

# Indications and endpoints for complicated skin and soft tissue infections

Matthew Dryden MD FRCPath  
Royal Hampshire Hospital,  
Winchester  
[matthew.dryden@wehct.nhs.uk](mailto:matthew.dryden@wehct.nhs.uk)

# Main clinical indications

- Cellulitis / erisipelas
- Major soft tissue abscess
- Surgical wound infection
- Infected burn
- Diabetic foot infection
- Infected ischaemic ulcer
- Min surface area of 75cm<sup>2</sup> of erythema, swelling or induration









# Cellulitis (loose subcutaneous tissue)

Streptococci  $\beta$ -haemolytic (Strep. pyogenes)









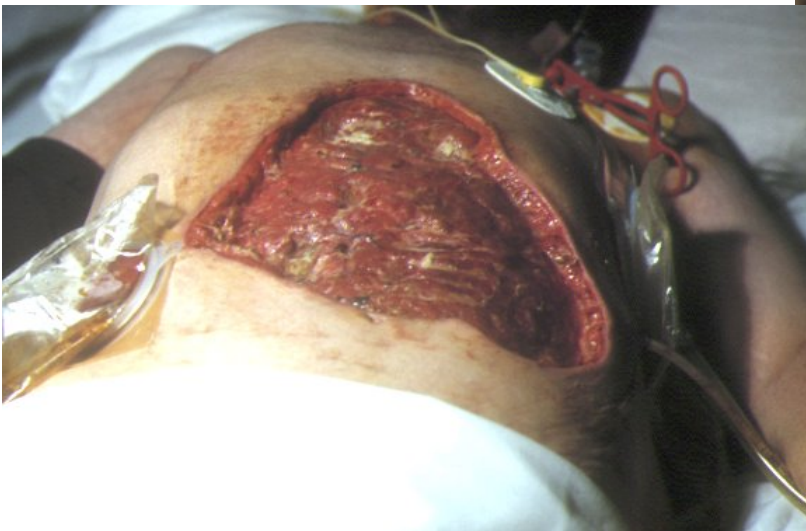
# Erysipelas – intradermal infection

Streptococci  $\beta$ -haemolytic (Strep. pyogenes)



# Necrotising fasciitis

- GAS or polymicrobial
- anaerobes often involved





# Clinical inclusion criteria

- Erythema
- Swelling
- Warmth
- Discharge
- Pain
- Fever  $\geq 38^{\circ}\text{C}$



# Microbiological criteria

- Infection site needs to be sampled
- Punch biopsy
- Aspirate
- Deep swab
- Tissue
- MRSA important in USA. Therefore FDA recommends that MRSA cases should be included

# Exclusion

- Recent antibiotic use. How long?
- Except
  - Surgical prophylaxis
  - Empirical treatment
  - Treatment failure
- Immunocompromised
- Osteomyelitis
- Diabetic foot infection / ischaemic leg
- Chronic use of antipyretics

## **Primary efficacy endpoint and timing of assessments for a noninferiority trial in ABSSSI**

- **Clinical response or clinical failure at 48 to 72 hours**
- Cessation of the spread of the redness, oedema, and/or induration
- Fall in fever
  
- NB controversy over when to assess efficacy endpoint: 72 hours or post-treatment

# Evaluation and endpoints

- Primary
  - Clinical outcome at end-of-study visit or test-of-cure visit
- Secondary
  - Microbiological outcome at EOT and EOS visits
  - Clinical outcome at EOT visit



# Other secondary endpoints

- Safety and tolerability
- Population PK data
- Duration of hospital stay
- Duration of IV therapy
- Medical resource use

# FDA recommendations 2010

**Primary efficacy endpoint and timing of assessments for a noninferiority trial in ABSSSI (clinical response or clinical failure at 48 to 72 hours):**

- *Clinical response:* Cessation of the spread of the redness, edema, and/or induration of the lesion or reduction in the size (length, width, and area) of redness, edema, and/or induration at 48 to 72 hours after enrollment *and* resolution (absence) of fever (i.e., temperature less than 37.7 degrees Celsius at 3 consecutive recordings by the same methodology every 6 hours between 48 and 72 hours)
- *Clinical failure:* Death; continued fever (i.e., temperature greater than or equal to 37.7 degrees Celsius); increase in the size (length, width, and area) of redness, edema, and/or induration of the lesion; or administration of rescue antibacterial drug therapy or administration of nontrial antibacterial drug therapy for treatment of ABSSSI before the primary efficacy endpoint assessment

# Clinical failures – FDA 2010

- Death – all causes
- Unplanned surgery or aspiration
- Persistent purulent discharge
- Initiating another antibiotic
- Patients who do not show reduction in size at 72 hours or resolution of lesion at 10 days and follow up visits

# Evaluation 2011 trial

## Criteria for Evaluation:

### Primary outcome:

- Cessation of spread or reduction in size of baseline lesion, absence of fever, and no rescue antibiotic medication at ECE (48 to 72 hours)

### Secondary outcomes:

#### *Efficacy outcomes*

- Clinical cure determined by the investigator at the EOT, Day 10, and PTE visits
- Clinical cure, determined by the investigator, overall and by pathogen, at the EOT visit, Day 10, and at the PTE visit

#### *Microbiological outcomes:*

- The microbiological response, overall and by pathogen, at the EOT visit, at Day 10, and at the PTE visit
- The microbiological relapse (or recurrence) at the PTE visit
- The clinical response (cessation of spread or reduction in size of baseline lesion/absence of fever and no rescue antibiotic medication and clinical cure) and microbiological response within the CE population and MicroE population respectively meeting SIRS criteria at screening (defined as two of the following: temperature  $>38^{\circ}\text{C}$ , pulse  $>90$  bpm, respiratory rate  $>20$  breaths per minute, WBC count  $>12,000\text{ mm}^3$  or  $<4,000\text{ mm}^3$  or  $>10\%$  bandemia) OR with positive blood cultures



# Discussion