AGENDA

Considerations in Justification of a Non-inferiority Margin for cSSSI

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Treatment of cSSSI

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Standard of Care for cSSSI Includes Antibiotic Treatment

- **cSSSI due to Gram-positive bacteria causes serious and life threatening complications in both healthy and debilitated individuals**
- **IDSA concluded that systemic antibiotics constitute the standard of care for treating patients with cSSSI†**
- **Increased morbidity and mortality is associated with no treatment**

† Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJC, Gorbach SL, Hischmann JV, Kaplan EL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. CID 2005; 41:1373-1406

Approved Treatments for cSSSI Utilized Active Control Trial Designs

Product Name	FDA Review Date	Non-inferiority Margin
Tygacil® (tigecycline)	2005	15%
Merrem® (meropenem)	2005	10%
Cubicin® (daptomycin)	2002	10%
Invanz® (ertapenem)	2001	10%
Levaquin® (levofloxacin)	2000	15% (inferred from results)
Zyvox® (linezolid)	2000	10%
Synercid® (quinupristin/dalfopristin)	1998	10% (cure rates >90%); 15% (cure rates <90-80%); 20% (cure rates <80%)

No Historical Data from Placebo-Controlled Trials in cSSSI

- **No studies were identified for placebo-controlled trials in *complicated* SSSI**
- **Six placebo-controlled studies for *uncomplicated* SSSI were identified**
- ***Assumption: placebo cure rates in patients with cSSSI are no greater than those seen in patients with uSSSI***

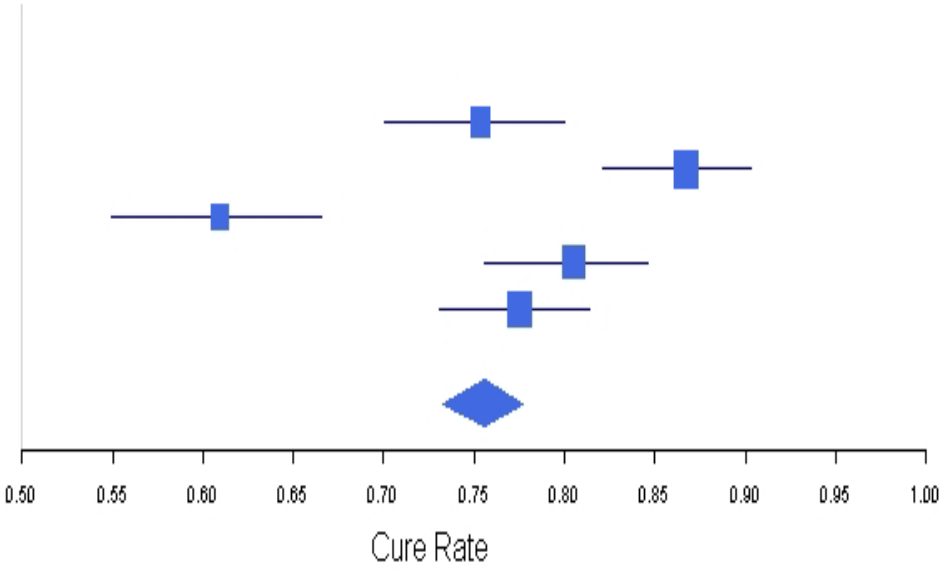
Methodology: Estimating Active Control Benefit

- Estimate the vancomycin cure rate for patients with cSSSI
- Estimate the placebo cure rate for patients with uSSSI
- Estimate treatment effect: the difference between vancomycin cure rates and placebo cure rates

Clinical Cure Rates for Vancomycin in Randomized Clinical Trials: All-Treated

Results of fixed-effects meta-analysis: Cure Rate 75.6% (95% CI 73.2% - 77.7%)

Study	Cures/N	Cure Rate	Lower Bound	Upper Bound
tigecycline (study 300)	217/288	0.753	0.700	0.800
tigecycline (study 305)	235/271	0.867	0.821	0.903
daptomycin (study 9801)	162/266	0.609	0.549	0.666
daptomycin (study 9901)	235/292	0.805	0.755	0.846
ceftobiprole (Noel, 2008)	300/387	0.775	0.731	0.814
Summary		**0.756**	**0.732**	**0.777**



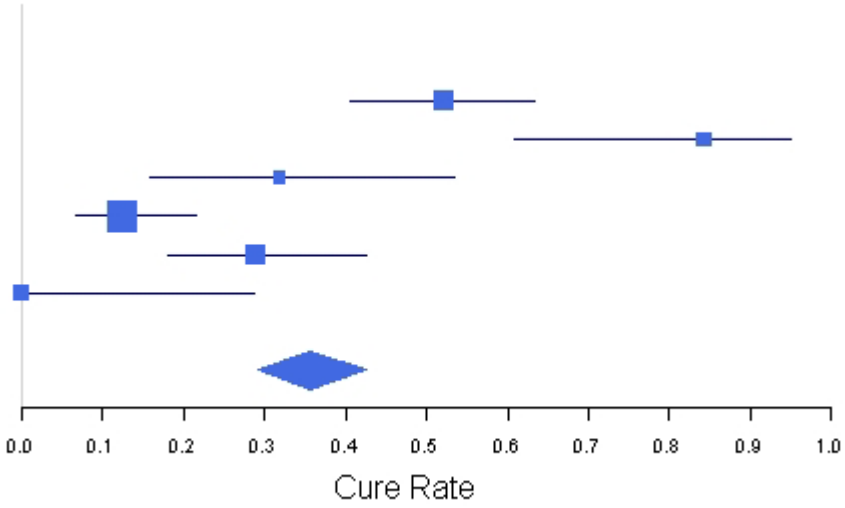
Vancomycin Cure Rates from Telavancin Studies Compare Favorably with the Meta-Analysis

	AT Cure Rate (95% CI)
Study 0017	74.8% (70.7, 78.9)
Study 0018	75.7% (71.8, 79.5)
Pooled	75.3% (72.5, 78.1)
Meta-analysis	75.6% (73.2, 77.7)

Placebo Cure Rates for uSSSI (impetigo) in Randomized Clinical Trials

Results of fixed-effects meta-analysis: Cure Rate 35.7% (95% CI 29.3% - 42.7%)

Study	Cures/N	Cure Rate	Lower Bound	Upper Bound
ALTABAX	37/71	0.521	0.406	0.634
Eells (1986)	16/19	0.842	0.608	0.948
Gould (1984)	7/22	0.318	0.160	0.534
Konig (2002)	10/80	0.125	0.069	0.217
Rojas (1985)	15/52	0.288	0.182	0.425
Ruby (1973)	0/20	0.000	0.000	0.287
Summary		**0.357**	**0.293**	**0.427**



Effect Size Estimate for Vancomycin vs Placebo from Meta-Analysis

- **Estimated placebo cure rate: 35.7%**
- **Estimated vancomycin cure rate: 75.6%**
- **Estimated difference: 39.9%**
  - **95% CI: (32.8%, 47.0%)**
- **Conservative estimate of vancomycin advantage over placebo: 32.8%**
  - **Based on lower bound of 95% CI of the difference**
  - **Pooled variance**

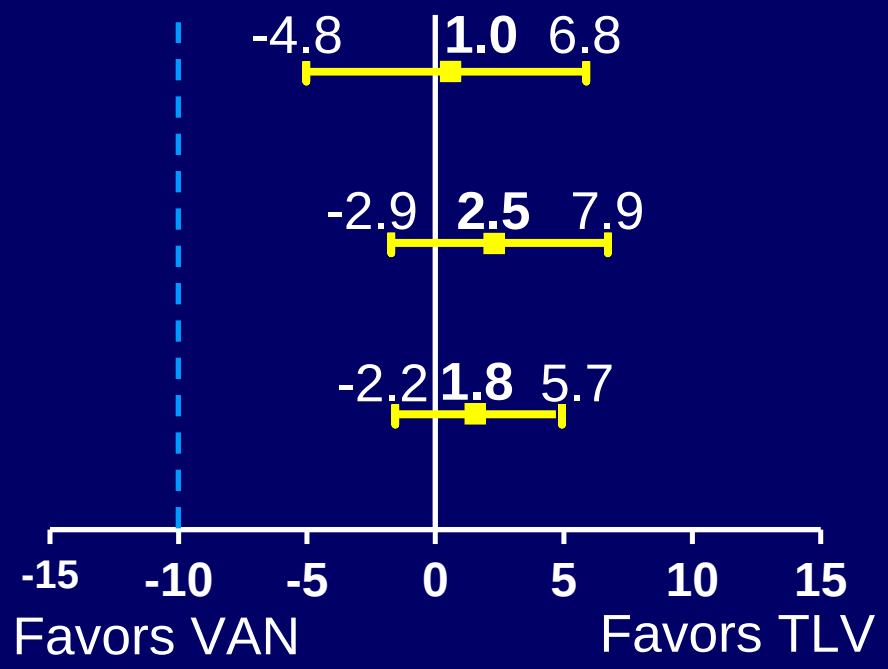
Telavancin Phase 3 Studies: Design

- Two identical protocols
  - Each had active-control with a NI objective
  - Designed to be pooled to analyze for MRSA superiority
- Enriched design: MRSA patients
- Assumed 40% of enrolled patients had MRSA
- Treatment: 7-14 days
  - Vancomycin: active control
  - Telavancin: experimental treatment
- Pre-specified NIM = 10%

Phase 3 Study Design: Power

- **Power for Non-inferiority**
  - **CE hypothesized cure rates: 85%**
  - **N = 700 (350/group)**
  - **Power = 98%**
- **Superiority Hypothesis**
  - **Power for pooled MRSA subgroup: 80%**
  - **8% treatment difference assumed**
  - **Assumes 264 CE MRSA/arm**

Difference in Cure Rates at Test of Cure in AT Population



Difference in Cure Rates
(TLV - VAN, %) with 95% Confidence Interval

	TLV % Cure (n/N) (95% CI)	VAN % Cure (n/N) (95% CI)
Study 0017	75.8 (323/426) (71.8, 79.9)	74.8 (321/429) (70.7, 78.9)
Study 0018	78.2 (358/458) (74.4, 81.9)	75.7 (364/481) (71.8, 79.5)
Study 0017 + 0018	77.0 (681/884) (74.3, 79.8)	75.3 (685/910) (72.5, 78.1)

Conclusion

- **Estimated vancomycin advantage over placebo is at least 32.8%**
- **10% is a conservative prospective NIM for cSSSi**
  - **Preserves >50% of the active treatment effect**
- **Pooled Phase 3 studies provides the most precise estimate of treatment effect and degree of non-inferiority**

Complicated Skin and Skin Structure Infection Trials

Placebo Controls and Non-inferiority Margins

Ralph Corey, MD

Professor of Medicine

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Staphylococci

"…… which, when limited in its extent and activity, causes acute suppurative inflammation (phlegmon), produces, when more extensive and intense in its action on the human system, the most virulent forms of septicaeia and pyaemia..."

Sir Alexander Ogston, 1882

Sulfanilamide – Dawning of the Antibiotic Era

Gerhard Domagk
Nobel Laureat

- 1934: Domagk's daughter severely ill with strep – given sulfa resulting in rapid recovery
- 1936: President Roosevelt's son, FDR Jr., thought to be dying – given sulfanilamide resulting in rapid recovery

Selected "Trials" 1922-1960

Author	Date	Disease	Therapy	Outcome
Lusk	1922	Erysipelas	Nat Hx	Death 6-9%
Ude	1930	Erysipelas	UVL, etc	Death 6-24%
Keefer	1937	GASB	CS	Skin Origin – 80% died
Snodgrass	1937	Erysipelas	Sulfa – UVL	Sulfa effective
Skinner	1941	SAB	CS Sul/PC	Skin Origin – 82% died
Keefer	1943	Various	CS Pen	2/3 survived
Florey	1944	SA hands	Alt pts	Pen effective
Kirby	1960	SAB	CS Vanc	61% cured

CS=Case series GASB=Group A Strep Bacteremia SAB=*S. aureus* Bacteremia
Nat Hx=natural history UVL=Ultraviolet light PC=Placebo

Sequelae of *S. pyogenes* cSSSI Pre-Antibiotics

- **Erysipelas**
  - **Frequent local damage**
  - **Death – 6-9%**
- **Blood Stream Infections (BSI) (N=246)**
  - **Skin Source (61 pts)**
    - **Mortality – 80%**

Keefer et al. Arch Int Med 60, 1084-97. 1937
Keefer et al. JAMA 122, 1217, 1943.
Lusk, W. Treatment of Erysipelas with Chinosol. Ann Surgery 1922.

Sequelae of *S. aureus* cSSSI Pre-Antibiotics

- **Abscess/cellulitis**
- **Fasciitis/myositis**
- **BSI (122 pts)**
  - **Skin source (60+ pts)**
    - **Mortality – 82%**

Skinner and Keefer.Arch Int Med. 1941

Problems: Data from the Pre-Antibiotic Era

- **No placebo controlled trials of cSSSI**
- **Patients have changed**
  - **Crowding, hygiene, number of cutaneous injuries**
  - **More invasive medical procedures**
  - **Elderly, diabetic, immunocompromised patients**
- **The bacteria have changed**
  - ***S. pyogenes***
    - **New toxins but stable resistance profile**
  - ***S. aureus***
    - **More virulent and resistant**

Group A Strep cSSSI in the 21st Century

- **Effective antibiotics and little resistance**
- **Rare Complications**
  - **Necrotizing fasciitis/myositis**
    - **300 U.S. fatalities/yr**
  - **Blood stream infection**
    - **0.3% of treated cSSSI patients**
  - **Endocarditis**
    - **0.3% due to Group A strep**

Infection Control and Hospital Epidemiology. Feb 2008
MMWR 1994 ICE database 10/08

S. aureus cSSSI in the 21st Century

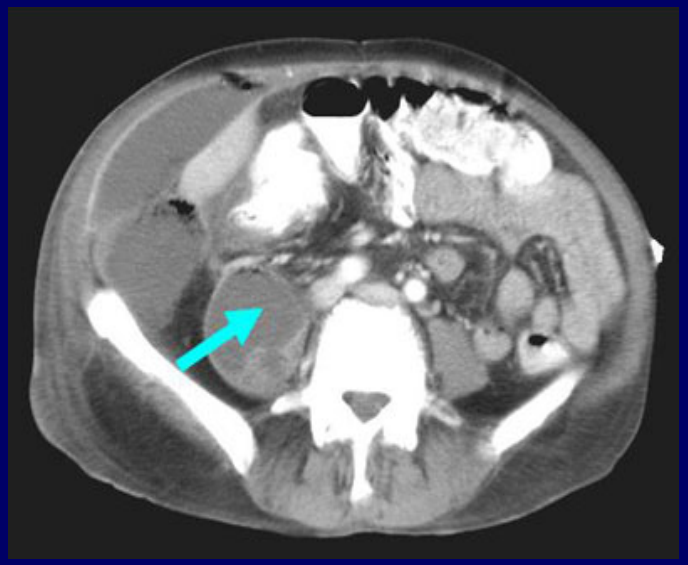
- Remains a daily, deadly adversary
  - Most common cause of cSSSI, BSI
- Local Complications
  - Large abscesses
  - Fasciitis
    - Major local morbidity - 100%

Cheng, N et al JBJSA 2006, 88, 1107

Miller, L et al. NEJM 356, 1445, 2006. Ruhe J, et al Clin Infect Dis. 2007 Mar 15;44(6):777-84.

S. aureus: Systemic Complications of cSSSI in the 21st Century

- **Blood stream infections**
  - **2-5%**
  - **Complication rate 34%**



Stryjewski, M. CID 46, 643, 2008.
Fowler, V et al. Arch Int Med 2003.

Clinical Dilemma

Not able to accurately differentiate between patients who, if not treated with an appropriate antibiotic, will:

- Survive without sequelae
- Develop local invasion, systemic complications, or die

Clinical Solution

Treat the majority of patients suffering from cSSSI with appropriate antibiotics

Conclusion

- Antibiotics are essential and provide a large benefit for the treatment of cSSSI due to *S. aureus* and *S. pyogenes*

Our Patients Need Options

- Are non-inferiority trials acceptable in patients with cSSSI?
  - Absolutely.
- Is a 10% margin acceptable?
  - Yes, …

Non-inferiority Margins

	Cure Rates	Effect Size	NIM
IDSA			
Cellulitis/erysipelas	66% vs 98%	28%	14%
Wounds/ulcers	36% vs 83%	42%	21%
Major abscesses	76% vs 96%	14%	7%
FDA			
Erysipelas/impetigo		18%	10%
Theravance			
Combined		32%	10+%

Our Goal

Provide our patients with the safest and most effective treatment possible