Delafloxacin: The One Fluoroquinolone to Rule Them All
The Use of Delafloxacin in Skin and Soft Tissue Infections

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Learning Objectives:
1. Describe skin and soft tissue infections (SSTIs) and current treatment guidelines
2. Describe the role of fluoroquinolones in the management of SSTIs
3. Review current evidence supporting the use of delafloxacin, a newly approved fluoroquinolone, for the management of SSTIs
4. Formulate an evidence based recommendation on the use of delafloxacin in SSTIs
I. **Skin and Soft Tissue Infections (SSTIs)**

A. Definitions

   a. SSTIs
      i. Infections involving the skin, subcutaneous tissue, fascia, or muscle
   b. Acute bacterial skin and skin-structure infections (ABSSSIs)
      i. FDA definition used for clinical trials, excluding deep space infections and necrotizing infections, where the lesion area measures at least 75 cm²

Table 1. Definitions of Common SSTIs²

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical Presentation and Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impetigo</td>
<td>• Localized infection of the upper layers of the skin&lt;br&gt;• Characteristic purulent crusts&lt;br&gt;• Lesions may have a bullous appearance</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>• Infection localized to the hair follicle&lt;br&gt;• Appear as small, yellow pustule</td>
</tr>
<tr>
<td>Furuncles</td>
<td>• Follicular infection extends from around the hair shaft to involve deeper areas of the skin&lt;br&gt;• Also known as carbuncles, abscesses, or boils</td>
</tr>
<tr>
<td>Eschar</td>
<td>• Piece of dead tissue that is cast off from the surface of the skin&lt;br&gt;• May involve epidermis alone or go into the dermis&lt;br&gt;• Seen after burns, insect bites, or infections</td>
</tr>
<tr>
<td>Erysipelas</td>
<td>• Well-demarcated, erythematous, indurated, rapidly spreading patch with a palpable advancing border on the face or extremities&lt;br&gt;• Fever and chills common</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>• Severe, rapidly spreading infection of subcutaneous adipose tissue often associated with systemic symptoms&lt;br&gt;• Pathogens enter through trauma, previous infections, or surgery</td>
</tr>
<tr>
<td>Necrotizing Fasciitis</td>
<td>• Infection of subcutaneous tissue and superficial fascia associated with rapidly progressive necrosis&lt;br&gt;• Systemic toxicity is present&lt;br&gt;• May be limb or life threatening</td>
</tr>
</tbody>
</table>

B. Epidemiology of SSTIs³⁴:

   a. In recent years, the United States has seen an increase in the number of ED visits due to SSTIs
      i. Between 1999 to 2007 there was a 3.1 fold increase (11% per year) for abscess SSTIs
      ii. According to an Agency for Healthcare Research and Quality (AHRQ) report, SSTIs were responsible for 600,000 hospitalizations in 2007
C. Pathophysiology\(^2\)

a. Skin serves as a protective barrier with natural defense mechanisms to discourage infection
   i. Skin is relatively dry with low pH
   ii. Continuous shedding of epidermis layer leads to shedding of bacterial flora
   iii. Sebaceous secretions are hydrolyzed to form free fatty acids which inhibit bacterial growth

b. Most skin infections occur due to the disruption of the skin barrier through
   i. Skin puncture
   ii. Abrasion
   iii. Comorbid conditions

c. Risk factors for SSTIs
   i. Excessive moisture of the skin
   ii. Inadequate blood supply
   iii. Availability of bacterial nutrients
   iv. Increased bacterial growth

D. Microbiology

a. The most common SSTIs pathogens are *Staphylococcus aureus* and *Streptococcus pyogenes*
   i. 45% of SSTIs in hospitalized patients are due to *S. aureus* with 36% of these cases being methicillin-resistant *Staphylococcus aureus* (MRSA)

<table>
<thead>
<tr>
<th>Causative Bacteria</th>
<th>Associated Risk Factors</th>
<th>Type of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enterococcus spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>Immunosuppression</td>
<td>Cellulitis, abscesses, wound infections, fasciitis</td>
</tr>
<tr>
<td><strong>Staphylococcus spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em> (MSSA and MRSA)</td>
<td>IV drug use, diabetic infections, wounds, human bites, neutropenia</td>
<td>Impetigo, furuncles, folliculitis, cellulitis</td>
</tr>
<tr>
<td><em>S. epidermidis</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Streptococcus spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (<em>S. pyogenes</em>)</td>
<td>Wounds, diabetes, poor hygiene</td>
<td>Impetigo, cellulitis, necrotizing fasciitis</td>
</tr>
<tr>
<td>Group B (<em>S. agalactiae</em>)</td>
<td>Diabetes</td>
<td>Cellulitis</td>
</tr>
<tr>
<td>Group C, D, and G</td>
<td>Stasis dermatitis, lymphedema</td>
<td>Wound infections, impetigo</td>
</tr>
<tr>
<td><strong>Gram Negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Nocardi a</em> spp.</td>
<td>Immunosuppression</td>
<td>Abscess</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Neutropenia, IV drug use, hot tub exposure, surgical wounds</td>
<td>Cellulitis, folliculitis</td>
</tr>
<tr>
<td><em>Pasteurella multocida</em></td>
<td>Cat bite wounds</td>
<td>Cellulitis</td>
</tr>
</tbody>
</table>
E. Treatment of SSTIs
   a. 2014 Infectious Diseases Society of America (IDSA) guidelines  
      i. Recommended antimicrobial treatments are based on most likely pathogen

![IDSA 2014 SSTIs Treatment Flowchart](image)

Figure 1 IDSA 2014 SSTIs Treatment Flowchart

b. Common pathogens  
   i. Non-purulent: *S. pyogenes*  
   ii. Purulent: *S. aureus*

F. Impact of MRSA Infections
   a. Common pathogen of SSTIs in community and health-care settings  
   b. Increased occurrence of MRSA SSTIs, possibly due to the increase in Community Acquired MRSA (CA-MRSA)  
      i. Involve previously healthy patients without direct or indirect contact with a health-care setting  
      ii. Produces a toxin called, Panton-Valentine leukocidin (PVL) which increases its virulence  
   c. CA-MRSA accounts for an annual burden of 478 million-2.2 billion dollars to third party payers and 1.4 billion-13.8 billion dollars  
      i. CA-MRSA associated with higher rate of reoccurrence, hospital readmission, longer hospital stay, and more expensive antimicrobial therapies

II. Fluoroquinolones
   A. History  
      a. First synthetic quinolone was nalidixic acid, produced in 1962
b. In the 1980s, the identification of the fluorine and piperazinyl-substituted
derivatives offered greater potency and extended the spectrum which led to the
development of the present day fluoroquinolones
c. Frequently utilized fluoroquinolones include ciprofloxacin, levofloxacin, and
moxifloxacin

B. Chemical Structure
a. Each quinolone in clinical use has the following:
   i. Dual ring structure with a nitrogen at position 1
   ii. A carbonyl group at position 4
   iii. A carboxyl group attached to the carbon at position 3 in the first ring

![Figure 2. Chemical structure of fluoroquinolones](http://www.scienceprofonline.com/microbiology/mode-of-action-of-quinolone-antibiotics.html)

b. Addition of a fluorine atom at position 6 greatly increased potency
c. Addition of a piperazinyl group or methyl-piperazinyl group has offered a greater
   potency to gram negative bacteria

C. Mechanism of Action
a. Bind to bacterial DNA gyrase and topoisomerase IV to rapidly inhibit DNA replication
   and transcription
   i. Depending on the bacteria and fluoroquinolone, one target may be
      preferential over the other
      1. In *E. coli*, DNA gyrase is the preferred target, followed by
topoisomerase IV
b. Considered bactericidal
   i. Concentration dependent (AUC/MIC)
      1. As peak concentrations increase, bactericidal activity increases

D. Adverse Effects
a. GI upset including nausea, vomiting, and diarrhea
b. Altered mental status/psychosis
c. Tendonitis and tendon rupture
   i. Increased risk with:
      1. Age >60
      2. Concomitant use of systemic corticosteroids
      3. Kidney, heart, or lung transplant
      4. Kidney failure
      5. Strenuous physical activity
6. History of tendon issues, such as rheumatoid arthritis
   d. QTc prolongation
e. Dysglycemia
   f. *Clostridium difficile* infections

E. Spectrum of activity:
   a. Ciprofloxacin is the most active against aerobic gram-negative bacteria, such as Enterobacteriaceae, *Haemophilus* spp., *P. aeruginosa*
   b. Levofloxacin and moxifloxacin demonstrate an increase in activity against gram positive organisms, specifically *S. pneumoniae*
   c. All clinically utilized fluoroquinolones have activity against mycobacteria, and many atypicals implicated in pneumonia

F. Pharmacokinetics
   a. Absorption
      i. Exceeds 50% for all fluoroquinolones
         1. Levofloxacin and moxifloxacin demonstrate 100% bioavailability
      ii. Peak concentrations typically occur within 1 to 3 hours of administration
   b. Distribution
      i. Typically high, exceeding the volume of total body water
      ii. Highest concentrations of drug are found in prostate tissue, stool, bile, lung, neutrophils, macrophages, urine and kidneys
   c. Metabolism
      i. Hepatically metabolized via glucuronidation
   d. Elimination
      i. Renally excreted with the exception of moxifloxacin which is primarily hepatic

G. Mechanism of Acquired Resistance\textsuperscript{11-12}
   a. Target Site Mutations
      i. Spontaneously occurs through mutations in chromosomal genes in the quinolone resistance-determining region (QRDR), that alter the DNA gyrase or topoisomerase IV
         1. Common gene mutations:
a. *gyrA*: clustered alterations in the subunit A of the DNA gyrase enzyme between amino acids 67 and 106
   i. Most common is the change of serine-83 to leucine or tryptophan
b. *parC*: mutation of topoisomerase IV, specifically in *S. aureus* and *S. pneumoniae*
   i. Most common mutation occurs at serine-80, which is changed to phenylalanine or tyrosine

2. When the preferred target obtains a mutation, fluoroquinolones still have the ability to bind to the second target
   a. Organisms that demonstrate high resistance to fluoroquinolones, can have mutations occurring in both DNA gyrase and topoisomerase IV
b. Plasmid mediated resistance has been noted in *Enterobacteriaceae*
   i. Genes are transferred on a plasmid known as the plasmid-mediated quinoline resistance genes, or PMQR
      1. The *qnr* gene, located in the PMQR, encodes a protein that can protect the DNA gyrase and topoisomerase IV
         a. The *qnr* protein binds to the target enzyme to prevent the fluoroquinolone and enzyme from interacting
   ii. Usually found in *Enterobacteriaceae* that have other chromosomal resistance markers, i.e. QRDR target mutations
c. Efflux
   i. Efflux pumps actively remove fluoroquinolones from the bacterial cell
      1. Common efflux pumps:
         a. NorA of *S. aureus*
         b. RND family of tripartite transporters of gram negative bacteria
      2. Repeated exposure to fluoroquinolones can select for bacteria that overexpress these efflux pumps

H. Rationale for use in SSTIs
   a. Fluoroquinolones are considered broad spectrum antibiotics that cover both gram-positive and gram-negative bacteria
   b. Most SSTIs are composed of *Staphylococcus* spp. or *Streptococcus* spp.
      i. However, wounds may contain mixed flora, including aerobic gram negative bacteria
   c. Quinolones were initially hoped to be a viable oral option for MRSA infections, yet rapid resistance developed making them an unreliable option for empiric therapy

III. Delafloxacin

A. History\textsuperscript{13-15}
   a. Trademark name, Baxdela™
b. First developed in 1999 to Abbott Park, USA and later licensed to Melinta Therapeutics, USA in 2006

c. Approved by the FDA on June 19, 2017 for the management of ABSSSI caused by gram positive and gram negative organisms, including MRSA

d. While delafloxacin is currently approved by the FDA, Melinta has not released delafloxacin to market

B. Recommended Doses:

a. IV: 300 mg twice daily
   i. Renal dosing for eGFR of 15-29 ml/min/1.73m²
      1. 200 mg twice daily
      2. Reduced dose is due to cyclodextrin being used as an IV vehicle, which can accumulate in patients with decreased renal function and cause further renal toxicities, as well as liver toxicities
   ii. Renal dosing for eGFR <15 mL/min/1.73m²
      1. Delafloxacin is not recommended

b. Oral: 450 mg twice daily

c. No hepatic impairment dose adjustments are required

C. Chemical Structure

a. Unique Features

![Chemical Structure of Delafloxacin](https://www.medchemexpress.com/Delafloxacin.html)

i. Presence of a heteroaromatic substitute at position 1

ii. Weak polarity associated with chlorine atom at position 8

iii. Lack of a basic group in position 7

   1. Renders an anionic state at neutral pH and uncharged at slightly acidic pH (≤ 5.5)

   2. Compared to moxifloxacin at lower pHs, delafloxacin accumulates more in the cells and demonstrates a higher potency against *S. aureus*.¹⁶
D. *In Vitro* Data\textsuperscript{17}

a. Based on data from the United States and Europe in 2014

<table>
<thead>
<tr>
<th>Table 3. Gram Positive and Gram Negative Active of Delafloxacin and Comparator Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organism Group (no. of isolates)/ antimicrobial agent</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>MSSA (777)</strong></td>
</tr>
<tr>
<td>Delafloxacin</td>
</tr>
<tr>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Oxacillin</td>
</tr>
<tr>
<td>Linezolid</td>
</tr>
<tr>
<td>Vancomycin</td>
</tr>
<tr>
<td><strong>MRSA (573)</strong></td>
</tr>
<tr>
<td>Delafloxacin</td>
</tr>
<tr>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Linezolid</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>Vancomycin</td>
</tr>
<tr>
<td><strong>S. pneumoniae (450)</strong></td>
</tr>
<tr>
<td>Delafloxacin</td>
</tr>
<tr>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Amoxicillin-Clavulanic acid</td>
</tr>
<tr>
<td>Ceftaroline</td>
</tr>
<tr>
<td>Moxifloxacin</td>
</tr>
<tr>
<td><strong>S. pyogenes (433)</strong></td>
</tr>
<tr>
<td>Delafloxacin</td>
</tr>
<tr>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Amoxicillin-Clavulanic acid</td>
</tr>
<tr>
<td>Vancomycin</td>
</tr>
<tr>
<td><strong>E. coli (500)</strong></td>
</tr>
<tr>
<td>Delafloxacin</td>
</tr>
<tr>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Aztreonam</td>
</tr>
<tr>
<td>Ceftiraxone</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td><strong>E. coli with ESBL phenotype (92)</strong></td>
</tr>
<tr>
<td>Delafloxacin</td>
</tr>
<tr>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Aztreonam</td>
</tr>
<tr>
<td>Ceftiraxone</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td><strong>P. aeruginosa (200)</strong></td>
</tr>
<tr>
<td>Delafloxacin</td>
</tr>
<tr>
<td>Aztreonam</td>
</tr>
<tr>
<td>Cefepime</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
</tbody>
</table>

Stauffer 9
E. Pharmacokinetics
d. Similar to other fluoroquinolones

F. Adverse Events:
e. Similar to other fluoroquinolones
f. No clinically relevant QTc prolongation

G. Spectrum of Activity

[Image of Gram Positives:
- Streptococcus spp.
- Enterococcus faecalis
- Staphylococcus aureus (MSSA and MRSA)]

[Image of Gram Negatives:
- Escherichia coli
- Klebsiella pneumoniae
- Enterobacter cloacae
- Pseudomonas aeruginosa]

Figure 5 Common Pathogens for Delafloxacin Use

H. Evidence of Resistance
g. Delafloxacin has demonstrated activity against strains that are resistant to other fluoroquinolones
i. Possibly due to delafloxacin targeting DNA gyrase and topoisomerase IV equally
ii. Will require mutations in both targets to be considered resistant
iii. Thought to be a poor substrate to the efflux pumps

IV. Clinical Question

When presented with an acute bacterial skin and skin-structure infection, should delafloxacin be utilized over conventional established empiric therapy?

V. Literature Review

Table 4.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Objective</td>
</tr>
<tr>
<td>Methods</td>
</tr>
</tbody>
</table>
| Population | Inclusion criteria: 
- > 18 years of age 
- Diagnosis of a cSSSI defined as those involving subcutaneous tissues or requiring surgical intervention, with at least one of the following: |
A wound that developed 30 days after surgery, trauma, or an animal/insect bite and must have:
- Purulent fluid from the wound or three or more of the following: fever, swelling, erythema of ≥ 10mm, pain, or tenderness

An abscess, without an open wound, that had developed during the 7 days prior to enrollment, with purulent fluid
- Required to have evidence of a loculated fluid collection that required intervention within 48 hours of enrollment and erythema and/or induration of ≥ 20 mm in diameter or tenderness

Cellulitis that developed during the 7 days before enrollment with advancing erythema, edema, or induration
- Must also have one of the following: fever, a white blood cell count of $10 \times 10^9/L$ or ≥ 10% band forms, or lymphangitis and adenopathy

Exclusion criteria:
- Known hypersensitivity to fluoroquinolones, tetracyclines, or tetracycline derivatives
- Pregnancy or lactation
- Presence of diabetic foot ulcers, prosthetic device infections, osteomyelitis, septic arthritis, necrotizing fasciitis, and severely impaired arterial blood supply

Study Design
- Phase 2, multicenter, randomized, double-blind study
- Randomization stratified by infection type: abscess, wound infection, or cellulitis
- Treatment was given for 5-14 days dependent on investigator’s judgement
- Intervention:
  - Delafloxacin 300 mg IV twice daily
  - Delafloxacin 450 mg IV twice daily
  - Tigecycline 100 mg IV x 1 dose, followed by 50 mg IV twice daily

Outcomes
- Efficacy analysis of the clinical response rates in the delafloxacin versus tigecycline arms in the CE population at the TOC visit

Statistics
- Fisher’s exact test utilized for comparisons
- ITT population: all randomized patients who received at least one dose of the study drug
- mITT population: included all ITT patients who had a clinical diagnosis of cSSSI
- CE population: mITT patients who received at least 80% of study drug therapy, had a test-of-cure (TOC) visit, did not receive any concomitant, systemic antibacterial agents, and a culture attempted at screening
- ME population: all CE patients who had a pathogen isolated at screening that was susceptible to a study drug
- All patients who received at least one dose of the study drug were evaluated for safety and tolerability
### Results

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Baseline Characteristic</th>
<th>Delafloxacin 300 mg IV (n=49)</th>
<th>Delafloxacin 450 mg IV (n=51)</th>
<th>Tigecycline 50 mg IV (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td>42.7</td>
<td>37.2</td>
<td>40.4</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td></td>
<td>31 (63.3)</td>
<td>36 (70.6)</td>
<td>35 (70)</td>
</tr>
<tr>
<td>Race, Caucasian (%)</td>
<td></td>
<td>39 (79.6)</td>
<td>44 (86.3)</td>
<td>40 (80)</td>
</tr>
</tbody>
</table>

- cSSSIs diagnosis across all groups similar

### Clinical Outcomes
- Clinical cure rates at the TOC visit in CE population
  - Delafloxacin 300 mg: 94.3%
  - Delafloxacin 450 mg: 92.5%
  - Tigecycline: 91.2%
- All three treatments were effective in treating MRSA infections
  - Efficacy rates trended higher with delafloxacin over tigecycline, although not statistically significant
- No documentation of persistent pathogens in any of the treatment arms

### Safety and Tolerability
- Delafloxacin was generally well tolerated
  - Most frequent adverse event was GI upset, specifically nausea, vomiting and diarrhea
- 1 patient in the delafloxacin 450 mg IV group experienced generalized seizures
- 11 delafloxacin patients experienced low blood sugar
  - Nine occurred in the 450 mg IV group
  - One case was symptomatic

### Conclusion
- Delafloxacin is a safe and efficacious option for cSSSIs

### Strengths
- Multicenter, randomized, double blind study
- Studied delafloxacin at both the recommended dose and a higher dose

### Limitations
- Sponsored by Melinta, Inc.
- Small sample size
- Generalizability is limited
- Did not compare delafloxacin to a current recommended therapy for ABSSSI
- Designed the trial based on the 1998 FDA guidance, and thus did not include the primary endpoint of a decrease by 20% in lesion size at 48-72 hours after starting therapy
- Selected for patients with gram positive infections, specifically S. aureus

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Table 5.


<table>
<thead>
<tr>
<th>Objective</th>
<th>To evaluate the efficacy and safety of delafloxacin in the treatment of acute bacterial skin and skin structure infections</th>
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<tbody>
<tr>
<td>Methods</td>
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<tr>
<td>Population</td>
<td>Inclusion Criteria</td>
</tr>
</tbody>
</table>

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*Intention-to-Treat; b Modified Intention-to-Treat; c Clinically Evaluable; d Microbiologically Evaluable*
• > 18 years of age
• Diagnosed with an ABSSSI (defined as cellulitis, wound infection, major cutaneous abscess or burn infection) characterized by the following
  o ≥75 cm² of erythema or induration
  o At least one sign of systemic infection
    ▪ Fever > 38°C
    ▪ Lymphangitis
    ▪ White blood cell count >15000 cells/mm³
    ▪ Serum CRP level >5.0 mg/L
• Required to receive IV antibiotics

Exclusion Criteria
• Hypersensitivities or allergies to any of the antibiotics
• Concurrent skin conditions at the infection site
• Severely inadequate blood supply to a limb containing the ABSSSI
• Severely immunocompromised
• Hypertension (>180 mmHg systolic or ≥110 mmHg diastolic)
• Body weight >140 kg
• Use of potentially effective systemic antibiotic therapy for >24 hours within 14 days of enrollment
• Use of more than one dose of an antibiotic potentially effective against the ABSSSI under study within 24 hr before enrollment

Study Design
n=256
• Multicenter, randomized, double-blind
• Randomized on a 1:1:1 ratio to 300 mg IV twice daily delafloxacin, 600 mg IV linezolid, or 15 mg/kg vancomycin (based on actual body weight)
• Delafloxacin was mixed with D5W and administered every 12 hours
• Vancomycin levels drawn on day 2 or 3 and on day 6±1
  o Doses were adjusted for target troughs of 15-20 µg/mL
• Patients with proven or presumptive gram negative infections could add aztreonam in a blinded fashion to the linezolid and vancomycin groups
• Treatment to start within 24 hours after screening
• Patients to follow-up on day 14 + 1 and ≥12 hr after final study drug dose
• Late follow up occurred on days 21-28
• Unplanned debridement procedures completed >48 hours after study enrollment was considered a treatment failure

Outcomes
Primary Endpoint:
• Investigator’s assessment of cure, defined as a complete resolution of baseline signs and symptoms at follow-up
Secondary Endpoint:
• Reduction in the total area of erythema and induration
• Assessment of bacterial eradication

Statistics
• Clinical efficacy measured using ITT population, defined as all randomized patients
• Microbiological outcomes analyzed in the ME population defined as all patients with an identified pathogen at baseline known to have caused
an ABSSSI who received at least eight study drug infusions or ≥80% of total anticipated doses

- Continuous variables compared among treatment groups using an analysis of covariance model
- Categorical variables were compared separately by Cochran-Mantel-Haenszel test stratified by infection type
- Statistical significance set at P<0.05
- Mean differences between treatments were expressed as vancomycin minus delafloxacin
- Post-hoc analysis was to be conducted to assess the cure rate in obese (BMI ≥ 30) and non-obese (BMI < 30) patients
- Sample size calculation:
  - Originally set at 240 based on clinical and practical considerations, however there was an imbalance due to stratification parameters
  - Thus, increased sample size to 256

### Results

#### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Delafloxacin (n=81)</th>
<th>Linezolid (n=77)</th>
<th>Vancomycin (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>39.7</td>
<td>44.8</td>
<td>44.8</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>49 (60.5)</td>
<td>52 (67.5)</td>
<td>51 (52)</td>
</tr>
<tr>
<td>Race, Caucasian (%)</td>
<td>63 (77.8)</td>
<td>58 (75.3)</td>
<td>74 (75.5)</td>
</tr>
</tbody>
</table>

- Obese patients: 42.2% of total ITT population
- Most frequent ABSSSI category was cellulitis at 44.9%
- Most common pathogen isolated was MRSA at 67.2% of 177 S. aureus isolates
- Mean duration of therapy was 7.6, 7.4, 7.8 days for delafloxacin, linezolid, and vancomycin respectively

#### Outcomes

**Clinical Efficacy:**
Subjective clinical efficacy cure rates

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Delafloxacin (n=81)</th>
<th>Linezolid (n=77)</th>
<th>Vancomycin (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>57 (70.4)</td>
<td>50 (64.9)</td>
<td>53 (54.1)*</td>
</tr>
<tr>
<td>Improved</td>
<td>11 (13.6)</td>
<td>13 (16.9)</td>
<td>26 (26.5)</td>
</tr>
<tr>
<td>Failure</td>
<td>5 (6.2)</td>
<td>3 (3.9)</td>
<td>7 (7.1)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>8 (9.9)</td>
<td>11 (14.3)</td>
<td>12 (12.2)</td>
</tr>
</tbody>
</table>

*P<0.05 versus delafloxacin

- In a post-hoc analysis, delafloxacin demonstrated statistically significant cure rates over vancomycin in obese patients
  - 78.8% in delafloxacin vs. 48.8% in vancomycin
    - CI, -50.7% to -9.3%; P=0.009

**Microbiological Efficacy (n = 125):**

- No statistically significant results were noted
- Delafloxacin eradicated comparatively to linezolid and vancomycin
None of the treatment arms had documented eradication.

Safety:
- 74.4% of the delafloxacin group, 72.0% of linezolid group and 64.6% of vancomycin group reported one or more adverse events
  - Nausea, vomiting, and diarrhea common in delafloxacin group
  - Nausea common in linezolid
  - Pruritus common in vancomycin group
- Liver toxicity reported in 5 patients
  - Two delafloxacin and three vancomycin
  - Did not cause discontinuation or serious adverse events
- No reports of hypoglycemia, although five reports of hyperglycemia
- 13 patients experienced serious adverse events, although none were considered to be related to the study drug
- Reported serious adverse event of convulsions occurred in patients with a history of seizure disorder
- No clinically relevant changes to QTc interval

**Conclusion**

**Author’s Conclusion**
- This study supports the evidence that delafloxacin can be used to treat ABSSSI, specifically those infected with MRSA

**Strengths**
- Multicenter, randomized, double-blind study
- Compared delafloxacin to IDSA recommended therapies
- Utilized therapeutic drug monitoring of vancomycin

**Limitations**
- Sponsored by Melinta, Inc.
- Small sample size
- Focus on *post-hoc* analysis and the importance the author’s associated with it
- Cure rates were based on the investigator’s judgement of eradication of the signs and symptoms of ABSSSI

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**Table 6.**

**Objective**
- To establish the non-inferiority in safety and efficacy of delafloxacin compared with vancomycin plus aztreonam for the treatment of ABSSSI.

**Methods**

**Inclusion Criteria**
- >18 years
- Diagnosis of ABSSSI as cellulitis/erysipelas, wound infection, major cutaneous abscess or burn
  - >75 cm² of erythema
  - ≥2 signs of systemic infection

**Exclusion Criteria**
- Recent antibiotic use within the last 14 days
- Infection related to
  - Prosthetic joint
  - Diabetic foot infections
<table>
<thead>
<tr>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomyelitis</td>
</tr>
<tr>
<td>Decubitus ulcer</td>
</tr>
<tr>
<td>Endocarditis</td>
</tr>
<tr>
<td>Necrotizing fasciitis, anaerobic cellulitis</td>
</tr>
<tr>
<td>Sustained shock for &gt;2 hrs</td>
</tr>
<tr>
<td>Burns &gt;10% of BSA</td>
</tr>
</tbody>
</table>

**Study Design**

- Phase 3, multicenter, randomized, double-blind, active controlled study
- **Intervention**
  - Delafloxacin 300 mg IV BID
  - Vancomycin 15 mg/kg plus aztreonam 2 g Q12HR
    - Vancomycin levels drawn on Day 2 and Day 6
    - Dose adjustments based on target trough of 15-20 µg/mL
    - Aztreonam discontinued when cultures came back negative for gram negative pathogens
  - Treated for at least 5 days but no more than 14 days
    - Based on investigators’ assessment of improvement
  - Contact with the patients at screening, daily during treatment, 14 days after treatment for follow-up, and 28 days after treatment

**Outcomes**

**Clinical Efficacy:**
- FDA defined objective response at 48-72 hr following initiation
  - >20% reduction in erythema of lesion based on digital planimetry
  - No signs of clinical failure defined as
    - <20% reduction in erythema
    - Administration of a rescue dose of an antibiotic
    - Unplanned surgical intervention
    - Death within 74 hr of initiation

**Microbiological Efficacy:**
- Based on eradication of pathogens obtained from baseline culture

**Safety and Tolerability Assessments:**
- Included all reported adverse events, physical examinations, vital signs, 12 lead ECGs at baseline and if indicated as needed, and clinical laboratory tests
- Treatment-emergent adverse events defined as those that occurred or worsened after the first dose of the study drug through the 28 day follow-up

**Statistics**

**Clinical Efficacy:**
- ITT population: everyone who was randomized to a study drug

**Microbiological Efficacy:**
- MITT\(^a\) population: Those patients in the ITT population who had a positive culture

**Safety and Tolerability Assessments:**
- Patients in the ITT population who received at least one dose of the study drug
Two sided 95% CI calculated for the objective response was based on difference between delafloxacin and vancomycin/aztreonam. Investigator assessed progress rates used a non-stratified method proposed in a previous study. Non-Inferiority was met if this 95% CI was >-10% with mean difference between treatments expressed as delafloxacin minus vancomycin/aztreonam.

### Results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Delafloxacin (n=331)</th>
<th>Vancomycin/Aztreonam (n=329)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>46.3</td>
<td>45.3</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>206 (62.2)</td>
<td>209 (63.5)</td>
</tr>
<tr>
<td>Race, Caucasian (%)</td>
<td>297 (89.7)</td>
<td>304 (92.4)</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m² (%)</td>
<td>120 (36.3)</td>
<td>94 (28.6)</td>
</tr>
<tr>
<td>Pathogen at baseline (MITT), (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. aureus*</td>
<td>159 (65.4)</td>
<td>165 (66.8)</td>
</tr>
<tr>
<td>MSSA</td>
<td>78 (32.1)</td>
<td>91 (36.8)</td>
</tr>
<tr>
<td>MRSA</td>
<td>82 (33.7)</td>
<td>74 (30.0)</td>
</tr>
</tbody>
</table>

*40% of S. aureus isolates were levofloxacin non-susceptible

Median duration of treatment:
- Delafloxacin: 5 days
- Vancomycin: 5.5 days
- Aztreonam/Placebo: 2 days

### Clinical Efficacy:
- **Objective response:**
  - Mean difference: -2.6 (-8.78, 3.57)
    - Non-inferior, not significant
- **Investigator rated response:**
  - Trended higher in delafloxacin group
  - At the 28 day follow-up, obese patients demonstrated statistically significant cure rates in the delafloxacin group

### Microbiological Efficacy:
- **MRSA Infections**
  - Objective response:
    - Mean difference: -2.0 (-8.39, 4.16)
    - Similar eradication rates, not significant
  - Of note, 100% of MRSA levofloxacin non-susceptible infections in the delafloxacin group had eradicated pathogens

### Safety:
- Majority of adverse events were not attributed to the study drug
  - Lower percentage in the delafloxacin group
- Common reported AEs:
  - GI upset in delafloxacin group
  - One event of hypoglycemia in delafloxacin
  - Two events of hyperglycemia in delafloxacin

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*Stauffer 17*
### Conclusion

<table>
<thead>
<tr>
<th>Author's Conclusion</th>
<th>Delafloxacin monotherapy is non-inferior to vancomycin/aztreonam for the treatment of ABSSSI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strengths</strong></td>
<td>• Large, randomized trial&lt;br&gt;• Compared delafloxacin to a similarly broad-spectrum antimicrobial regimen&lt;br&gt;• Therapeutic drug monitoring of vancomycin was performed&lt;br&gt;• Cure was based on objective response, i.e. digital measurements of erythema, rather than solely the investigators’ assessment&lt;br&gt;• Repeated results of previous Phase 2 trial showing better cure rates in delafloxacin group compared to vancomycin and aztreonam in obese patients</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>• Sponsored by Melinta, Inc.&lt;br&gt;• Selected for patients with gram positive infections, especially <em>S. aureus</em>&lt;br&gt;• Study was not stratified for obesity at enrollment</td>
</tr>
</tbody>
</table>

*MITT: Microbiological Intention-to-Treat*

## VI. Recommendation for Use

A. While some data supports the use of delafloxacin in patients with ABSSSI, this agent should not supplant the use of existing treatment options
   a. Delafloxacin has not demonstrated better efficacy over traditional therapy, only that it is non-inferior to traditional therapy
      i. Findings for obese patients require more in depth analysis
   b. The majority of SSTIs are of gram positive etiology; there are numerous, well-established antimicrobials that cover these pathogens
      i. Established regimens also adequately cover gram negative pathogens
   c. Existing treatment options are likely to be more affordable than delafloxacin

B. In patients with recurrent MRSA ABSSSIs, who have failed other therapy, delafloxacin could prove to be beneficial

## VII. Future Considerations

A. More robust prospective, randomized controlled studies could shed light on the potential superiority of delafloxacin to established therapies, especially those targeting gram negative pathogens

B. Further analysis of delafloxacin for the treatment of ABSSSI in obese patients
   a. As a primary outcome
   b. Against another non-weight based antimicrobials

C. Use of this drug in the gram negative arena where other fluoroquinolones are lost due to resistance

D. Studies are currently being conducted to evaluate the use of delafloxacin for the treatment of community acquired pneumonia (CAP)
   a. Delafloxacin has marked activity against MRSA, as well as other common respiratory pathogens
b. A Phase 3, multicenter, randomized, double-blind, comparator-controlled study to evaluate the safety and efficacy of intravenous to oral delafloxacin in adult subjects with community-acquired bacterial pneumonia
   i. Currently recruiting patients
   ii. Comparing the use of delafloxacin to moxifloxacin in patients with CAP
VIII. References


