agents because patients infected with bacteria resistant to the approved comparator drug used in a clinical trial are excluded from enrollment in that trial. Since these excluded patients are the very patients for whom a new antimicrobial agent is likely to be superior to the approved comparator drug, antimicrobial clinical trials are inherently biased against finding superiority of the new agent. Therefore non-inferiority (NI) trials have become the standard method by which investigational antimicrobial agents are tested for efficacy.

Critical to the design of a planned NI trial is the selection of the NI margin of efficacy that is acceptable in the study. For example, a 10% margin of NI means that the investigational drug will be considered non-inferior if it is no worse than 10% less efficacious than the standard comparator drug. In general, the wider the NI margin, the smaller the required patient sample size to demonstrate NI, but the less precise the estimate of relative efficacy. Therefore, selecting an appropriate margin of NI requires a balance between the practicality of conducting the study and the need for clinicians and the relevant government regulatory agency to ensure that the new drug is not unacceptably worse than the comparator drug. Recent controversy over acceptable margins of

NI for registration clinical trials has served as a major impediment to successful development of new antibiotics, in particular [4, 5].

In October of 2007, the United States (US) Food and Drug Administration (FDA) issued a draft guidance addressing the conduct of NI clinical trials for investigational antimicrobial agents [6]. The guidance states that, "If NI studies are being considered, a comprehensive synthesis of the evidence that supports the effect size of the active control and the proposed NI margin should be assembled." However, the guidance does not explicitly describe how the effect size of a standard comparator should be determined, particularly for diseases lacking placebo-controlled trials.

As for many infectious diseases, selection of an appropriate NI margin is problematic for clinical trials of complicated skin and skin structure infections (cSSSI), because antimicrobials became available in an era prior to randomized, placebo-controlled trials. Complicated SSSI are among the most common medical conditions in the US and throughout the world, and impart a substantial morbidity and cost to the US and global health care systems [7-14]. Furthermore, the spread of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has made it increasingly difficult to treat cSSSI with currently available antimicrobials, and has provided a major impetus to develop new antimicrobial agents for these infections [12, 14-22]. Indeed, several antimicrobial agents with activity against MRSA will likely be submitted for regulatory review by the FDA within the next several years.

As an example of rational NI margin justification in a manner compliant with FDA [23] and International Congress on Harmonization (ICH) E9 and E10 guidances [1, 2], we sought to define appropriate NI margin(s) for clinical trials of antimicrobial agents in the treatment of cSSSI. As a basis for margin justification, we conducted a systematic review of historical literature to determine

the effect size of a “gold standard” antimicrobial agent relative to no active therapy against these infections.

## Methods

### Systematic Review

We conducted a systematic review of the peer-reviewed literature on the clinical cure rates and mortality from skin infections in the pre-antibiotic and immediate post-antibiotic era (1900-1950). We chose 1950 as the last year of the search because penicillin resistance became widespread in both hospital in-patient and community settings in the 1950s [24-29]. Thus PubMed, ScienceDirect, and Google were searched for English language articles from 1900-1950 on: (cellulitis OR erysipelas), (wound AND infection), or (abscess OR carbuncle). In addition, pertinent references from identified articles were reviewed. To enable calculations of weighted averages, manuscripts included in the analysis were required to describe clinical cure or mortality rates in sufficient detail so that numerators (i.e. number cured or failed) and denominators (i.e. total number of infected patients) of success or failure could be determined.

### Definitions and Statistics

Definitions of clinical cure or failure were adapted from each manuscript based on the criteria available in the manuscript. Where available, criteria used to indicate failure included death, septic complications, progressive worsening of infection after initiation of therapy, persistence of lesions after completion of therapy or for ≥ 28 days while receiving therapy, relapse or recurrence of infection after termination of therapy, failure to heal wounds or wound dehiscence, failure of skin grafts, or amputation.

Upon review of the identified manuscripts, skin infections were divided into one of three major cSSSI categories: 1) cellulitis/erysipelas; 2) infections of trauma, surgical, or combat wounds

or ulcers; 3) major abscesses. To focus on major abscesses which are consistent with complicated infection, patients with a furuncle, which we equated with simple abscess (i.e. uncomplicated infection [30]), were excluded from the analysis whenever they were described separately from patients with a major abscess or carbuncle.

Treatments were divided into: 1) no active antimicrobial therapy; 2) sulfonamide therapy; 3) penicillin (PCN) therapy. Weighted averages of successful treatment were calculated across studies. Confidence intervals were calculated using standard linear combination variance formulas [31]. This method allowed inclusion of one-armed studies and non-randomized two-armed studies that is not possible with meta-analytic techniques [32]. Antimicrobial efficacy was conservatively defined as: (the lower limit of the 95% CI of success with antimicrobial therapy) – (the upper limit of the 95% CI of success with no antimicrobial therapy).

Egger's test for publication bias and the Chi Squared Q test for heterogeneity were calculated using Comprehensive Meta-Analysis Software (Biostat, Englewood, New Jersey). A Chi Squared or Fisher's Exact test was used to compare proportions of cure or mortality. A two-tailed p value $\leq 0.05$ was considered significant.

## Results

Literature Summary

A total of 90 peer-reviewed publications between 1900 and 1950 were identified that met criteria for inclusion into weighted average calculations, describing outcomes for >28,000 patients with a cSSSI (Tables 1-5). Of these, sixteen studies reported only mortality rates, and were included only in the overall mortality analyses (Tables 4-5).

An additional study described a variety of staphylococcal and streptococcal infections treated with PCN, however specific cure rates for skin infections could not be determined [33]. As well, Bedford, Griffiths et al., and King reported highly favorable impact of PCN on time to cure of cSSSI, but the studies were excluded from the overall analysis of antimicrobial efficacy because they did not quantify number of patients cured or failed [34-36]. Studies of chlortetracycline or streptomycin treatment of cSSSIs were also excluded [37-39]. Finally, other studies describing outcomes in erysipeloid (i.e. cellulitis caused by *Erysipelothrix rhusiopathiae*) were excluded [40, 41], since these cases are very rare in modern studies of cSSSI.

Two additional studies, which were not included in the calculated weighted averages, reported population-based mortality rates from erysipelas spanning the pre- and post-antibiotic eras (Figure 1). In the first study, Hoyne et al. described the percent mortality of patients with erysipelas treated at Cook County Hospital from 1929-1938 [42]. Within a year of availability of sulfonamides, the mortality rate fell from almost 12% to slightly less than 4%, and within another year the mortality rate had fallen to 2% (Figure 1A). In another study, Madsen reported the population-based mortality rates for erysipelas over a 90-year period using a national database in Norway [43]. The magnitude of mortality reduction reported after the availability of first sulfonamides and then PCN was dramatic (Figure 1B).

Cure rates for cellulitis/erysipelas

Thirty-seven studies provided quantitative estimates of the cure rates for cellulitis/erysipelas for children and adults treated with no active antimicrobial agent, or treated with systemic therapy with a sulfonamide or PCN (Table 1). β-hemolytic streptococci (predominantly group A streptococci) were the predominant organisms found when microbiological studies were performed, with *Staphylococcus aureus* the second most common (Table 1 and [44]).

No difference in cure rates for topical creams/ointments, ultraviolet radiation therapy, X-ray therapy, active vaccination, anti-toxin serum, bacteriophage therapy, or injections of autologous blood was found for cellulitis/erysipelas (data not shown). Therefore, all non-antimicrobial treatments were grouped under "Other" for analysis (Table 1). The average cure rates for cellulitis/erysipelas were 66% for non-antimicrobial-treated, 91% for sulfonamide-treated, and 98% for PCN-treated patients. The lower limit of efficacy of PCN was 28%, determined by comparing the lower bound of its 95% CI for the cure rate to the upper bound of the 95% CI for the cure rate with no antimicrobial therapy (i.e. 96% - 68%, Table 1).

Two additional studies reported the efficacy of PCN treatment for a combined total of 37 patients with cellulitis/erysipelas [45, 46]. However, in these studies, many patients received topical or local PCN in lieu of systemic PCN, resulting in a lower cure rate of 89% (80-98%).

Significant heterogeneity was detected in studies reporting cure rates for no antimicrobial therapy or a sulfonamide (Q test p value $< 0.001$ for both). However, no heterogeneity was detected in studies reporting PCN cure rates ($p = 0.9$). Heterogeneity was largely accounted for by differences in the factors used by the studies to define failure. Specifically, studies tended to report

higher cure rates when they considered fewer factors in the definition of failure. In contrast, studies reported lower cure rates when they considered more factors in the definition of failure.

Publication bias was not detected by Egger's test for any of the groups (P = 0.6, 0.1, and 0.4 for no antimicrobial, a sulfonamide, and PCN, respectively).

Cure rates for wound/ulcer infections

Twenty-three studies reported outcomes of traumatic, surgical, or combat wound or ulcer cutaneous infections (Table 2). *S. aureus* was the most common pathogen isolated, with streptococci (predominantly β-hemolytic streptococci) the second most common. Several studies also reported culturing *Enterococcus* spp., gram-negative rods, and/or anaerobes from polymicrobial wound infections. In many of these studies, it was difficult to distinguish how many patients received topical/local versus systemic antimicrobial therapy.

The cure rate was 36%, 73%, or 83% for patients treated with no antimicrobial, a sulfonamide, or PCN, respectively. PCN again was superior to sulfonamide therapy ($p < 0.001$). The lower CI limit of PCN efficacy compared to that for no antimicrobial therapy was 42% (i.e. 81% - 39%). Significant heterogeneity in cure rates was detected for all three treatment groups (Q test p value < 0.001) due to the diverse types of wounds and the mixture of studies using topical/local versus systemic routes of antimicrobial administration.

Publication bias was not detected by Egger's test for any of the groups (P = 0.1, 0.9, and 0.1 for no antimicrobial, sulfonamides, and PCN, respectively).

Seven studies were identified in which 109 patients were clearly described to have received only systemic, and not topical/local, PCN treatment of wound/ulcer infections [47-53]. The cure rate in these studies of systemic PCN therapy was 89% (83-95%). There was no significant

heterogeneity in these studies of systemic PCN (P = 0.5), and no evidence of publication bias (P = 0.3).

Cure rates for major abscesses

Thirty-four studies reported cure rates for children and adults with a major abscess treated with no antimicrobial agent or with systemic sulfonamide or PCN (Table 3). *S. aureus* was by far the most common etiologic organism identified, with streptococci much less commonly identified. Abscesses (mostly carbuncles) in the historical literature were typically complicated, and accompanied by fever and other systemic signs of illness. Furuncles constituted <10% of the analyzed cases.

The cure rate for major abscesses was 76% with no antimicrobial treatment, 87% with sulfonamide treatment, and 96% with PCN. PCN again was superior to sulfonamide treatment ($p < 0.001$). The lower limit of PCN efficacy compared to no active antimicrobial was 14% (i.e. 94% - 80%, Table 3). When studies that included any furuncles were excluded from the analysis, the cure rates were marginally changed (77% [72-81%] for no antimicrobial treatment versus 97% [95-100%] with PCN). In contrast, in three studies including 69 patients primarily treated with local or topical PCN rather than systemic therapy, cure rates (84% [76-93%]) were not significantly different from placebo [45-47].

Significant heterogeneity in cure rates was detected in studies of no antimicrobial therapy (Q test p value < 0.001), but not for studies of PCN (p = 0.8). Publication bias was not detected (P = 0.3 and 0.4 for no antimicrobials or PCN, respectively).

Mortality rates for skin infections

Preliminary analyses indicated that UV therapy slightly reduced mortality of cellulitis/erysipelas relative to other non-antimicrobial treatments. Therefore, analysis of mortality rates of cellulitis/erysipelas was separated into four treatment groups: non-antimicrobial treatments not including UV therapy ("Other", Table 4), UV therapy, sulfonamides, and PCN. Fifty-two studies were identified that reported mortality rates and precise patient numbers for cellulitis/erysipelas. UV therapy, sulfonamides, and PCN all significantly reduced the mortality of cellulitis/erysipelas compared to other non-antimicrobial treatments (Table 4, $p < 0.001$ for all three comparisons). Sulfonamides and PCN were also more effective than UV therapy ($p < 0.001$ for both comparisons), and PCN was more effective than sulfonamides ($p = 0.02$ by Fisher Exact test). PCN mediated a 10% absolute reduction in mortality from cellulitis/erysipelas compared to no antimicrobial therapy.

Mortality data were not provided in studies of wound infections. However, mortality data were available from 33 studies of major abscesses (Table 5). In four studies, sulfonamides did not significantly reduce mortality versus no antimicrobial therapy. In contrast, PCN mediated a 6% absolute reduction in mortality from major abscesses relative to no antimicrobial therapy ($p < 0.001$).

Modern Dose Escalation Data

A recent, phase II dose-escalation study of dalbavancin for cSSSI provided evidence of the minimal efficacy of active antimicrobial therapy for this disease. Seltzer et al. randomized patients with cSSSI to a single infusion of 1100 mg of dalbavancin or a single 1000 mg infusion followed by a 500 mg infusion 1 week later [54]. The clinical cure rate at the test-of-cure visit for the clinically evaluable population was 94% for patients treated with 2 doses of dalbavancin, and 62% for

patients treated with 1 dose of dalbavancin. For the intention-to-treat (ITT) population, the cure rate was 91% versus 60%. Compared to the single dose dalbavancin regimen, the 2 dose regimen was therefore 32% more effective in the clinically evaluable population, and 31% more effective in the ITT population.

## Discussion

A comprehensive review of the historical literature of cSSSI from the pre- and immediate post-antibiotic era revealed a substantial treatment effect with the use of an antimicrobial agent versus no antimicrobial agent, with respect to both clinical cure and mortality rates. PCN was more efficacious than sulfonamides, a finding which is consistent with both extensive historical experience and the fact that sulfonamide monotherapy has not been used clinically since the advent of combination sulfonamide-dihydrofolate reductase inhibitors (e.g. trimethroprim). Therefore, PCN was the clear gold-standard antimicrobial agent, based upon which NI margins should be justified.

ICH E9 and E10 guidances indicate that NI margins should be chosen which preserve a clinically meaningful fraction of the lower limit of the established efficacy of the comparator drug [1, 2]. In practice, preservation of 50% of the efficacy of the "gold-standard" comparator relative to placebo/no therapy is often suggested as reasonable when setting NI margins [55-59]. We found that the lower limit of efficacy of PCN versus no antimicrobial treatment was 28% for cellulitis/erysipelas, 42% for wound/ulcer infections, and 14% for major abscesses. Therefore, to preserve half of those effects, NI margins should be: 14% for cellulitis/erysipelas, 21% for wound/ulcer infections, and 7% for major abscess. In practice, cSSSI studies typically enroll mixtures of these patient populations. Therefore, the NI margin for a specific cSSSI trial should be weighted for the proportion of enrolled patients with cellulitis/erysipelas, wound or ulcer infections, and abscesses. For example, if a 1:1:1 ratio of patients with cellulitis:wound/ulcer infection:abscesses were enrolled, the NI margin should be 14% (average of 14%, 21%, and 7%).

No FDA or ICH guidance has officially set a requirement for precisely how much of the effect of the "gold-standard" comparator drug relative to placebo must be preserved in the NI

margin [59]. Rather, the emphasis in the guidelines is that the fraction of efficacy preserved in the margin should be justified based upon retention of clinically significant efficacy. We considered our suggestion to preserve 50% of the "gold-standard" comparator's efficacy to be conservative. In modern trials, inadequately treated cSSSI are rarely fatal, likely because alternative antimicrobial regimens are available for salvage therapy, and also because inadequate treatment is still superior to no antimicrobial therapy for these infections. Similarly, while sulfonamide therapy was inferior to PCN therapy in the historical literature, it was still far superior to no antimicrobial therapy. Based on the low mortality rates for cSSSI when antimicrobial therapy is administered, a case for preserving a smaller amount of the "gold-standard" comparator's clinical cure efficacy, resulting in wider NI margins, could be made for individual studies, especially if the new agent offered other clinical benefits [59], such as enhanced activity against antimicrobial-resistant bacteria, enhanced safety profile, etc., compared to currently available agents.

Our calculations for antibiotic efficacy were also conservative in that they were generated by subtracting the upper limit of the 95% CI of no antimicrobial therapy efficacy from the lower limit of the 95% CI of PCN efficacy. Hence, our calculations likely resulted in under-estimates of the actual efficacy of PCN relative to no antimicrobial therapy. Indeed, the upper limit of PCN efficacy versus no active antimicrobial therapy was 36% for cellulitis/erysipelas, 53% for wound/ulcer infections, and 27% for major abscesses.

In accordance with FDA guidance [30], we specifically excluded analysis of furuncles, because furuncles/uncomplicated abscesses are often curable with incision and drainage alone [14, 21, 22, 60]. The mortality rate of abscesses receiving no antimicrobial therapy in the historical datasets (Table 5) reinforces the fact that these infections represented cSSSI, rather than uncomplicated infections.

Mortality is not viable as the only outcome measure for modern cSSSI clinical trials, because the mortality of cSSSI treated with active antimicrobial agents is extremely low. Nevertheless, we included the mortality data to provide additional clinical context, underscoring the under-appreciated efficacy of antimicrobial agents for therapy of cSSSI. Indeed, the fact that cellulitis/erysipelas caused an 11% mortality rate in the pre-antibiotic era has been largely forgotten in the antibiotic era.

The robustness of our analysis is substantiated by population-based studies of mortality from erysipelas reported from two different groups of investigators using data from two different continents, which demonstrated significant reductions in mortality after the introduction of sulfonamides, and again after introduction of PCN [42, 43]. Furthermore, the greater efficacy of systemic versus topical/local PCN therapy emphasizes the robustness of the analysis, as does the similar microbiology in historical and modern cSSSI studies. Finally, the efficacy of two versus one doses of dalbavancin in a modern study of cSSSI provided an estimate of antibiotic efficacy that was similar to the historical datasets, and that was conservative, since one dose of dalbavancin was presumably more effective than placebo.

The primary limitations of our analysis include the heterogeneity of outcomes from patients receiving no active antimicrobial agent, the potential for publication bias, and the large proportion of single-armed, observational studies in the analysis. The heterogeneity of outcomes with no antimicrobial therapy was largely accounted for by higher cure rates reported when fewer criteria were used to define failure, and thus likely biased towards a lower efficacy of antimicrobial agents rather than a higher efficacy. For wound/ulcer infections, heterogeneity was driven by inclusion of patients who received topical/local antimicrobial therapy in the analysis. Despite introduction of heterogeneity, retention of studies including topical/local PCN resulted in a more conservative

estimate of antibiotic efficacy, as the efficacy of PCN relative to no antimicrobial therapy was higher (53% [44% - 62%]) in the seven studies that exclusively evaluated systemic therapy.

We found no statistical evidence of publication bias. However, given the limitations of such analyses [61], we cannot exclude the possibility that publication bias existed. If publication bias did exist, it likely affected the publication of results for both antimicrobial and non-antimicrobial therapeutic efficacy. For example, published cases in which topical ointments or dye solutions, or UV or X-ray therapy, were used to treat skin infections are likely selected for those cases in which more favorable results were seen. Thus, publication bias was equally likely to result in apparent increases in cure rates reported for non-antimicrobial as for antimicrobial treatment of cSSSI.

Ideally, rigorous establishment of the magnitude of efficacy of antimicrobial versus no antimicrobial therapy for cSSSI would rely upon contemporary, double-blinded, placebo-controlled trials. However, sulfonamides and PCN were among the first effective drugs ever used [62-65], and their availability pre-dates by several decades the widespread use of randomized, placebo-controlled trials. Furthermore, the early evidence of antimicrobial efficacy was overwhelming in both non-clinical models of infection and observational and controlled clinical investigations [55, 63, 65-67], which precluded the withholding of active antimicrobial therapy from infected patients. Nor can placebo-controlled trials of antimicrobial agents be conducted today for most types of infections [55, 68]. Therefore, placebo-controlled trials of antimicrobial therapy of cSSSI will likely never be performed.

Although relying upon datasets that are heterogeneous and heavily weighted by single-armed studies are limitations of the current analysis, these limitations must be considered in the context of the public health imperative to develop new antimicrobial agents for resistant infections.

The Infectious Diseases Society of America (IDSA) and its Antimicrobial Availability Task Force (AATF) are critically concerned about the convergence of the global increase in antimicrobial resistant infections and the concomitant decline in development of new antimicrobial agents [3, 16, 69, 70]. These factors have coalesced to create an urgent need to re-invigorate antimicrobial development [3]. Antimicrobial agents are unique, not just among all drugs, but among all technologies, in that they continually lose efficacy over time in a transmissible manner. Therefore, unlike any other class of drugs, there is a perpetual need to develop new antimicrobial agents to enable treatment of bacteria continually becoming resistant to current drugs.

The ICH E10 guidance emphasizes that, "The determination of the margin in a non-inferiority trial is based on both statistical reasoning and clinical judgment" [2]. Therefore, in light of: 1) the critical need for new antimicrobial agents, 2) the robustness of the datasets reviewed, 3) the conservative nature of the calculations, 4) the evidence of a large magnitude of antimicrobial efficacy for treatment of cSSSI, and 5) our compliance with critical features of the ICH E9 and E10 and FDA guidances, we believe the findings in the current manuscript are sufficient to enable a rational justification for NI margins for cSSSI clinical trials. Finally, the methodology used may be adaptable to new drugs for other diseases for which the results of placebo-controlled clinical trials are not available, but for which there is a critical public health need.

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**Table 1. Clinical Cure Rates for Cellulitis/Erysipelas**

| | Treatment | | | |
|---|---|---|---|---|
| **Author/Yr** | **Other*** | **Sulfa** | **PCN** | **Disease: Comment** |
| Henderson ’07 [71] | 1/1 | | | No specific treatment |
| Gray ’08 [72] | 4/6 | | | Serum therapy |
| Choksy ’11 [73] | 46/72 | | | Topical magnesium sulfate, failure = progression despite treatment or death |
| MacMillan ’20 [74] | 2/8 | | | Orbital cellulitis, no medical treatment, failure = death or blindness |
| Lusk ’22 [75] | 64/98 | | | Topical ointment, failure = progression for ≥3 d, relapse/recurrence, death |
| Russell ’22 [76] | 1/1 | | | “anti-streptococcal vaccine” |
| Hodges ’25 [77] | 2/2 | | | Treated with X rays |
| Platou ’26 [78] | 29/41 | | | X rays or topical, failure = progression, septic complications, death |
| Benson ’30 [79] | 221/470 | | | Anti-toxin serum or nothing, failure = progression, septic complications, death |
| Ude ’31 [80] | 349/472 | | | X-rays, cream, or anti-toxin, failure = progression or death |
| Tonndorf ’36 [81] | | 22/22 | | Systemic prontosil |
| Meyer-Heine ’36 [82] | | 148/150 | | Systemic prontosil, failure = progression |

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| Breen ’37 [83] | 4/10 | 42/46 | | Systemic prontosil vs. no treatment for concurrent controls, which were “milder cases”, failure = progression, lack of improvement, or death |
| Snodgrass ’37 [84] | 75/152 | 106/160 | | Systemic prontosil vs. no treatment, randomized by alternation, failure = septic complications, recurrence, death |
| Snodgrass ’37 [85] | 86/135 | 117/135 | | Systemic sulfanilamide, failure = septic complications, recurrence, death |
| Snodgrass ’38 [86] | | 209/238 | | Various systemic sulfonamide regimens, failure = septic complications, recurrence, death |
| Nelson ’39 [87] | | 321/344 | | Systemic sulfanilamide, failure = septic complications, death |
| Hoyne ’39 [42] | 636/829 | 164/169 | | Systemic sulfanilamide vs. historical controls, failure = progression or death |
| Siegel ’40 [88] | | 289/303 | | Systemic sulfanilamide, failure = septic complications or death |
| Herrell ’42 [89] | | 0/1 | 1/1 | Facial cellulitis, progressed despite oral sulfadiazine, cured with systemic PCN—*S. aureus* |
| Lyons ’43 [90] | | | 19/20 | Systemic PCN, failure = lack of improvement—12 *S. aureus*, 5 $\beta$ |

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| | | | hemolytic streptococci, 2 unknown |
| Keefer ’43 [47] | | 1/1 | Systemic PCN, facial cellulitis |
| Herrell ’43 [48] | | 3/3 | Systemic PCN—*S. aureus* |
| Lockwood ’43 [91] | | 3/3 | Systemic PCN for facial cellulitis—2 *S. aureus*, 1 non-hemolytic *Streptococcus* |
| Ory ’44 [92] | | 2/3 | Systemic PCN—failure = 1 death (underlying aplastic anemia) |
| Dawson ’44 [50] | | 2/2 | Systemic PCN—1 β hemolytic *Streptococcus* and 1 mixed *S. aureus* and β hemolytic *Streptococcus* |
| Hamilton ’45 [93] | | 19/20 | Systemic PCN, 5 cases failed prior sulfonamide, failure described only as “failure”—1 α hemolytic *Streptococcus* and 1 *S. aureus*, others not described |
| Ross ’45 [94] | | 2/2 | Systemic PCN |
| Forbes ’46 [95] | 5/5 | | Systemic sulfamerazine in children |
| Romansky ’46 [96] | | 33/33 | Systemic PCN for mixed SSSIs |
| Hirsh ’46 [97] | | 9/9 | Systemic PCN—3 β hemolytic streptococci, 6 unknown |
| Rose ’46 [98] | | 5/5 | Systemic PCN |
| Robinson ’48 [99] | | 1/1 | Systemic PCN |

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| Robinson ’48 [100] | | | 10/10 | Systemic PCN, 4 of the cases referenced to a prior publication—all with β hemolytic streptococci |
| Altemeier ’48 [52] | | | 31/32 | Systemic PCN—1 patient with cellulitis with “questionable” response, 20 *S. aureus*, 8 streptococci, 4 mixed *S. aureus*/streptococci |
| Southworth ’49 [53] | | | 47/47 | Systemic PCN |
| Bunn ’50 [101] | | | 5/5 | Systemic PCN—2 β hemolytic streptococci, 3 *S. aureus* |
| Hirsh ’50 [102] | | | 3/3 | Systemic PCN |
| | **Other** | **Sulfa** | **PCN** | |
| **Overall** | 1520/2294 | 1423/1573 | 196/200 | |
| **% (95% CI)** | 66% (64-68%) | 91% (89-92%) | 98% (96-99%) | |
| **Effect Size** | | 24% (21-28%) | 32% (28-36%) | |

*Other refers to non-antimicrobial therapies including topical creams (e.g. magnesium sulfate, glycerin, etc.), blood transfusion, injection of anti-streptococcal serum into lesions, X-ray or UV therapy, or bacteriophage therapy.

**Table 2. Clinical Cure Rates for Trauma/Surgery/Combat Wound/Ulcer Infections**

| | Treatment | | | |
|---|---|---|---|---|
| **Author/Yr** | **Other*** | **Sulfa** | **PCN** | **Disease: Comment** |
| Fleming ’19 [103] | 53/100 | | | WWI, 100% culture positive with β hemolytic streptococci, 47% bacteremic |
| Purdie ’37 [104] | | 1/1 | | Chronic draining wounds post-puerperal fever treated with systemic sulfonamide—group A *Streptococcus* |
| Colebrook ’41 [105] | | 30/38 | | Infected WWII wounds treated topically—29 group A, 1 group B, 3 group C, 4 group D *Streptococcus* |
| Pulvertaft ’43 [106] | | | 15/15 | WWII wounds treated with local PCN, success = microbial eradication—mixture of infections with *S. aureus*, streptococci, gram negative rods, and/or anaerobes |
| Lyons ’43 [90] | | | 20/27 | WWII wounds treated with topical or systemic PCN—23 *S. aureus*, 2 mixed *S. aureus* / streptococci |
| Florey ’43 [107] | 0/6 | 8/10 | 164/171 | WWII wounds, treated with topical or systemic PCN, or topical sulfonamide or merthiolate—*S. aureus* and streptococci predominant |

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| Keefer ’43 [47] | | 7/10 | Surgical infections or infected ulcers treated with systemic PCN—8 *S. aureus*, 2 streptococci |
| Herrell ’43 [48] | | 2/2 | 1 post-op wound infection, 1 infected ulcer treated with systemic PCN—*S. aureus* |
| Taylor ’44 [45] | | 1/1 | Infected ulcer treated with topical PCN—*S. aureus* |
| Thomson ’44 [108] | 11/85 | 26/61 | WWII wounds treated with topical PCN or not, success = microbial eradication—*S. aureus* and streptococci were predominant |
| Florey ’44 [109] | 5/102 | 61/110 | WWII hand wounds, alternated to receive topical PCN or control, success = clinical and microbiological—*S. aureus* and streptococci predominant |
| Johnson ’44 [110] | | 13/13 | Surgical wounds treated with topical PCN—*S. aureus* and streptococci predominant |
| Bentley ’44 [49] | | 9/11 | Surgical wounds prophylaxed with oral sulfonamide, 11 breakthrough infections treated with systemic PCN—*S. aureus* and streptococci were predominant |

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| Dawson ’44 [50] | | | 5/6 | Infected surgical wounds treated with systemic PCN, 1 failure = necrotizing ulcer—5 *S. aureus*, 1 mixed *S. aureus*/streptococci |
| Brown ’44 [111] | | 52/68 | 215/236 | WWII wounds treated with topical sulfonamide or PCN |
| d’Abreu ’44 [112] | 2/40 | | 24/25 | WWII infected wounds treated with local or systemic PCN (some local sulfonamide with local PCN) |
| Jeffrey ’44 [113] | | 17/100 | 500/600 | WWII combat wounds treated topically with sulfonamide or PCN (some of the patients cited from an unknown previous study) |
| Bentley ’45 [114] | 89/116 | 190/213 | 236/255 | Combat wounds alternately treated with topical sulfonamide, PCN, or control, success = no wound infection—predominantly *S. aureus* and streptococci |
| Hamilton ’45 [93] | | | 37/47 | Surgical and combat wounds treated with systemic or topical PCN—predominantly *S. aureus* or streptococci, some mixed infections with *Enterococcus* |

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| Lyons ’46 [51] | | | 26/26 | WWII wounds infected despite topical sulfonamides treated with systemic PCN—*S. aureus*, streptococci, anaerobes |
| Meleney ’46 [46] | | | 67/105 | Post-op or trauma wounds treated with topical or systemic PCN |
| Altemeier ’48 [52] | | | 36/42 | Infected surgical wounds or ulcers treated with systemic PCN—24 *S. aureus*, 4 streptococci, 14 mixed *S. aureus*/streptococci |
| Southworth ’49 [53] | | | 12/12 | Infected surgical wounds treated with systemic PCN |
| | **Other** | **Sulfa** | **PCN** | |
| **Overall** | 160/449 | 385/531 | 1476/1775 | |
| **% (95% CI)** | 36% (32-39%) | 73% (70-76%) | 83% (81-85%) | |
| **Effect Size** | | 37% (30-43%) | 48% (42-53%) | |

*Other refers to non-antimicrobial therapies including topical creams (e.g. magnesium sulfate, glycerin, etc.), blood transfusion, injection of anti-streptococcal serum into lesions, X-ray or UV therapy, or bacteriophage therapy.

**Table 3. Clinical Cure Rates for Major Abscesses**

| | Treatment | | | |
|---|---|---|---|---|
| **Author/Yr** | **Other*** | **Sulfa** | **PCN** | **Disease: Comment** |
| Walters ’09 [115] | 1/1 | | | “vaccine” plus citric acid for carbuncle—*S. aureus* |
| Reynolds ’13 [116] | 2/2 | | | Sulfuric acid for carbuncle—1 grew *S. aureus* |
| Ross ’17 [117] | 1/1 | | | X rays for carbuncle |
| Lewis ’23 [118] | 10/16 | | | X-rays for carbuncles, failure ≡ > 28 days to resolve |
| Hodges ’24 [119] | 8/9 | | | X-rays for carbuncles, failure = extension post-treatment |
| Hodges ’25 [77] | 15/17 | | | X rays for “local inflammations” and carbuncles, failure = “benefit did not appear” |
| Carp ’27 [120] | 129/153 | | | X-rays, surgery, or blood injected into carbuncles, failure = “unsuccessful” |
| Light ’30 [121] | 34/50 | | | X-rays for carbuncles, failure = “received no benefit” |
| Jern ’34 [122] | 24/34 | | | Bacteriophages for carbuncles and furuncles, failure = “slight benefit” or “no benefit”—all *S. aureus* |

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| King ’37 [123] | 22/37 | | | X-rays, failure = not “successful” |
| Barber ’38 [124] | | 1/1 | | Systemic sulfonamide for carbuncle—*S. aureus* |
| Abrahamson ’39 [125] | | 2/6 | | Systemic sulfonamide for bacteremic facial carbuncles, failure = death—*S. aureus* |
| Beling ’40 [126] | | 38/40 | | Systemic sulfonamide for carbuncles (n = 13), furuncles (n = 12), or abscesses (n = 15), failure = slow recovery—all *S. aureus*, a few with mixed streptococci |
| Abraham ’41 [67] | | | 1/1 | Systemic PCN for carbuncle—*S. aureus* |
| Melton ’41 [127] | | 19/22 | | Topical sulfonamide for carbuncles, failure = deaths, all seen in patients moribund prior to treatment—*S. aureus* |
| McLoughlin ’42 [128] | 10/20 | | | Surgery and/or X-rays for carbuncles, failure = deaths, skin grafts, > 30 days in hospital—*S. aureus* when reported |
| Keefer ’43 [47] | | | 25/28 | Systemic PCN for carbuncles, abscesses, or furuncles, failure = “no effect”—all due to *S. aureus* except 1 *Streptococcus* |
| Herrell ’43 [48] | | | 1/1 | Subcutaneous PCN for bacteremic, multiple abscesses—*S. aureus* |

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|---|---|---|
| Dawson ’44 [50] | 2/2 | Systemic PCN for carbuncles (also 3 furuncles cured)—*S. aureus* |
| Hamilton ’45 [93] | 13/13 | Systemic PCN for carbuncles and furuncles |
| Hirsh ’46 [97] | 1/2 | Systemic PCN for abscesses, failure = “unimproved”—1 due to *S. aureus* |
| Romansky ’46 [96] | 18/18 | Systemic PCN for carbuncles (n = 10) or abscesses (n = 8)—also cured 75/75 furuncles |
| Rose ‘46 | 9/9 | Systemic PCN for carbuncles (n = 6) or abscesses (n = 3) |
| Wheatley ’47 [129] | 4/4 | Systemic PCN for carbuncles (n = 3), or abscess (n = 1) |
| Gottleib ’47 [130] | 17/17 | Systemic PCN for carbuncles or “boils” |
| Robinson ’48 [100] | 21/22 | Systemic PCN for “skin infections”, including carbuncles and abscesses, failure = an abscess requiring incision and drainage, which was found to be sterile |
| Wellman ’48 [131] | 62/67 | Systemic PCN for skin infections (carbuncles, furuncles, cellulitis, lymphangitis), failure = “doubtful value” |

| | | | | |
|---|---|---|---|---|
| Altemeier ’48 [52] | | | 33/34 | Systemic PCN for abscesses (n = 31) or carbuncles (n = 4)—17 *S. aureus*, 8 strep, 14 mixed *S. aureus*/streptococci, failure = “questionable” |
| Davies ’48 [132] | | | 30/30 | Systemic PCN for abscesses (“severe boils”) or carbuncles |
| Bate ’49 [133] | | | 20/20 | Systemic PCN for carbuncles |
| Southworth ’49 [53] | | | 21/21 | Systemic PCN for carbuncles or furuncles |
| Bunn ’50 [101] | | | 4/4 | Systemic PCN for abscesses |
| | **Other** | **Sulfa** | **PCN** | |
| **Overall** | 254/336 | 60/69 | 282/293 | |
| **% (95% CI)** | 76% (71-80%) | 87% (80-94%) | 96% (94-98%) | |
| **Effect Size** | | 11% (0-23%) | 21% (14-27%) | |

*Other refers to non-antimicrobial therapy including topical creams (e.g. magnesium sulfate, glycerin, etc.), blood transfusion, injection of anti-streptococcal serum into lesions, X-ray or UV therapy, or bacteriophage therapy.

**Table 4. Mortality Rates from Cellulitis/Erysipelas**

| Author/Yr | Other* | UV | Sulfa | Penicillin |
|---|---|---|---|---|
| Henderson ’07 [71] | 0/1 | | | |
| Waddelow ’07 [134] | 19/46 | | | |
| Gray ’08 [72] | 2/6 | | | |
| Choksy ‘11[73] | 20/72 | | | |
| Erdman ’13 [135] | 93/800 | | | |
| MacMillan ’20 [74] | 2/8 | | | |
| Lusk ’22 [75] | 6/95 | | | |
| Hodges ’25 [77] | 0/2 | | | |
| Platou ’26 [78] | 5/21 | | | |
| Borovsky ’27 [136] | 4/14 | | | |
| Schaffer ’27 [137] | 34/101 | | | |
| Seegel ’29 [138] | 55/281 | | | |
| Benson ’30 [79] | 45/470 | | | |
| Ude ’31 [80] | 49/325 | 11/147 | | |
| Symmers ’32 [139] | 1,709/17,616 | | | |
| Nightingale ’34 [140] | 44/130 | 11/51 | | |

| | | | | |
|---|---|---|---|---|
| Lavender ’35 [141] | 6/64 | 1/26 | | |
| Keefer ’36 [142] | 230/1400 | | | |
| Tonndorf ’36 [81] | | | 0/22 | |
| Meyer-Heine ’36 [82] | | | 0/150 | |
| Fox ’37 [143] | 35/378 | | | |
| Breen ’37 [83] | 0/10 | | 2/46 | |
| Snodgrass ’37 [84] | 4/48 | 6/104 | 5/160 | |
| Snodgrass ’37 [85] | | 4/135 | 5/135 | |
| Snodgrass ’38 [86] | | | 5/242 | |
| Nelson ’39 [87] | 44/406 | 376/4473 | 9/344 | |
| Hoyne ’39 [42] | 93/829 | | 5/169 | |
| Siegel ’40 [88] | | | 4/303 | |
| Herrell ’42 [89] | | | † | 0/1 |
| Lyons ’43 [90] | | | | 0/20 |
| Keefer ’43 [47] | | | | 0/1 |
| Herrell ’43 [48] | | | | 0/3 |
| Ory ’44 [92] | | | | 1/3 |
| Dawson ’44 [50] | | | | 0/2 |
| Portnoy ’44 [144] | | | | |
| Ross ’45 [94] | | | | 0/2 |
| Hamilton ’45 [93] | | | | 0/20 |
| Forbes ’46 [95] | | | | 0/5 |

| | |
|---|---|
| Hirsh ’46 [97] | 0/9 |
| Meleney ’46 [46] | 0/36 |
| Romansky ’46 [96] | 0/33 |
| Rose ’46 [98] | 0/5 |
| Robinson ’48 [99] | 0/1 |
| Robinson ’48 [100] | 0/10 |
| Wellman ’48 [131] | 0/67 |
| Altemeier ’48 [52] | 0/31 |
| Hirsh ’49 [145] | 0/3 |
| Southworth ’49 [53] | 0/47 |
| Bunn ’50 [101] | 0/5 |
| Hirsh ’50 [102] | 0/3 |

| | **Other** | **UV** | **Sulfa** | **Penicillin** |
|---|---|---|---|---|
| **Overall** | 2528/23657 | 409/4936 | 35/1593 | 1/325 |
| **% (95% CI)** | 10.7% (10.3-11.1%) | 8.3% (7.5-9.1%) | 2.2% (1.5-2.9%) | 0.3% (0-0.8%) |
| **Effect Size** | | ⁻2.4% (⁻1.3 - ⁻3.6%) | ⁻8.5% (⁻7.4 - ⁻9.6%) | ⁻10.4% (⁻9.5 - ⁻11.1%) |

*Other refers to non-antimicrobial therapies including topical creams (e.g. magnesium sulfate, glycerin, etc.), blood transfusion, injection of anti-streptococcal serum into lesions, X-ray therapy (but not UV therapy), or bacteriophage therapy.

[†]Switched from sulfadiazine to PCN, so censored from survival for sulfonamide

**Table 5. Mortality Rates for Carbuncles/Furuncles**

| Author/Yr | Other* | Penicillin |
|---|---|---|
| Walters ’09 [115] | 0/1 | |
| Reynolds ’13 [116] | 0/2 | |
| Ross ’17 [117] | 0/1 | |
| Martin ’22 [146] | 12/90 | |
| Lewis ’23 [118] | 0/16 | |
| Hodges ’24 [119] | 0/9 | |
| Hodges ’25 [77] | 0/17 | |
| Carp ’27 [120] | 11/153 | |
| Light ’30 [121] | 2/50 | |
| Anon ’35 [147] | 13/206 | |
| Mitchiner ’35 [148] | 13/240 | |
| Abraham ’41 [67] | | 0/1 |
| McLoughlin '42 [128] | 4/20 | |
| Keefer ’43 [47] | | 0/34 |
| Herrell ’43 [48] | | 0/1 |
| Dawson ’44 [50] | | 0/5 |
| Taylor ’44 [45] | | 0/2 |
| Hamilton ’45 [93] | | 0/13 |
| Maes ’46 [149] | 9/211 | |
| Meleney ’46 [46] | | 0/60 |
| Romansky ’46 [96] | | 0/18 |

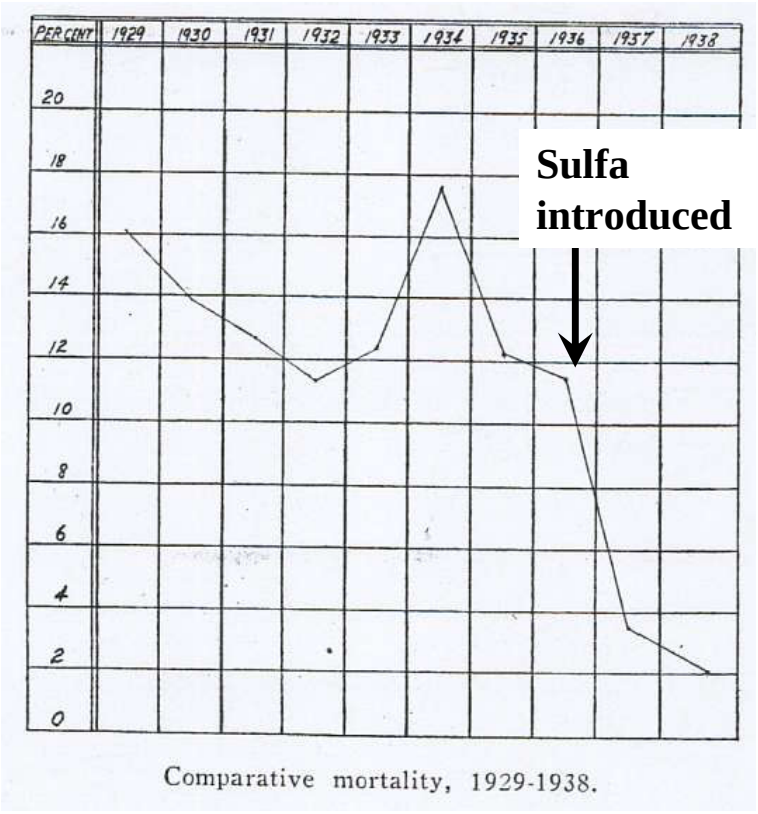
| | | |
|---|---|---|
| Rose ’46 [98] | | 0/9 |
| Wheatley ’47 [129] | | 0/4 |
| Gottleib ’47 [130] | | 0/17 |
| Robinson ’48 [100] | | 0/22 |
| Wellman ’48 [131] | | 0/62 |
| Altemeier ’48 [52] | | 0/35 |
| Davies ’48 [132] | | 0/30 |
| Southworth ’49 [53] | | 0/21 |
| Bate ’49 [133] | | 0/20 |
| Bunn ’50 [101] | | 0/4 |
| | **Other** | **PCN** |
| **Overall** | 64/1016 | 0/337 |
| **% (95% CI)** | 6% (5-8%) | 0% (0-0%) |
| **Effect Size** | | ¯6% (¯5 - ¯8%) |

*Other refers to non-antimicrobial therapy including topical creams (e.g. magnesium sulfate, glycerin, etc.), blood transfusion, injection of anti-streptococcal serum into lesions, X-ray therapy (but not UV therapy), or bacteriophage therapy.

## Figure Legends

**Figure 1. Mortality rates from erysipelas before and after the introduction of antimicrobial agents.** A) Mortality of erysipelas at Cook County Hospital in Chicago, IL, from 1929-1938. Sulfonamides became generally available in 1936. Adapted from Hoyne et al. [42] with permission. B) Mortality of erysipelas from a national registry in Norway. Sulfonamides became generally available between 1936 and 1937. Penicillin was first used in patients in 1941, but did not become generally available for civilian use until after World War II, between 1946 and 1947. Adapted from Madsen [43] with permission.

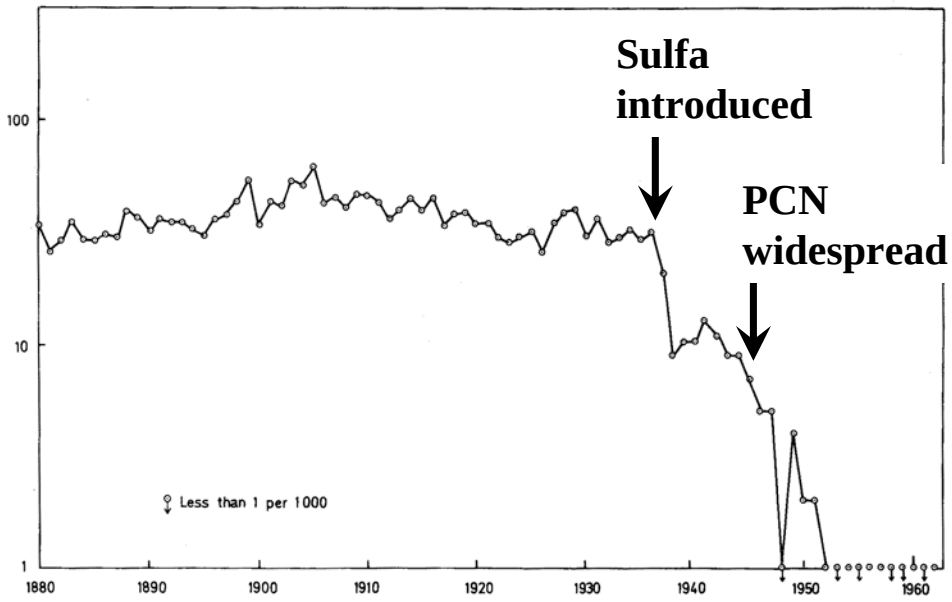
**A)**




Comparative mortality, 1929-1938.

**% Mortality**

**B)**




**Mortality Per 1000**