Guideline-Based Approach to the Management of CABP and ABSSSI

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FDA Guidance for Industry: ABSSSI

Includes

- Cellulitis
- Erysipelas
- Major cutaneous abscess
- Burn infections
- Specified to at least 75 cm^2 of redness, edema, or induration with lymph node enlargement or systemic symptoms (such as fever >100.4°F)
- Efficacy assessment at 3 days

Excludes

- Bite wounds
- Bone and joint infections
- Necrotizing fasciitis
- Diabetic foot infections
- Decubitus ulcers
- Catheter site infections
- Myonecrosis
- Ecthyma gangrenosum

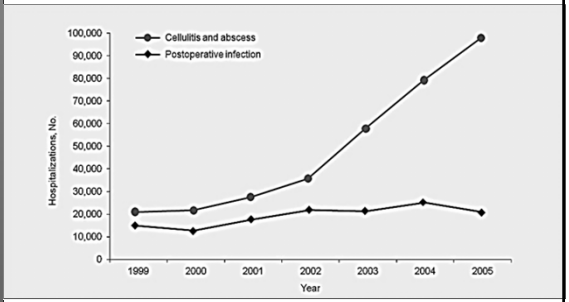
Rajan S. *Cleve Clin J Med*. 2012;79(1):57-66.
U.S. Department of Health and Human Services. Guidance for industry. Acute bacterial skin and skin structure infections: developing drugs for treatment. (URL in ref list).

Impact of ABSSSI in U.S.

- Cellulitis and abscesses
  - Responsible for 600,000 hospitalizations annually
  - 9 million office visits
  - Hospital admissions due to ABSSSI increased by 29% from 2000 to 2004
- Study of purulent soft tissue infections in emergency departments across the US found that 76% of cases were due to S. aureus, and 59% by CA-MRSA
- Considered an epidemic in the US over the last decade
- For hospitalized patients: mean length of stay: 6.1 ± 6.0 days and mean costs: $6830 ± $7100

Gunderson CG. *Am J Med*. 2011; 124:1113-22; Corey GR et al. *Clin Infect Dis*. 2011; 52(Suppl 7):S469-76; Edelsberg J et al. *Emerg Infect Dis*. 2009; 15:1516-8 ; *N Engl J Med;* 2006;355:666-74; *Am J Infect Control*. 2010;38(1):44-49.

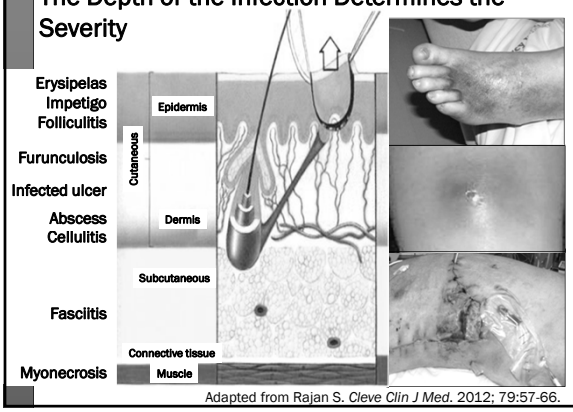
Hospitalizations Due to MRSA-associated Complicated Skin and Skin Structure Infections are Increasing



Adapted from Klein E et al. *Emerg Infect Dis*. 2007;13(12):1840-46.

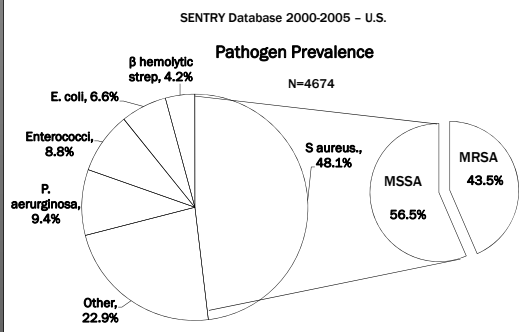
See enlargement p. 38

The Depth of the Infection Determines the Severity



Adapted from Rajan S. *Cleve Clin J Med*. 2012; 79:57-66.

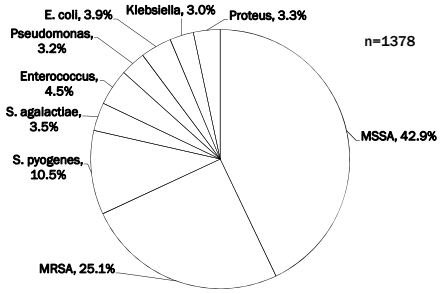
Most Common Pathogens in cSSSIs



Adapted from Sader HS et al. *Int J Antimicrob Agents*. 2007; 30:514-20.

Canvas Pathogen Prevalence

Integrated Analysis of CANVAS 1&2 Ceftaroline Skin Study ABSSSI



Adapted from Corey GR et al. *Clin Infect Dis*. 2010; 51:641-50.

General Treatment Principles for ABSSSI

- Decision for inpatient vs outpatient treatment
- Incision and drainage mainstay of treatment for abscesses
- Purulent vs Nonpurulent
- Appropriate antibiotic therapy
  - Likely pathogens
  - Local resistance patterns
  - Clinical efficacy and safety
  - Drug interaction potential
  - PK/PD
  - Cost
  - Patient risk factors, drug allergies

Tognetti L et al. *Eur Acad Dermatol Venereol*. 2012;26(8):931-941; Eckmann C et al. *Eur J Med Res*. 2010;15(12):554-63; Liu C et al. *Clin Infect Dis*. 2011; 52:e18-55.

Treatment Failures

- Up to 22.8% failure rate with initial antibiotic
  - 5.4 days additional LOS
  - $5,285 additional inpatient charges
- Treatment failure associated with a 3-fold increase in mortality
- Independent predictors of clinical failure
  - Inadequate empiric antibiotic therapy (OR 9.25; $p<0.01$)
  - BMI ≥40 (OR, 4.10; $p=0.02$)
  - Inadequate antibiotic dosing upon discharge (OR, 3.64; $p<.01$)
  - Recent antimicrobial therapy (OR, 2.98; $p=0.03$)

Edelsberg J et al. *Infect Control Hosp Epidemiol*. 2008; 29(2):160-69.
Halilovic J et al. *J Infect*. 2012; 65(2):128-34.

Cellulitis and Erysipelas

- Most common pathogens β-hemolytic strep and *S. aureus*, including MRSA; gram-negative bacilli rare
- Most erysipelas caused by β-hemolytic strep
- Study of nonpurulent cellulitis found β-hemolytic strep in 73%, unidentifiable etiology in 27% of cases
- Overall clinical response rate to beta-lactam therapy in nonpurulent cellulitis of 96%
- CA-MRSA most common in purulent cellulitis

Liu C et al. *Clin Infect Dis*. 2011; 52:e18-55.
Baddour LM. UpToDate. (URL in ref list).

Cellulitis Guideline Recommendations

- Outpatient Management of Nonpurulent Cellulitis
  - Empiric therapy for infection due to β-hemolytic streptococci recommended (A-II)
  - Role of CA-MRSA unknown
  - Empiric coverage for CA-MRSA recommended in patients who do not respond to beta-lactam therapy
- Purulent Cellulitis
  - MRSA coverage should be provided

Liu C et al. *Clin Infect Dis*. 2011; 52:e18-55.

Hospitalized Patient With ABSSSI

- Deeper soft-tissue infections, surgical/traumatic wound infection, major abscesses, cellulitis, and infected ulcers and burns
- Empiric therapy for MRSA should be considered pending culture results
  - Vancomycin - Daptomycin - Tigecycline
  - Linezolid - Clindamycin - Ceftaroline
- B-lactam may be considered in hospitalized patients with nonpurulent cellulitis with modification to MRSA-active therapy if there is no clinical response

Liu C et al. *Clin Infect Dis*. 2011; 52:e18-55.

Antimicrobial Therapy for ABSSSI

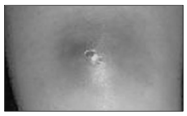
Diagnosis	Treatment	Coverage	Comment
Erysipelas	B-lactam	Strep pyogenes	
Abscess, furuncle, carbuncle	Incision and drainage	None	
Outpatient Purulent cellulitis +/- abscess	Clindamycin TMP/SMZ Doxycycline Minocycline Linezolid	B-hem strep and MRSA MRSA MRSA MRSA B-hem strep and MRSA	• CA-MRSA most common • Swelling may obscure purulence determination • Static except TMP/SMZ
Outpatient Nonpurulent cellulitis	B-lactam Clindamycin Linezolid B-lactam + TMP/SMZ or Doxycycline or Minocycline	B-hem strep B-hem strep and MRSA B-hem strep and MRSA B-hem strep and MRSA	• Consider B-hem strep and MSSA • Role of CA-MRSA unknown
Complicated SSSI or hospitalized cellulitis	Vancomycin Linezolid Daptomycin Clindamycin Ceftaroline	B-hem strep and MRSA B-hem strep and MRSA B-hem strep and MRSA B-hem strep and MRSA B-hem strep and MRSA	

Rajan S. *Cleve Clin J Med*. 2012; 79:57-66; Gunderson CG. *Am J Med*. 2011; 124:1113-22; Tognetti L et al. *J Eur Acad Dermatol Venereol*. 2012; 26:931-41.

See enlargement p. 38

Patient Case

- 22-year-old female presents with tender lesion on posterior LLE accompanied by purulence and surrounding erythema



- Suffered a mosquito bite and has been scratching
- Vital signs
  - Temp = 101.0º BP = 115/75
  - WBC = 12.0 HR = 85

What evidence-based management should this patient receive?

Audience Response: Patient Case

How should this patient be managed?

a. Mupirocin ointment
b. Excision and drainage alone
c. Excision, drainage, and amoxicillin/clavulanate
d. Excision, drainage, and doxycycline

The Pharmacist's Role in Managing ABSSSI

- Maintaining knowledge of local pathogen prevalence and resistance patterns
- Reviewing patient risk factors for MDRO, comorbidities, and previous antibiotic exposure
- Ensuring appropriate antibiotic dosing and evaluating efficacy and safety
- Providing evidence-based recommendations regarding effective therapy for all severities of SSSIs
- Determining the most cost-effective drug therapy and how to incorporate newer antibiotics

Love BL. *US Pharm*. 2007; 32(4):HS5-HS12.

Evidenced-based Management of CABP

CABP Defined

- Acute pulmonary infections
  - Fever or hypothermia
  - Chills or rigors
  - Cough
  - Chest pain
  - Dyspnea or tachypnea
  - New lobar or multilobar infiltrate on a chest radiograph
  - Hypoxemia with a PO_2<60mm Hg
  - Leukocytosis, leukopenia, or bandemia
- Efficacy assessment day 3
- Excludes
  - Atypical pneumonia
  - Viral pneumonia
  - Aspiration pneumonia
  - HAP and VAP
  - Prior receipt of antibacterials
  - Bronchial obstruction or a history of post-obstructive pneumonia NOT COPD
  - Patients with primary or metastatic lung cancer
  - Cystic fibrosis, *Pneumocystis jiroveci* , active tuberculosis

HAP = hospital acquired pneumonia; VAP = ventilator associated pneumonia

U.S. Department of Health and Human Services. Guidance for industry. Community-acquired bacterial pneumonia: developing drugs for treatment. (URL in ref list).

Burden of Disease: CABP

- Leading cause of death due to infection
  - Eighth leading cause of death overall
  - Accounts for more than 55,000 deaths annually
- 5-6 million cases annually resulting in 1.2 million hospitalizations in the US in 2006
  - Annual number of hospitalizations due to pneumonia estimated to rise to 2.6 million by 2040
- Mortality rate <5% in outpatients to >30% in intubated ICU patients
- Annual cost >$17 billion in US

Nair GB et al. *Med Clin North Am*. 2011; 95(6):1143-61; File TM Jr et al. *Postgrad Med*. 2010;122(2):130-41; Wroe PC et al. *J Infect Dis*. 2012; 205(10):1589-92.

Treatment Outcomes in CABP

- Data from early antibiotic era suggest antibiotic effect on acute symptoms <24hr with appropriate clinical response <3-4 days
- 10-25% of patients do not have an appropriate clinical response (10% go on to have life-threatening pneumonia)
- Mortality rates unchanged since 1950s
- Significant 30-day readmission rates
  - 20.1% all cause
  - 5.8% for recurrent pneumonia

U.S. Department of Health and Human Services. Guidance for industry. Community-acquired bacterial pneumonia: developing drugs for treatment. (URL in ref list); Arancibia et al. *Am J Respir Crit Care Med* 2000; 162:154-60; Jencks SF, et al. *N Engl J Med*. 2009; 360:1418-28.

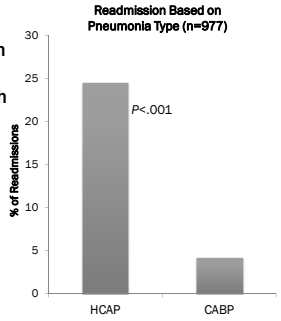
Risk Factors for 30-day Hospital Readmission

- Pneumonia Related
  - Treatment Failure (HR=2.8)
  - Number of instability factors at discharge (HR=2.9)
  - Positive blood cultures (HR=2.8)
- Pneumonia Unrelated
  - Age >65 (HR=7.1)
  - Decompensation of comorbidities (HR=4.7)
  - Severity index (HR=1.9)

Capelastegui A et al. *Chest*. 2009; 136(4):1079-85.

Readmissions: HCAP vs CAP Patients

- HCAP patients 7x more likely to be readmitted
- CHF and COPD most common readmission diagnoses
- Comorbidities associated with readmission risk
- HCAP readmission risk
  - Long-term care (OR=2.2)
  - Immunosuppression (OR=1.9)
  - Prior antibiotics (OR=1.7)
  - Prior hospitalization (OR=1.7)



Shorr AF et al. *Clin Infect Dis*. 2013; 57(3):362–7.

CMS CABP Performance Measures

- Blood cultures 24 hours prior to or 24 hours after arrival for ICU patients (prior to antibiotics)
- Guideline concordant antibiotic therapy
- 30-day risk-standardized readmission measures
  - Includes all types of pneumonia (HAP, VAP, HCAP, CABP)
- Mortality
- Reduced Medicare payments for "higher-than-expected" readmission rates

Centers for Medicare & Medicaid Services. The Joint Commission. Specifications manual for national hospital inpatient quality measures. (URL in ref list).

Treatment Approach in CABP

- Chest x-ray
- Likely pathogens
- Appropriate cultures
- Urinary antigens, PCR for pathogen-directed therapy, biomarkers (e.g. procalcitonin, CRP)
- Severity scoring
  - Most likely pathogens
  - Determination of site of care
- Appropriate management of comorbid diseases
- Assess instability factors
- Identify factors associated with poor prognosis/severe illness/readmission
  - RR >30 breaths/min
  - DBP <60 mm Hg
  - SBP <90 mm Hg
  - Heart rate >125 bpm
  - Temp <95°F or >104°F
  - Chest x-ray
    - Multilobar infiltrates
    - Rapid progression of infiltrates
    - Pleural effusion
    - Necrotizing pneumonia

Nair GB et al. *Med Clin North Am*. 2011; 95(6):1143-61.

CAP Severity Assessment: CURB-65

- British Thoracic Society Scoring Tool
- Score: 0–5, with 1 point for each of the following
  - Confusion
  - BUN >19.6 mg/dL
  - RR ≥30 breaths/min
  - SBP <90 mm Hg or DBP ≤60 mm Hg
  - Age ≥65 yr
- 2 points - consider hospital admission
- ≥3 points - consider ICU admission

CURB-65 Score	Mortality	Disposition
0	Low (0.6%)	Outpatient
1	Low (2.7%)	Outpatient
2	Moderate (6.8%)	Out/Inpatient
3	Severe (14.0%)	Inpatient
4	High (27.8%)	Inpatient/ICU
5	High (27.8%)	Inpatient/ICU

Lim WS. *Thorax*. 2007; 62(4):287-88; Mandell L et al. *Clin Infect Dis.* 2007; 44(suppl 2):S27-S72; Ebell MH. *Fam Pract Manag.* 2006; 13(4):41-44.

Common Causative CABP Pathogens For Inpatients

Hospitalized (non-ICU)[a]	Severe (ICU)[a]
S. pneumoniae	S. pneumoniae
M. pneumoniae	Legionella spp.
C. pneumoniae	H. influenzae
H. influenzae	Gram-negative bacilli
Legionella spp.	S. aureus (MSSA, MRSA)
Respiratory viruses[b]	

[a]Excluding *Pneumocystis* spp.
[b]Influenza A and B, adenovirus, respiratory syncytial virus, parainfluenza

One study in MICU patients (n=198) demonstrated 35% bacterial infection and 36% viral infection

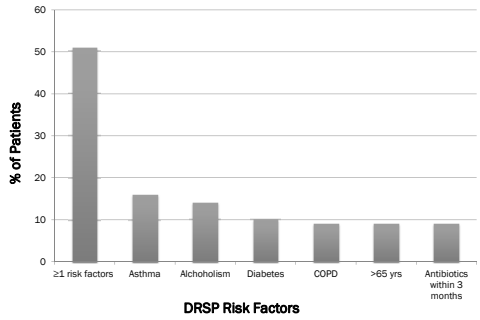
Adapted from File TM. *Lancet*. 2003; 362:1991-2001.
Choi SH et al. *Am J Respir Crit Care Med*. 2012; 186:325-32.

Drug-Resistant *Streptococcus pneumoniae* (DRSP)

- *S pneumoniae* is the most common cause of CAP
- Risk factors
  - Age <2yr or >65yr
  - B-lactam therapy within 90 days
  - Alcoholism
  - Medical comorbidities
  - Immunosuppressive illness or therapy
  - Exposure to a child in daycare
- Multidrug resistant (MDR) *S pneumoniae*—strains that are resistant to at least 3 drugs—are increasingly common
- Controversial whether drug resistant *strep pneumo* is implicated in treatment failures or worse outcomes

Roson B et al. *Clin Infect Dis.* 2001; 33:158-65; Mandell LA et al. *Clin Infect Dis.* 2007; 44 (suppl 2):S27-72; File TM Jr. *Clin Microbiol Infect*. 2006; 12(suppl 3):31-41. Liapikou A et al. *Expert Opin Pharmacother*. 2013; 14:1319-32.

Risk Factors for DRSP



Jenkins TC et al. *Acad Emerg Med*. 2012; 19:703-6.

See enlargement p. 39

CA-MRSA in CABP

- 627 adults hospitalized with CAP
- Respiratory or blood cultures taken from 595
- Pathogen identified in 17% of patients
- 2.4% had CA-MRSA
- CA-MRSA pneumonia associated with high mortality
- Mortality estimates range from 56%–63%
- Treatment options: Linezolid, Vancomycin, Ceftaroline, Tigecycline?
- Cavitary or necrotic pneumonia
- Increasing pleural effusion
- Gross hemoptysis
- Neutropenia
- Concurrent infection
- Erythematous skin rash
- Previously healthy
- Summer season
- Pneumococcal vaccination
- GPCC on gram stain

Wunderink RG. *Infect Dis Clin North Am*. 2013; 27:177-88; Moran GJ et al. *Clin Infect Dis*. 2012; 54:1126-33; Kallen AJ et al. *Ann Emerg Med*. 2009; 53:358-65; Karampela I et al. *Minerva Anestesiol*. 2012; 78:930-40

CABP with Pseudomonal Risk

- **Recent CMS category for CABP**
- **Risk factors include:**
  - **Bronchiectasis**
  - **Advanced COPD with concomitant corticosteroids**
  - **Multiple antibiotic use**
- **Antipseudomonal/antipneumococcal β-lactam + antipseudomonal fluoroquinolone or aminoglycoside**

Centers for Medicare & Medicaid Services. The Joint Commission. Specifications manual for national hospital inpatient quality measures. (URL in ref list).
Mandell L et al. *Clin Infect Dis*. 2007; 44(Suppl 2):S27-S72

Inpatient Treatment

- Cochrane review of 28 trials (n=5939) no benefit of atypical coverage in clinical efficacy or mortality in non-severe hospitalized CAP patients
- Combination therapy lowers 30-day mortality in moderate-severe but not in low severity disease
- ICU patients with CAP and shock had lower mortality with combination therapy (OR=1.69)
- Macrolide therapy may have immunomodulatory effect (modulating host inflammatory response) in addition to antimicrobial effect
- Comparative efficacy of B-lactam monotherapy, B-lactam-macrolide, or quinolone monotherapy unknown

Irfan M et al. *Curr Opin Pulm Med*. 2013; 19:198-208.
Sibila O et al. *Infect Dis Clin North Am*. 2013; 27:133-47.

Empiric Antibiotic Treatment

Non-ICU
β-lactam + Macrolide
Antipneumococcal Quinolone
β-lactam + Doxycycline
Tigecycline

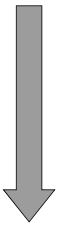
Non-ICU with Pseudomonal Risk
Antipseudomonal β-lactam + Antipseudomonal Quinolone
Antipseudomonal β-lactam + Aminoglycoside + Quinolone
Antipseudomonal β-lactam + Aminoglycoside + Macrolide

ICU
β-lactam + Macrolide
β-lactam + Quinolone
β-lactam + Aminoglycoside + Macrolide
β-lactam + Aminoglycoside + Quinolone

CMS recommendations from a consensus of CDC, IDSA, ATS, CIDS/CTS; Centers for Medicare & Medicaid Services. The Joint Commission. Specifications manual for national hospital inpatient quality measures. (URL in ref list).

Adherence to Guidelines and Appropriate Therapy

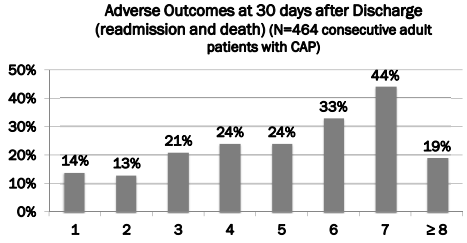
- Mortality
- Treatment Failures
- Time to clinical stability
- Length of stay
- Readmissions



- Hospital and infection related mortality
- Days of antimicrobial therapy
- Antimicrobial resistance
- Cost of hospitalization

Ferrer M et al. *Clin Chest Med*. 2011; 32(3):491-505; Kollef MH et al. *Chest*. 1999; 115(2):462-74; Engemann JJ et al. *Clin Infect Dis*. 2003; 36(5):592-98. Lodise TP et al. *Clin Infect Dis*. 2002; 34(7):922-29; Song X et al. *Infect Control Hosp Epidemiol*. 2003; 24(4):251-56. File TM et al. *Clin Infect Dis*. 2011; 53(suppl 1):S15-S22; Toubes E et al. *Clin Infect Dis*. 2003; 36(6):724-30.

Delay in Time to Clinical Stability Associated with Worse Clinical Outcomes



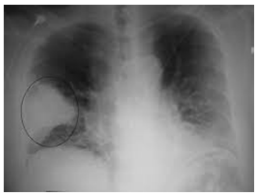
- Some patients with CAP who experienced a delay in reaching clinical stability during hospitalization had a higher risk of adverse outcomes following hospital discharge.
- Average time to clinical stability = 4 days

Aliberti S et al. *Chest*. 2011; 140:482-88; Menendez R et al. *Clin Infect Dis*. 2004; 39(12):1783-90

Patient Case

- 66 year old male with PMHx: COPD, CHF
- Cares for 4 year old son after school
- Finished azithromycin for exacerbation of chronic bronchitis 2 days ago

- Temp: 103° - BP 128/80 mmHg
- HR=110 - Rhonchi: RML, RLL
- O2 Sat: 90% room air
- CURB-65 score = 3; admitted to general medicine



What antibiotics would you choose?

Audience Response: Patient Case

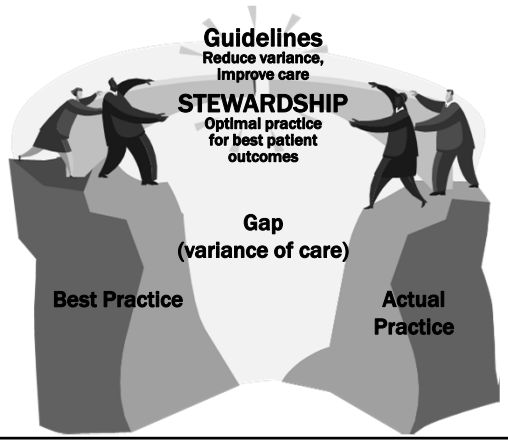
Which antimicrobials for our patient?

a. Ceftriaxone + azithromycin
b. Respiratory quinolone monotherapy
c. Ceftriaxone monotherapy
d. Ceftriaxone + respiratory quinolone

Opportunities For Pharmacists

- Review appropriate antibiotic therapy (guidelines)
- Assess clinical stability and review cultures day 2-3
- Short course therapy for clinically stable
  - No difference in therapy outcomes <7 days vs longer courses
- Assess non-responders
  - Resistant or unusual organism
  - Nosocomial pathogen
  - Empyema, necrotizing pneumonia, metastatic infection
- Antibiotic de-escalation
- Intravenous-to-oral conversions

Dimopoulos G et al. *Drugs*. 2008; 68(13):1841-54; Mandell L et al. *Clin Infect Dis*. 2007; 44(suppl 2):S27-S72; Scalera NM et al. *Curr Infect Dis Rep*. 2013; 15(2):191-95; File TM. *J Manag Care Pharm*. 2009; 15(suppl 2):S5-S11.



New and Emerging Therapies for the Management of CABP and ABSSSI

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Chicago State University College of Pharmacy
Infectious Diseases Pharmacist
Northwestern Memorial Hospital
Chicago, Illinois

Relevant Guidelines – ABSSSI, CABP

- Stevens DL, Bisno AL, Chabers HF, et al. Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections. *Clinical Infectious Diseases*. 2005;41:1373-1406.
- Mandell LA, Wunderink RG, Anzeuto A, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. *Clinical Infectious Diseases*. 2007;44(Suppl 2):S27-S72.
- Liu C, Bayer A, Cosgrove SE, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Infections in Adults and Children. *Clinical Infectious Diseases*. 2011; 52:e18-55.

"Newer" Established Options

Daptomycin

- Cyclic lipopeptide
- Approved 2003
  - cSSSI
- Level A-I recommendation in SSTI, MRSA guidelines
- Bactericidal against Gram positive (GP) organisms
- Available i.v. only
  - Once daily dosing
- Highest direct drug cost
- Excellent safety profile

Linezolid

- Oxazolidinone
- Approved in 2000
  - cSSSI, CABP
- Level A-I recommendation in SSTI, MRSA guidelines
- Active against GP organisms
- Available i.v., PO formulations
- Higher direct drug cost
- Drug interactions with SSRIs
- Myelosuppression
  - >2 weeks therapy

Stevens et al. *Clin Infect Dis*. 2005; 41:1373-1406.
Liu et al. *Clin Infect Dis*. 2011; 52:1-38.

Audience Response: New/Emerging Treatment for ABSSSI?

Which of the following antimicrobials was most recently approved by the FDA for the treatment of ABSSSI?

a. Ceftaroline
b. Dalbavancin
c. Tedizolid
d. Telavancin

Ceftaroline fosamil

- Advanced generation cephalosporin
  - Approved in 2010
- FDA indications include:
  - ABSSSI
    - *S. pyogenes, S. agalactiae, S. aureus* (including MRSA), *H. influenzae, E. coli, Klebsiella* spp.
  - CABP
    - *S. pneumoniae, S. aureus* (MSSA only), *H. influenzae, E. coli, Klebsiella* spp.
- Recently approved in Europe for CAP and cSSTI

Farrell et al. *Diag Microbiol Infect Dis.* 2013; 75(1):86–88.
TEFLARO (ceftaroline fosamil) [prescribing information]. 2013 Jul.

Activity of Ceftaroline against Contemporary Gram-Positive Organisms Collected in the USA in 2008

		Ceftaroline MIC (mg/L)		
Organism and phenotype	N	range	50%	90%
Streptococcus pneumoniae				
Penicillin susceptible (MIC ≤2 mg/L)	770	≤0.008–0.5	≤0.008	0.12
Penicillin non-susceptible (MIC ≥4 mg/L)	121	0.06–0.5	0.25	0.25
Levofloxacin resistant	4	≤0.008–0.12	NA	NA
Multidrug resistant	123	0.06–0.5	0.25	0.25
Ceftriaxone resistant	20	≤0.008–0.5	0.25	0.5
Staphylococcus aureus				
Oxacillin susceptible	1711	≤0.008–0.5	0.25	0.25
Oxacillin resistant	2254	0.12–2	1	1

Adapted from Critchley et al. *J Antimicrob Chemother.* 2011; 66 Suppl 3: iii45–iii51.

See enlargement p. 39

Activity of Ceftaroline against Contemporary Gram-Negative Organisms Collected in the USA in 2008

		Ceftaroline MIC (mg/L)		
Organism and phenotype	N	range	50%	90%
Haemophilus influenzae (β-lactamase positive)	106	≤0.008–0.12	≤0.008	0.03
Haemophilus influenzae (β-lactamase negative)	275	≤0.008–0.06	≤0.008	0.015
Escherichia coli (ceftazidime susceptible)	1036	0.015–>16	0.12	0.5
Klebsiella pneumoniae (ceftazidime susceptible)	517	≤0.008–>16	0.12	0.25

Adapted from Critchley et al. *J Antimicrob Chemother.* 2011; 66 Suppl 3: iii45–iii51.

See enlargement p. 40

Ceftaroline for ABSSSI?

- CANVAS 1 & 2
  - Phase 3, randomized, multinational studies
- Compared ceftaroline 600 mg i.v. every 12 hr vs. vancomycin/aztreonam (1 g each i.v. every 12 hrs) x 5-14 days
- Primary outcome was clinical cure rate for clinically evaluable and modified intent-to-treat populations

Corey et al. *J Antimicrob Chemother.* 2010; 65 Suppl 4: i.v.41–51.
Wilcox et al. *J Antimicrob Chemother.* 2010; 65 Suppl 4: i.v.53–65.

Pooled Results from CANVAS 1 & 2

Clinical Response at Test of Cure, Exploratory Modified Intent-to-treat Population

Study	Cure		Failure		Difference (95% CI)
	Ceftaroline	V/A	Ceftaroline	V/A	
CANVAS 1	177/200 (88.5)	178/209 (85.2)	23/200 (11.5)	31/209 (14.8)	3.3 (−3.3, 10.0)
CANVAS 2	172/200 (86.0)	161/188 (85.6)	28/200 (14.0)	27/188 (14.4)	0.4 (−6.7, 7.5)
Integrated CANVAS	349/400 (87.3)	339/397 (85.4)	51/400 (12.8)	58/397 (14.6)	1.9 (−2.9, 6.7)

Adapted from Friedland et al. *Antimicrob Agents Chemother.* 2012; 56(5):2231-6.

Pooled Results from CANVAS 1 & 2

Clinical Response on Day 3, Exploratory Modified Intent-to-treat Population

Study	No. (%) of patients with status/total				Difference (95% CI)	p Value
	Responder		Nonresponder			
	Ceftaroline	V/A	Ceftaroline	V/A		
CANVAS 1	148/200 (74.0)	135/209 (64.6)	52/200 (26.0)	74/209 (35.4)	9.4 (0.4 - 18.2)	0.04
CANVAS 2	148/200 (74.0)	128/188 (68.1)	52/200 (26.0)	60/188 (31.9)	5.9 (−3.1 -14.9)	0.2
Integrated CANVAS	296/400 (74.0)	263/397 (66.2)	104/400 (26.0)	134/397 (33.8)	7.7 (1.3 - 14.0)	0.018

Adapted from Friedland et al. *Antimicrob Agents Chemother.* 2012; 56(5):2231-6.

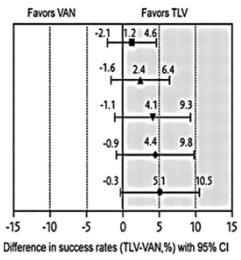
Telavancin for ABSSI?

- Lipoglycopeptide antibiotic
- FDA approved for complicated skin/skin structure infections caused by Gram-positive organisms (GPOs) in 2009
  - Widely active against GPOs including MRSA
  - Administered once daily and requires no therapeutic drug monitoring (TDM)
  - Pregnancy Category C: Teratogenic in animal studies

Vibativ (telavancin) prescribing information. 2013 Jun.

Pooled Results from ATLAS Studies Comparing Telavancin (TLV) with Vancomycin (VAN)

Success rates in clinical, microbiologic, and overall therapeutic response.



	TLV % success (N)	VAN % success (N)
Clinical cure in CE patients	88.3% (745)	87.1% (744)
Overall therapeutic response* in ME patients	88.6% (527)	86.2% (536)
Clinical cure in ME patients with MRSA infection	90.6% (278)	86.4% (301)
Microbiological eradication in ME patients with MRSA infection	89.9% (278)	85.4% (301)
Overall therapeutic response* in ME patients with MRSA infection	89.9% (278)	84.7% (301)

Stryjewski et al. *Clin Infect Dis.* 2008; 46(11):1683-93; by permission of Oxford University Press.

See enlargement p. 40

Pooled Results from ATLAS Studies

Laboratory abnormalities and QT corrected (QTc) interval changes in the all-treated population.

Variable	Proportion of patients (%) Telavancin treatment arm	Vancomycin treatment arm
Hematocrit		
<30% in male patients	5/369 (1)	4/391 (1)
<28% in female patients	12/303 (4)	6/290 (2)
Eosinophilia (eosinophil count >500 cells/mL)	16/837 (2)	15/845 (2)
Leukopenia (leukocyte count <2800 cells/mL)	8/571 (1)	10/568 (2)
Platelet count ≤75 × 10^9 platelets/L	2/694 (<1)	0/707
AST level ≥3 × ULN	13/686 (2)	22/726 (3)
ALT level ≥3 × ULN	16/703 (2)	28/754 (4)
Potassium concentration		
<3 meq/L	16/841 (2)	7/847 (<1)
>5.5 meq/L	21/841 (2)	18/847 (2)
Serum creatinine concentration		
≥1.5 mg/dL and at least 50% greater than baseline	52/822 (6)	19/856 (2)
1.5–1.9 mg/dL	28/822 (3)	15/856 (2)
2.0–2.9 mg/dL	17/822 (2)	2/856 (<1)
≥3 mg/dL	7/822 (<1)	2/856 (<1)
Increase in QTc interval >60 msec	11/929 (1)	5/938 (<1)
QTc interval >500 msec	1/929 (<1)	2/938 (<1)

NOTE. Laboratory abnormalities at end of therapy, compared with baseline values. The denominator for each parameter is the number of patients in the treatment group who had that parameter assessed at baseline (and at least 1 subsequent time) and for whom the baseline assessment findings were normal. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Stryjewski et al. *Clin Infect Dis.* 2008; 46(11):1683-93; by permission of Oxford University Press.

See enlargement p. 41

Telavancin for ABSSSI?

- Results from ATLAS studies earned a level A-I IDSA recommendation for hospitalized patients with cSSTI
- In 2013 the drug received additional FDA approval for hospital- or ventilator-acquired bacterial pneumonia caused by sensitive *S. aureus*
- Updated boxed warning about increased risk of mortality in patients with pre-existing renal dysfunction, risk of nephrotoxicity, and risk of fetal development toxicity

Liu C et al. *Clinical Infectious Diseases*. 2011; 52:e18-55; U.S. Food and Drug Administration. FDA approves Vibativ for hospitalized patients with bacterial pneumonia. (URL in ref list).

Tigecycline for ABSSSI, CABP?

- Tetracycline-class (glycycline) antibiotic
- Approved by FDA in 2005
  - cSSTI
  - CABP
- Broadly active against Gram-positive, anaerobic, most Gram-negative organisms
- FDA re-evaluated trial data in 2010, 2013
- Boxed warning for increased risk of death for labeled and off-label indications

U.S. Food and Drug Administration. Tygacil (tigecycline): drug safety communication—increased risk of death. (URL in ref list).

FDA Warnings - Tigecycline

Pooled results from clinical trials evaluating tigecycline

	Tigecycline deaths/ total patients (%)	Comparator Antibiotics deaths/total patients (%)	Risk Difference (95% CI)
Overall Adjusted (2010)	150/3788 (4.0%)	110/3646 (3.0%)	0.6 (0.1 - 1.2)
Overall Adjusted (2013)	66/2640 (2.5%)	48/2628 (1.8%)	0.6 (0.0 - 1.2)

- The greatest increase in risk of death seen in patients with VAP, an unapproved use
- "Alternatives to tigecycline should be considered in patients with severe infections"

U.S. Food and Drug Administration. FDA drug safety communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new boxed warning. (URL in ref list).

See enlargement p. 41

Audience Response: New/Emerging Treatment for CABP?

Which of the following newer antimicrobials was most recently approved for the treatment of CABP?

a. Ceftaroline
b. Ceftobiprole
c. Cethromycin
d. Nemonoxacin

Ceftaroline for CABP?

- FOCUS 1 & 2
  - Phase 3, randomized, multinational studies
- Compared 5-7 days of ceftaroline 600 mg i.v. every 12 hrs vs. ceftriaxone 1 g i.v. every day
- Hospitalized patients with PORT risk class III & IV
- Primary outcome was non-inferiority in clinical cure rates for CE and modified intent-to-treat efficacy

File TM et al. *Clin Infect Dis.* 2010; 51:1395-1405

Pooled Results from FOCUS 1 & 2

Clinical Cure Rates by Study Population at the Test-of-Cure Visit.

Variable	CE	MITTE	ME	mMITTE
FOCUS 1				
Ceftaroline	194/224 (86.6)	244/291 (83.8)	62/69 (89.9)	66/75 (88.0)
Ceftriaxone	183/234 (78.2)	233/300 (77.7)	54/71 (76.1)	60/80 (75.0)
Difference, % (95% CI)	8.4 (1.4–15.4)	6.2 (−0.2 to 12.6)	13.8 (1.3–26.4)	13.0 (0.7–25.2)
FOCUS 2				
Ceftaroline	193/235 (82.1)	235/289 (81.3)	69/85 (81.2)	72/90 (80.0)
Ceftriaxone	166/215 (77.2)	206/273 (75.5)	57/76 (75.0)	66/88 (75.0)
Difference, % (95% CI)	4.9 (−2.5 to 12.5)	5.9 (−1.0 to 12.7)	6.2 (−6.7 to 19.2)	5.0 (−7.4 to 17.4)
Integrated FOCUS				
Ceftaroline	387/459 (84.3)	479/580 (82.6)	131/154 (85.1)	138/165 (83.6)
Ceftriaxone	349/449 (77.7)	439/573 (76.6)	111/147 (75.5)	126/168 (75.0)
Weighted treatment difference, % (95% CI)	6.7 (1.6–11.8)	6.0 (1.4–10.7)	9.7 (0.7–18.8)	8.7 (−0.0 to 17.4)

NOTE. Data are proportion (%) of patients, unless otherwise indicated. CE, clinically evaluable population; CI, confidence interval; FOCUS, Ceftaroline Community Acquired Pneumonia Trial versus Ceftriaxone in Hospitalized Patients; ME, microbiologically evaluable population; MITTE, modified intent-to-treat efficacy population; mMITTE, microbiological modified intent-to-treat efficacy population.

File TM et al. *Clin Infect Dis.* 2010; 51:1395-1405; by permission of Oxford University Press.

See enlargement p. 42

Pooled Results from FOCUS 1 & 2

Clinical Cure Rates by the Most Common Baseline Pathogens at Test-of-Cure Visit, Integrated Microbiological Modified Intent-to-Treat Efficacy Population.

	Proportion (%) of patients					
	FOCUS 1		FOCUS 2		Integrated FOCUS	
Variable	Ceftaroline group	Ceftriaxone group	Ceftaroline group	Ceftriaxone group	Ceftaroline group	Ceftriaxone group
Gram positive						
Streptococcus pneumoniae	24/27 (88.9)	20/30 (66.7)	35/42 (83.3)	28/40 (70.0)	59/69 (85.5)	48/70 (68.6)
MDRSP[a]	2/2 (100)	0/1 (0)	2/2 (100)	2/8 (25.0)	4/4 (100)	2/9 (22.2)
Staphylococcus aureus	8/10 (80.0)	9/14 (64.3)	10/15 (66.7)	9/16 (56.3)	18/25 (72.0)	18/30 (60.0)
MRSA[b]	NA	0/1 (0)	NA	1/1 (100)	NA	1/2 (50.0)
Gram negative						
Haemophilus influenzae	4/5 (80.0)	7/10 (70.0)	13/15 (86.7)	13/14 (92.9)	17/20 (85.0)	20/24 (83.3)
Haemophilus parainfluenzae	7/8 (87.5)	9/10 (90.0)	9/9 (100)	6/8 (75.0)	16/17 (94.1)	15/18 (83.3)
Klebsiella pneumoniae	7/8 (87.5)	3/5 (60.0)	7/7 (100)	7/8 (87.5)	14/15 (93.3)	10/13 (76.9)
Escherichia coli	8/8 (100)	5/7 (71.4)	2/4 (50.0)	4/6 (66.7)	10/12 (83.3)	9/13 (69.2)

NOTE. FOCUS, Ceftaroline Community Acquired Pneumonia Trial versus Ceftriaxone in Hospitalized Patients; MDRSP, multidrug-resistant *S. pneumoniae*; MRSA, methicillin-resistant *S. aureus*; NA, not applicable.

[a] MDRSP was defined in these studies as strains resistant to >2 antimicrobial classes of drugs, including penicillin, macrolides, tetracycline, fluoroquinolones, chloramphenicol, trimethoprim-sulfamethoxazole, and cephalosporins.

[b] Patients with confirmed or suspected community-acquired pneumonia caused by MRSA at baseline were excluded from the study.

File TM et al. *Clin Infect Dis*. 2010; 51:1395-1405; by permission of Oxford University Press.

See enlargement p. 42

Subgroup Analysis of Patients with *S. pneumoniae*

- Unadjusted and adjusted odds ratio suggesting favorable clinical response to ceftaroline in the subgroup of CABP patients with *S. pneumoniae* in the integrated FOCUS studies
- Composite of clinical cure and microbiological response at test of cure

Comparison	Odds Ratio	95% CI	p value
Unadjusted Odds Ratio	2.7	1.2 - 6.3	0.02
OR adjusted for smoking	2.6	1.1 – 6.2	0.03

Shorr AF et al. *Diagn Microbiol Infect Dis*. 2013; 75:298-303.

Investigational Drugs in Phase 3 Trials

ABSSSI

- Ceftobiprole
- Dalbavancin
- Delafloxacin
- Iclaprim
- Oritavancin
- Omadacycline
- Tedizolid (torezolid)

CABP

- Ceftobiprole
- Cethromycin
- Faropenem
- Nemonoxacin
- Solithromycin

Data from www.clinicaltrials.gov using search terms “Pneumonia, bacterial” and “Skin diseases, bacterial” and limited to “Phase 3”. (URLs in ref list).

Ceftobiprole

- Advanced generation cephalosporin with similar spectrum of activity to ceftaroline and cefepime combined
  - Active against *S. aureus* (MRSA), *Streptococcus* spp., most Gram-negative organisms including *P. aeruginosa!*
- Phase 3 studies completed in 2007 but FDA declined approval due to unverifiable data in some studies
- Approved by the European Union for CABP in 2013
  - Under Phase III study in U.S.

Basilea Pharmaceutica Ltd press release. Basilea's antibiotic ceftobiprole obtains regulatory approval in Europe for pneumonia. (URL in ref list).

Activity of Various Cephalosporins Against Gram-positive Organisms

Cephalosporin (generation)						
	1st	2nd	3rd	3rd	4th	5th
Representative	Cefazolin	Cefamandole	Ceftriaxone	Ceftazidime	Cefepime	Ceftobiprole
Relative bactericidal activity						
Gram-positive cocci						
MSSA	+++	+++	+++	+	+++	+++
MRSA	0	0	NA	0	0	+++
MRCoNS*	0	0	0	0	0	+++
Streptococcus spp.	+++	+++	+++	+++	+++	+++
PRSP**	NA	NA	++	+	++±	+++

*Methicillin-resistant coagulase negative *Staphylococcus*
**Penicillin-resistant *S. Pneumoniae*

Adapted from Deresinski SC. *Diagn Microbiol Infect Dis.* 2008; 61(1):82-5.

See enlargement p. 43

Activity of Various Cephalosporins Against Gram-negative Organisms

Cephalosporin (generation)						
	1st	2nd	3rd	3rd	4th	5th
Representative	Cefazolin	Cefamandole	Ceftriaxone	Ceftazidime	Cefepime	Ceftobiprole
Relative bactericidal activity						
Gram-negative bacilli						
Enterobacter cloacae	0	+	NA	+	++±	++±
Escherichia coli	++	++	+++	+++	+++	+++
Proteus vulgaris	0	+++	NA	+++	+++	+++
Pseudomonas aeruginosa	0	0	0	++	+++	+++
Serratia spp.	0	++	0	+++	+++	+++
Haemophilus influenzae	+	++	+++	+++	+++	+++

Adapted from Deresinski SC. *Diagn Microbiol Infect Dis.* 2008; 61(1):82-5.

See enlargement p. 43

Proportion of patients who experienced clinical cure and microbiological eradication at the test-of-cure visit [*n/N* (%)]

Outcome/population	Ceftobiprole	Ceftriaxone ± Linezolid	95% CI
Clinical cure			
CE patients	200/231 (86.6)	208/238 (87.4)	(−6.9 - 5.3)
ITT patients	240/314 (76.4)	257/324 (79.3)	(−9.3 - 3.6)
Patients receiving i.v. therapy only	77/103 (74.8)	73/101 (72.3)	(−9.6 - 14.6)
Switch to oral therapy	123/128 (96.1)	135/137 (98.5)	(−6.4 - 1.5)
Patients requiring antistaphylococcal therapy	17/21 (81.0)	25/34 (73.5)	(−15.0 - 29.8)
Microbiological eradication			
ME patients	60/68 (88.2)	69/76 (90.8)	(−12.6 - 7.5)
Microbiological ITT	70/87 (80.5)	79/97 (81.4)	(−12.4 - 10.4)

Adapted from Nicholson et al. *Int J Antimicrob Agents*. 2012; 39(3):240-6.

See enlargement p. 44

Nemonoxacin (IND)

- Novel non-fluorinated quinolone antibiotic
- Potent activity against CAP pathogens
  - *S. pneumoniae* including MDR strains, MRSA, Gram negative, and atypical organisms
- Additional mutation required beyond the two that cause resistance in fluorinated quinolones
- 2 different daily doses of nemonaxacin studied vs. levofloxacin for CAP (not CABP)

van Rensburg DJ et al. *Antimicrob Agents Chemother.* 2010; 54:4098-106.

Nemonoxacin vs. Levofloxacin for CAP

Clinical response at Test of Cure or End of Treatment visit

Population	No. of patients (%)			Difference in clinical-cure rates between treatment groups	
	Nemonoxacin		Levofloxacin 500 mg	Nemonoxacin 750 mg-levofloxacin 500 mg	Nemonoxacin 500 mg-levofloxacin 500 mg
	750 mg	500 mg			
Eval-ITT	71 (89.9)	67 (87.0)	72 (91.1)	−10.4 to 7.9	−13.9 to 5.7
Eval-PPc	66 (91.7)	64 (87.7)	65 (90.3)	−8.0 to 10.8	−12.8 to 7.6
ITT	66 (91.7)	64 (87.7)	65 (90.3)	−10.5 to 15.7	−18.6 to 9.1
PPc	66 (83.5)	64 (78.0)	65 (82.3)	−12.1 to 14.6	−18.7 to 9.1

Adapted from van Rensburg et al. *Antimicrob Agents Chemother. 2010 (54); 10:4098-106.*

See enlargement p. 44

Nemonoxacin vs. Levofloxacin for CAP

Baseline pathogen (n)	Bacteriological success/organisms isolated at baseline (%)			MIC range baseline (μg/ml)	
	Nemonoxacin		Levofloxacin 500 mg/day		
	750 mg/day	500 mg/day		Nemonoxacin	Levofloxacin
Typical pathogens					
H. influenzae (17)	5/6 (83.3)	4/4 (100.0)	7/7 (100.0)	≤0.008-0.06	≤0.008-0.03
S. pneumoniae (14)	5/5 (100.0)	3/4 (75.0)	5/5 (100.0)	0.06-0.12	0.5-1.0
S. aureus (4)	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)	0.03-0.06	0.12-0.5
Atypical pathogens					
M. pneumoniae (93)	26/29 (89.7)	25/31 (80.6)	31/33 (93.9)		
C. pneumoniae (23)	8/8 (100.0)	8/8 (100.0)	6/7 (85.7)		
L. pneumophila (8)	3/3 (100.0)	2/2 (100.0)	3/3 (100.0)		

Adapted from van Rensburg et al. *Antimicrob Agents Chemother. 2010 (54); 10:4098-106.*

See enlargement p. 45

Cethromycin

- Ketolide antibiotic class
  - Appears free of hepatoxicity, visual disturbances, myasthenia gravis seen with previous agents in ketolide class
- Oral, once-daily agent with activity against *S. pneumoniae, M. cattarhalis, H. influenzae* and atypical pathogens
- Studied vs. oral clarithromycin in ambulatory patients with mild to moderate CAP
  - Two Phase 3 studies

English ML et al. *Antimicrob. Agents Chemother.* 2012, 56(4):2037-47.

Cethromycin vs. Clarithromycin

Integrated primary efficacy analyses for studies CL05-001 and CL06-001: Clinical cure rates in the ITT and per protocol clinical populations.

	Cethromycin 300 mg QD	Clarithromycin 250 mg BID	Absolute Difference	CI for Clinical Cure Rates	Fisher's Exact test
Intent-to-treat	430/518 (83.0%)	430/507 (84.8%)	-1.8%	(-6.4% - 2.8%)	0.445
Per Protocol	410/442 (92.8%)	407/429 (94.9%)	−2.1%	(−5.4% - 1.2%)	0.208

Adapted from English ML et al. *Antimicrob Agents Chemother.* 2012; 56(4):2037-47.

Tedizolid for ABSSSI

- IND in the oxazolidinone class
- Inhibits protein synthesis by binding to the 23S RNA of the 50S ribosomal subunit
- Potent activity against Gram-positive bacteria including MRSA, VRE, *S. pneumoniae*
- Has i.v. and PO formulations
  - Once daily dosing (compared to BID for linezolid)
- Has been evaluated against linezolid for ABSSSI in 2 PHASE 3 trials

Prokocimer et al. *JAMA*. 2013; 309(6):559-69.

Tedizolid vs. Linezolid for ABSSSI (ESTABLISH-1)

Analysis of intent-to-treat (ITT) and Clinically Evaluable at End-of-treatment (EOT)

	Clinical Success Rate n(%)		Absolute Difference % (95% CI)
	Tedizolid (n=332)	Linezolid (n=335)	
Treatment Response at 48-72 hr Assessment (Intent-to-treat) (≥20% Decrease in lesion area, no fever criteria)	259 (78)	255 (76.1)	1.9 (-4.5 – 8.3)
Decrease in lesion area, no fever criteria	289 (87)	286 (85.4)	1.6 (-3.5 – 7.0)
Sustained treatment response at EOT (Intent-to-treat)	268 (80.7)	271 (80.9)	-0.2 (-6.5 – 5.8)
Clinically Evaluable at EOT (n=273) / (n=286)	239 (87.5)	294 (87.8)	0.4 (-5.8 – 6.0)

Adapted from Prokocimer et al. *JAMA*. 2013; 309(6):559-69.

See enlargement p. 45

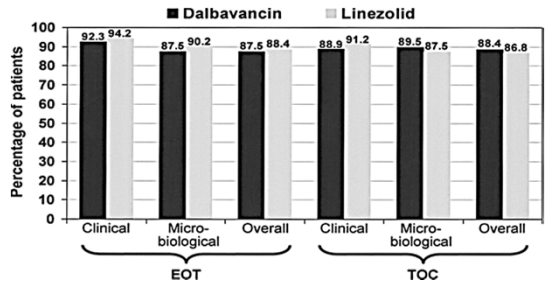
Dalbavancin

- Lipoglycopeptide with similar spectrum of activity to vancomycin
- Extremely long half-life (~8.5 days) allows for once WEEKLY dosing and no TDM
- Phase 3 study of cSSSI requiring i.v. therapy completed in 2005
  - Dalbavancin 1000 mg i.v. on day 1 → 500 mg i.v. on day 8 vs. linezolid 600 mg i.v. or i.v./orally every 12 hr for 14 days

Jauregui et al. *Clin Infect Dis*. 2005; 41;1407-15.

Dalbavancin vs. Linezolid

Summary of response end points in the evaluable populations illustrating clinical, microbiological, and overall (combined clinical/microbiological) success at end-of-therapy (EOT) and test-of-cure (TOC) visits.



Jauregui et al. *Clin Infect Dis*. 2005; 41;1407-15; by permission of Oxford University Press.

See enlargement p. 46

Dalbavancin

- 2007 - FDA requested more information before drug could be approved
- 2008 – drug was withdrawn and two new Phase 3 trials designed and initiated
- Studies currently underway for treatment of ABSSSI
  - DISCOVER-1 and DISCOVER-2
  - Dalbavancin vs. Vancomycin → PO linezolid

Clinicaltrials.gov database. Efficacy and safety of dalbavancin for the treatment of acute bacterial skin and skin structure infections. (URLs in ref list).

Audience Response: Medication with Safety Warnings

For which of the following medications has the FDA issued a warning discouraging use in the case of severe infections due to an increased risk of death?

a. Ceftaroline
b. Daptomycin
c. Telavancin
d. Tigecycline

Drug*	Indication	Pros	Cons
Ceftaroline	ABSSSI, CABP	Covers indications/all pathogens as sole therapy	i.v. only, twice-daily dosing, $$
Daptomycin	ABSSSI	Broad Gram (+), No Gram (-), Once-daily dosing	i.v. only, $$$
Linezolid	ABSSSI, CABP	Available i.v./oral. Broad Gram (+), no Gram (-) for pneumonia	$$$, some DDIs with MAOI, risk toxicity >2 weeks
Telavancin	ABSSSI	Broad, Once-daily, no TDM required	FDA boxed warning renal toxicity, teratogen, i.v. only, $$
Tigecycline	ABSSSI, CABP	Covers all pathogens as sole therapy	FDA boxed warning ↑ mortality, i.v. only, $$$
Ceftobiprole	ABSSSI, CABP	Similar to ceftaroline plus Pseudomonas?	Similar to ceftaroline ???
Cethromycin	CAP	Oral. Once-daily	Data limited to OP Tx
Dalbavancin	ABSSSI	Broad Gram (+), weekly dosing, no TDM required	i.v. only, No Gram (-)
Nemonoxacin	CAP	Broad coverage, oral, evades FQ Resistance?	Broad→collateral damage like FQs???

*Black text: FDA approved; Red text: Phase 3 investigational drug

See enlargement p. 46

Appropriate Management of CABP and ABSSSI: Balancing CMS Criteria, Clinical Guidelines, and Antimicrobial Stewardship

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Community-Acquired Bacterial Pneumonia

Background

- Pneumonia is the 2nd most common hospital discharge diagnosis for Medicare
  - Third most expensive condition
- CMS baseline data 2009-12 reported
- All-cause readmission rate: 10-24%
  - 9.5% may be preventable
  - $1 billion saved

Epstein AM et al. *N Engl J Med*. 2011; 365:2287-95; Andrews RM et al. Agency for Healthcare Research and Quality. 2007 Dec; Baker DW et al. *Arch Intern Med*. 2004; 164:538-44; Vecchiarino P et al. Heart Lung. 2004; 33:301-7; Medicare Payment Advisory Commission. Report to Congress: promoting greater efficiency in Medicare. 2007.

Pneumonia Mortality & Readmission

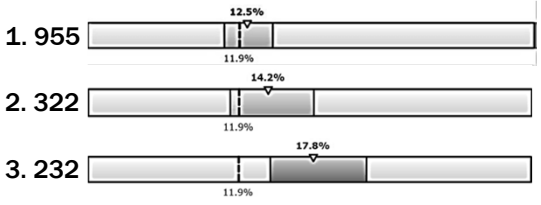
- 30-day all-cause from CMS database
- Risk-adjusted based on severity
- Compared with national average
- Reimbursement tied to your own "hospital-specific report" (HSR)
- Disproportionate share, safety net hospitals tend to be worse

Centers for Medicare & Medicaid Services. Hospital Compare. (URL in ref list).

Pneumonia 30-day Mortality

← Lower numbers are better ←

- Number of sampled patients



11.9% mortality rate nationally

Centers for Medicare & Medicaid Services. Hospital Compare. (URL in ref list).

Pneumonia 30-day Mortality

	Better	No different	Worse
Out of 4817 hospitals in the United States →	203 Better than U.S. National Rate	4014 No different than National Rate	223 Worse than U.S. National Rate
	377 hospitals in the United States did not have enough cases to reliably tell how well they are performing		
Out of 184 hospitals in the state of Illinois →	16 hospitals were Better than U.S. National Rate	157 hospitals were No different than U.S. National Rate	7 hospitals were Worse than U.S. National Rate
	4 hospitals in Illinois did not have enough cases to reliably tell how well they are performing		

Centers for Medicare & Medicaid Services. Hospital Compare. (URL in ref list).

Pneumonia 30-day Mortality

- 12% for decades
- Half die in the hospital
  - Bacteremia, Systolic BP <90mmHg
  - Respiration rate > 30/min, BUN >11 mmol/L
  - Arterial pH < 7.35, mechanical ventilation
  - Arterial Po2<60mmHg or Spo2<90%
- No significant risk factors identified for mortality after discharge

Metersky ML. *Chest*. 2012; 142:476-81.

Pneumonia Quality Measures

1. Oxygen Assessment (retired 2009)
2. Pneumococcal Vaccine (moved to IMM)
3. **Blood cultures (TJC only in 2013)**
4. Smoking cessation (moved to TOB 2012)
5. Antibiotic timing (retired)
6. **Initial Antibiotic Selection**
7. Influenza vaccine (moved to IMM 2012)
   - IMM = Immunizations, TOB = Tobacco

Centers for Medicare & Medicaid Services. The Joint Commission. Pneumonia Measures. (URL in ref list).

Blood Cultures

- PN-3 no longer required for CMS, but will become a Voluntary Measure
  - 3a remains for The Joint Commission only
    - Perform within 24 hours before or after ICU admission
  - 3b is being retired by TJC
    - Prior to antibiotic administration in the ED
      - Pre-treatment ↓ positive cultures by 50%

Centers for Medicare & Medicaid Services. The Joint Commission. Specifications manual for national hospital inpatient quality measures. (URL in ref list).

Blood Cultures

- Associated with decreased mortality
- Do they change therapy?
  - 5% have contaminants only
- 7% grow pathogens
  - *S. pneumoniae* 36-37%
  - *S. aureus* 14-17%
  - *E. coli* 12-14%
- 1 bottle for patients admitted to the ward with risk factors and 2 for the ICU proposed

Meehan TP. *JAMA* .1997; 278: 2080-4.
Metersky ML et al. *Am J Respir Crit Care Med.* 2004; 169:342-7.

Blood Cultures

<u>Positive cultures double with each risk factor</u>

- Admitted to the ICU
- Leukopenia or asplenia
- Chronic severe liver disease
- Active alcohol abuse
- Positive pneumococcal antigen test
- Cavitary infiltrates
- Pleural effusion

Metersky ML et al. *Am J Respir Crit Care Med*. 2004; 169:342-7.

Testing for Infection

- Lower respiratory tract cultures
- Sputum with WBCs
  - 50-60% yield when combined with blood and urinary antigen tests (for severe/ICU cases)
- Oral and pharyngeal samples
  - Adequate for viruses
- PCR panel is attractive
  - 74-80% yield

Johansson N et al. *Clin Infect Dis*. 2010; 50:202-9.
Radigan E et al. Poster presented at ID Week 2012. Abstract 733. (URL in ref list).
Huijskens EG et al. *Influenza Other Respir Viruses*. 2013 Aug 20.

Antibiotic Timing

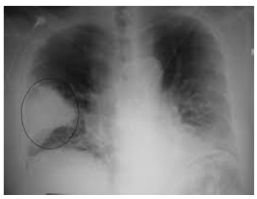
- Initiation of therapy, 8 vs. 4 hours of presentation
  - Within 6 hours or while in the ED
- Led to misdiagnosis of CAP
- Resulted in overutilization of antibiotics
- Measure now retired
- Order sets still a good idea

Kanwar M et al. *Chest*. 2007; 131:1865-9.

Patient Case

- 66 year old male with PMHx: COPD, CHF
- Cares for 4 year old son after school
- Finished azithromycin for exacerbation of chronic bronchitis 2 days ago

- Temp: 103° - BP 128/80 mmHg
- HR=110 - Rhonchi: RML, RLL
- O2 Sat: 90% room air
- CURB-65 score = 3; admitted to general medicine



What antibiotics would you choose?

Empiric Antibiotic Treatment

Non-ICU
β-lactam + Macrolide
Antipneumococcal Quinolone
β-lactam + Doxycycline
Tigecycline

Non-ICU with Pseudomonal Risk
Antipseudomonal β-lactam + Antipseudomonal Quinolone
Antipseudomonal β-lactam + Aminoglycoside + Quinolone
Antipseudomonal β-lactam + Aminoglycoside + Macrolide

ICU
β-lactam + Macrolide
β-lactam + Quinolone
β-lactam + Aminoglycoside + Macrolide
β-lactam + Aminoglycoside + Quinolone

CMS recommendations from a consensus of CDC, IDSA, ATS, CIDS/CTS
Centers for Medicare & Medicaid Services. The Joint Commission. Specifications manual for national hospital inpatient quality measures. (URL in ref list).

Case Continued

- What else would you want to know?
- PMH = COPD, controlled on tiotroprium, fluticasone/salmeterol & albuterol
  - Negative for cancer, HIV, asplenia or any other immunocompromising risk factor
- Sputum: >25 PMN & <10 epithelial cells/HPF
  - Lancet-shaped gram-positive cocci in pairs

S. pneumoniae Susceptibility

- Penicillin (low-dose): 58%
- Erythromycin/azithromycin: 60%
- Cefuroxime: 72% or Tetracycline/ Doxycycline: 75%
- Amoxicillin (+/- clavulanate): 83%
- Ceftriaxone: 89%, Tigecycline 93%
- Levofloxacin, Ceftaroline: 99%
- Vancomycin, Linezolid >99.9%

Pfaller MA et al. *Clin Infect Dis*. 2012; 55(Suppl 3):S187-93.

Antibiotic Selection List

- β -lactam = Ampicillin/Sulbactam, Ceftaroline, Ceftriaxone, Cefotaxime, Ertapenem
- Antipneumococcal/Antipseudomonal β -lactam = Cefepime, Doripenem, Imipenem, Meropenem, Piperacillin/Tazobactam
- Macrolide = Erythromycin, Azithromycin
- Antipneumococcal Quinolone = Levofloxacin, Moxifloxacin
- Antipseudomonal Quinolone = Ciprofloxacin, Levofloxacin
- Aminoglycoside = Gentamicin, Tobramycin, Amikacin

Case Continued

- Appropriate antibiotics decrease the risk of a length of stay > 9 days
  - 50% vs. 70%
- Our patient improved in 3 days on recommended therapy
- Switched from i.v. to PO
  - Oral intake, stable vitals, no sepsis or exacerbated co-morbidities

Wilson KC et al. *Am J Respir Crit Care Med*. 2011; 183:1454-62.

Antimicrobial Stewardship

- 3-step pathway reduced LOS, 3.9 vs. 6 days
  1. Early mobilization, sitting up within 24 hours
  2. i.v. to PO criteria, 2 vs. 4 days
  3. Objective discharge criteria
     - Return to baseline mental status
     - Adequate oxygenation
     - On oral therapy

  = Similar readmissions, but fewer adverse drug reactions, 4.5 vs. 15.9%

Carratala J. *Arch Intern Med*. 2012; 172: 922-8.

Antimicrobial Stewardship

- 1,356 patients reviewed by team
  - 23% had antibiotics stopped
  - 34% switched to oral
  - 21% could be discharged
- 20% of readmissions related to pneumonia
  - 74% due to co-morbidity
    - CAD, OR = 2.7 and COPD, OR = 2.3
  - Lack of education, OR = 2.0
  - Unemployment, OR = 3.7

Dryden M. *J Antimic Chemo*. 2012; 67: 2289-96.
Jasti H. *Clin Infect Dis*. 2008; 46: 550-6.

Audience Response: Discharge Antibiotics

What oral CABP regimen are you most likely to recommend for prescribers to use when de-escalating treatment at your institution?

a. Fluoroquinolone monotherapy
b. Cephalosporin (+/- azithromycin)
c. Azithromycin monotherapy
d. Doxycycline monotherapy
e. Amoxicillin monotherapy

Collateral Damage

- Most antibiotics increase risk of *Clostridium difficile* infection
  - Fluoroquinolones and cephalosporins: high
  - Macrolides and penicillins: low
- Tetracyclines do not
  - Protective effect from doxycycline
- Azithromycin and cardiac risk

Brown KA. *Antimicrob Agents Chemother*. 2013.
Doernberg SB et al. *Clin Infect Dis*. 2012; 55:615-20.
Ray WA et al. *N Engl J Med*. 2012; 366:1881-90.
Svanstrom H et al. *N Engl J Med*. 2013; 368:1704-12.

Audience Response: Case Question

What is the total duration of CABP antibiotics that you would recommend to treat this patient?

a. 5 days
b. 7 days
c. 10 days
d. 14 days

Duration

- 3 days can be effective
- Guidelines recommend 5 days minimum
- Afebrile for 48-72 hours
- Bacteremia does not need to increase duration of recommended therapy
- Education reduces average duration from 10 to 7 days

El Moussaoui R. *BMJ* 2006; 332: 1355.
Ramirez JA et al. *Arch Intern Med*. 2001; 161: 848-50.
Avdic E. *Clin Infect Dis*. 2012; 54: 1581-7.

Audience Response: Case Question

According to the CDC, what vaccine(s) should we recommend (that could potentially reduce the risk of future mortality or readmission)?

66 year old immunized with quadrivalent influenza vaccine in October 2013 & PPSV23 in 2003.

a. PCV13 (Prevnar13®)
b. PPSV23 (Pneumovax®)
c. PCV13, then PPSV23
d. PPSV23, then PCV13
e. PPSV23 and Tdap

Immunizations

- 13-valent pneumococcal conjugate vaccine (PCV13, Prevnar13®) now FDA-approved for >50 yr
  - ACIP recommends giving it to adults of any age who are immunocompromised at this time
- 23-valent pneumococcal polysaccharide vaccine (PPSV23, Pneumovax®) still primarily for >65 yr
  - 4 fewer cases of death per 1,000
  - Will boost the response to PCV13

Centers for Disease Control and Prevention. *Morb Mortal Wkly Rep*. 2012; 61(40):816-9. Bridges CB et al. *MMWR Surveill Summ*. 2013; 62:9-19. Wilson KC et al. *Am J Respir Crit Care Med*. 2011; 183:1454-62.

Acute Bacterial Skin & Skin Structure Infections

Severity Scoring

- CREST Guidelines for Cellulitis
- Standard Early Warning System (SEWS)
  - Temp, RR, SaO_2, BP, HR, responsiveness/pain

Class	Patients	Description	30-day Mortality	Inadequate Therapy
Overall	205	Inpatients	9%	43% (overtreated)
1	45%	No sepsis or co-morbidities	1%	14%
2	32%	Significant co-morbidity, but no sepsis	14%	39%
3	17%	Sepsis, but SEWS<4	17%	39%
4	6%	Sepsis, and SEWS>4	33%	92%

Clinical Resource Efficiency Support Team (CREST). CREST guidelines on the management of cellulitis in adults. *DHSS Northern Ireland*; 2005:1-31. Paterson R et al. *Clin Med*. 2006; 6:281-4. Marwick C et al. *J Antimicrob Chemother*. 2011; 66:387-97.

MRSA and ABSSSI

- 59% MRSA from purulent infections in ED
  - 17% MSSA, 7% strep, 8 other, 9% unknown
- 33.2% of inpatients in large U.S. database
  - Risk factors included:
    - Younger age (30-39 yr) and black race
    - No diabetes mellitus, cancer, or renal dysfunction
    - Cardiac dysrhythmia prior to encounter

Moran GJ et al. *N Engl J Med*. 2006; 355:666-74.
Zilberberg MD et al. *BMC Infect Dis*. 2012; 12:154.

Skin Infection Testing

- Wound cultures
- Blood cultures for severe disease
- Serologies for ASO and anti-DNAase-B
  - Non-purulent infections: 73% beta-hemolytic Streptococcus, 27% unknown
- PCR (Cepheid GeneXpert)
  - Approved for use in soft tissue infections
  - 1 hour to detect *S. aureus* and whether MRSA

Jeng A et al. *Medicine* (Baltimore). 2010; 89:217-26.

Treatment

- Empiric therapy against *Pseudomonas aeruginosa* is usually unnecessary except in high-risk patients
- Diabetic foot infections
  - Exposure to water
  - High local prevalence
    - Warm climate
  - Previously treated

Lipsky BA et al. *Clin Infect Dis*. 2012; 54:e132-73.

Treatment

- Non-purulent cellulitis
  - 96% of patients still respond to beta-lactam
  - Higher failure rate with TMP-SMX
- Consider MRSA
  - Purulent infections ("spider bite")
  - Young patients, especially athletes
  - High local prevalence of colonization
  - Those with prior history or treatment failure
  - Clinically severe infections / systemic toxicity

Jeng A et al. *Medicine* (Baltimore). 2010; 89:217-26.; Elliott DJ et al. *Pediatrics*. 2009; 123:e959-66.; Liu C et al. *Clin Infect Dis*. 2011; 52:e18-55.

Discharge Antibiotics

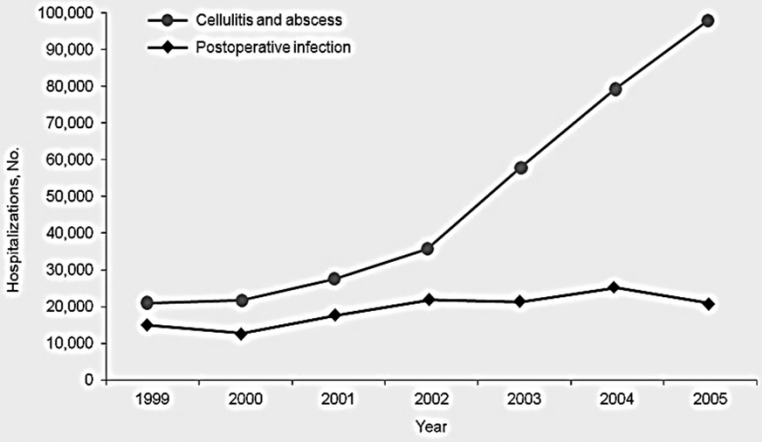
- Most CA-MRSA respond to TMP-SMX, clindamycin and doxycycline
  - Lower-than-recommended doses have been associated with treatment failure
- Hospital strains usually require TMP-SMX, doxycycline, linezolid or i.v. therapy
- Incision and drainage alone is often adequate, but can result in relapse

Halilovic J et al. *J Infect*. 2012; 65:128-34.
Duong M et al. *Ann Emerg Med*. 2010; 55:401-7.
Schmitz GR et al. *Ann Emerg Med*. 2010; 56:283-7.

Conclusion

- Empiric treatment of pneumonia is still important
  - Preventing readmission and mortality after discharge is a new focus
- Pharmacists can also play an important role in properly managing skin infections
- Ensure appropriate therapy and step-down
  - Adequate dosing and follow-up for both

Hospitalizations Due to MRSA-associated Complicated Skin and Skin Structure Infections are Increasing



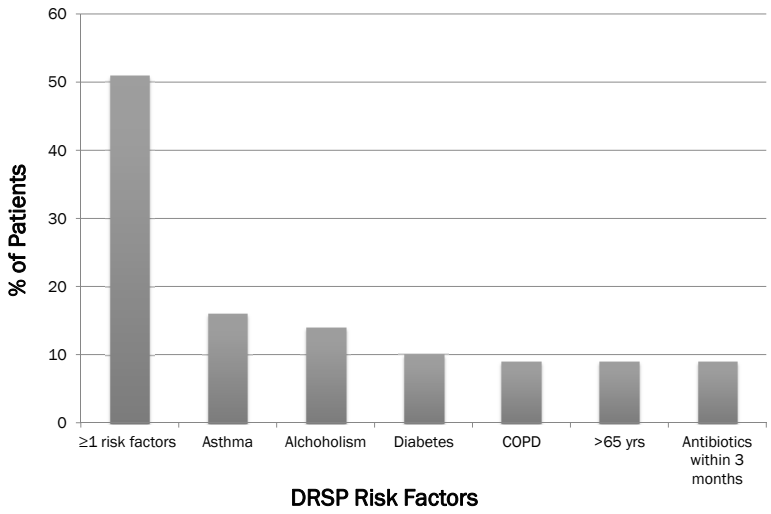
Adapted from Klein E et al. *Emerg Infect Dis*. 2007;13(12):1840-46.

Antimicrobial Therapy for ABSSSI

Diagnosis	Treatment	Coverage	Comment
Erysipelas	B-lactam	Strep pyogenes	
Abscess, furuncle, carbuncle	Incision and drainage	None	
Outpatient Purulent cellulitis +/- abscess	Clindamycin TMP/SMZ Doxycycline Minocycline Linezolid	B-hem strep and MRSA MRSA MRSA MRSA B-hem strep and MRSA	• CA-MRSA most common • Swelling may obscure purulence determination • Static except TMP/SMZ
Outpatient Nonpurulent cellulitis	B-lactam Clindamycin Linezolid B-lactam + TMP/SMZ or Doxycycline or Minocycline	B-hem strep B-hem strep and MRSA B-hem strep and MRSA B-hem strep and MRSA	• Consider B-hem strep and MSSA • Role of CA-MRSA unknown
Complicated SSSI or hospitalized cellulitis	Vancomycin Linezolid Daptomycin Clindamycin Ceftaroline	B-hem strep and MRSA B-hem strep and MRSA B-hem strep and MRSA B-hem strep and MRSA B-hem strep and MRSA	

Rajan S. *Cleve Clin J Med*. 2012; 79:57-66; Gunderson CG. *Am J Med*. 2011; 124:1113-22; Tognetti L et al. *J Eur Acad Dermatol Venereol*. 2012; 26:931-41.

Risk Factors for DRSP



Jenkins TC et al. *Acad Emerg Med*. 2012; 19:703-6.

Activity of Ceftaroline against Contemporary Gram-Positive Organisms Collected in the USA in 2008

		Ceftaroline MIC (mg/L)		
Organism and phenotype	N	range	50%	90%
Streptococcus pneumoniae				
Penicillin susceptible (MIC ≤2 mg/L)	770	≤0.008–0.5	≤0.008	0.12
Penicillin non-susceptible (MIC ≥4 mg/L)	121	0.06–0.5	0.25	0.25
Levofloxacin resistant	4	≤0.008–0.12	NA	NA
Multidrug resistant	123	0.06–0.5	0.25	0.25
Ceftriaxone resistant	20	≤0.008–0.5	0.25	0.5
Staphylococcus aureus				
Oxacillin susceptible	1711	≤0.008–0.5	0.25	0.25
Oxacillin resistant	2254	0.12–2	1	1

Adapted from Critchley et al. *J Antimicrob Chemother.* 2011; 66 Suppl 3: iii45–iii51.

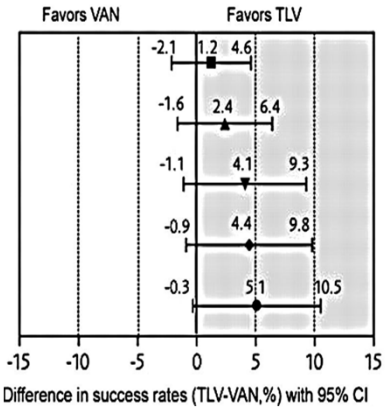
Activity of Ceftaroline against Contemporary Gram-Negative Organisms Collected in the USA in 2008

		Ceftaroline MIC (mg/L)		
Organism and phenotype	N	range	50%	90%
Haemophilus influenzae (β-lactamase positive)	106	≤0.008–0.12	≤0.008	0.03
Haemophilus influenzae (β-lactamase negative)	275	≤0.008–0.06	≤0.008	0.015
Escherichia coli (ceftazidime susceptible)	1036	0.015–>16	0.12	0.5
Klebsiella pneumoniae (ceftazidime susceptible)	517	≤0.008–>16	0.12	0.25

Adapted from Critchley et al. *J Antimicrob Chemother.* 2011; 66 Suppl 3: iii45–iii51.

Pooled Results from ATLAS Studies Comparing Telavancin (TLV) with Vancomycin (VAN)

Success rates in clinical, microbiologic, and overall therapeutic response.



	TLV % success (N)	VAN % success (N)
Clinical cure in CE patients	88.3% (745)	87.1% (744)
Overall therapeutic response* in ME patients	88.6% (527)	86.2% (536)
Clinical cure in ME patients with MRSA infection	90.6% (278)	86.4% (301)
Microbiological eradication in ME patients with MRSA infection	89.9% (278)	85.4% (301)
Overall therapeutic response* in ME patients with MRSA infection	89.9% (278)	84.7% (301)

Stryjewski et al. *Clin Infect Dis.* 2008; 46(11):1683-93; by permission of Oxford University Press.

Pooled Results from ATLAS Studies

Laboratory abnormalities and QT corrected (QTc) interval changes in the all-treated population.

Variable	Proportion of patients (%)	
	Telavancin treatment arm	Vancomycin treatment arm
Hematocrit		
<30% in male patients	5/369 (1)	4/391 (1)
<28% in female patients	12/303 (4)	6/290 (2)
Eosinophilia (eosinophil count >500 cells/mL)	16/837 (2)	15/845 (2)
Leukopenia (leukocyte count <2800 cells/mL)	8/571 (1)	10/568 (2)
Platelet count ≤75 × 10^9 platelets/L	2/694 (<1)	0/707
AST level ≥3 × ULN	13/686 (2)	22/726 (3)
ALT level ≥3 × ULN	16/703 (2)	28/754 (4)
Potassium concentration		
<3 meq/L	16/841 (2)	7/847 (<1)
>5.5 meq/L	21/841 (2)	18/847 (2)
Serum creatinine concentration		
≥1.5 mg/dL and at least 50% greater than baseline	52/822 (6)	19/856 (2)
1.5–1.9 mg/dL	28/822 (3)	15/856 (2)
2.0–2.9 mg/dL	17/822 (2)	2/856 (<1)
≥3 mg/dL	7/822 (<1)	2/856 (<1)
Increase in QTc interval >60 msec	11/929 (1)	5/938 (<1)
QTc interval >500 msec	1/929 (<1)	2/938 (<1)

NOTE. Laboratory abnormalities at end of therapy, compared with baseline values. The denominator for each parameter is the number of patients in the treatment group who had that parameter assessed at baseline (and at least 1 subsequent time) and for whom the baseline assessment findings were normal. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Stryjewski et al. *Clin Infect Dis.* 2008; 46(11):1683-93; by permission of Oxford University Press.

FDA Warnings - Tigecycline

Pooled results from clinical trials evaluating tigecycline

	Tigecycline deaths/ total patients (%)	Comparator Antibiotics deaths/total patients (%)	Risk Difference (95% CI)
Overall Adjusted (2010)	150/3788 (4.0%)	110/3646 (3.0%)	0.6 (0.1 - 1.2)
Overall Adjusted (2013)	66/2640 (2.5%)	48/2628 (1.8%)	0.6 (0.0 - 1.2)

- **The greatest increase in risk of death seen in patients with VAP, an unapproved use**
- **"Alternatives to tigecycline should be considered in patients with severe infections"**

U.S. Food and Drug Administration. FDA drug safety communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new boxed warning. (URL in ref list).

Pooled Results from FOCUS 1 & 2

Clinical Cure Rates by Study Population at the Test-of-Cure Visit.

Variable	CE	MITTE	ME	mMITTE
FOCUS 1				
Ceftaroline	194/224 (86.6)	244/291 (83.8)	62/69 (89.9)	66/75 (88.0)
Ceftriaxone	183/234 (78.2)	233/300 (77.7)	54/71 (76.1)	60/80 (75.0)
Difference, % (95% CI)	8.4 (1.4–15.4)	6.2 (−0.2 to 12.6)	13.8 (1.3–26.4)	13.0 (0.7–25.2)
FOCUS 2				
Ceftaroline	193/235 (82.1)	235/289 (81.3)	69/85 (81.2)	72/90 (80.0)
Ceftriaxone	166/215 (77.2)	206/273 (75.5)	57/76 (75.0)	66/88 (75.0)
Difference, % (95% CI)	4.9 (−2.5 to 12.5)	5.9 (−1.0 to 12.7)	6.2 (−6.7 to 19.2)	5.0 (−7.4 to 17.4)
Integrated FOCUS				
Ceftaroline	387/459 (84.3)	479/580 (82.6)	131/154 (85.1)	138/165 (83.6)
Ceftriaxone	349/449 (77.7)	439/573 (76.6)	111/147 (75.5)	126/168 (75.0)
Weighted treatment difference, % (95% CI)	6.7 (1.6–11.8)	6.0 (1.4–10.7)	9.7 (0.7–18.8)	8.7 (−0.0 to 17.4)

NOTE. Data are proportion (%) of patients, unless otherwise indicated. CE, clinically evaluable population; CI, confidence interval; FOCUS, Ceftaroline Community Acquired Pneumonia Trial versus Ceftriaxone in Hospitalized Patients; ME, microbiologically evaluable population; MITTE, modified intent-to-treat efficacy population; mMITTE, microbiological modified intent-to-treat efficacy population.

File TM et al. *Clin Infect Dis.* 2010; 51:1395-1405; by permission of Oxford University Press.

Pooled Results from FOCUS 1 & 2

Clinical Cure Rates by the Most Common Baseline Pathogens at Test-of-Cure Visit, Integrated Microbiological Modified Intent-to-Treat Efficacy Population.

	Proportion (%) of patients					
	FOCUS 1		FOCUS 2		Integrated FOCUS	
Variable	Ceftaroline group	Ceftriaxone group	Ceftaroline group	Ceftriaxone group	Ceftaroline group	Ceftriaxone group
Gram positive						
Streptococcus pneumoniae	24/27 (88.9)	20/30 (66.7)	35/42 (83.3)	28/40 (70.0)	59/69 (85.5)	48/70 (68.6)
MDRSP[a]	2/2 (100)	0/1 (0)	2/2 (100)	2/8 (25.0)	4/4 (100)	2/9 (22.2)
Staphylococcus aureus	8/10 (80.0)	9/14 (64.3)	10/15 (66.7)	9/16 (56.3)	18/25 (72.0)	18/30 (60.0)
MRSA[b]	NA	0/1 (0)	NA	1/1 (100)	NA	1/2 (50.0)
Gram negative						
Haemophilus influenzae	4/5 (80.0)	7/10 (70.0)	13/15 (86.7)	13/14 (92.9)	17/20 (85.0)	20/24 (83.3)
Haemophilus parainfluenzae	7/8 (87.5)	9/10 (90.0)	9/9 (100)	6/8 (75.0)	16/17 (94.1)	15/18 (83.3)
Klebsiella pneumoniae	7/8 (87.5)	3/5 (60.0)	7/7 (100)	7/8 (87.5)	14/15 (93.3)	10/13 (76.9)
Escherichia coli	8/8 (100)	5/7 (71.4)	2/4 (50.0)	4/6 (66.7)	10/12 (83.3)	9/13 (69.2)

NOTE. FOCUS, Ceftaroline Community Acquired Pneumonia Trial versus Ceftriaxone in Hospitalized Patients; MDRSP, multidrug-resistant *S. pneumoniae*; MRSA, methicillin-resistant *S. aureus*; NA, not applicable.

[a] MDRSP was defined in these studies as strains resistant to ≥2 antimicrobial classes of drugs, including penicillin, macrolides, tetracycline, fluoroquinolones, chloramphenicol, trimethoprim-sulfamethoxazole, and cephalosporins.

[b] Patients with confirmed or suspected community-acquired pneumonia caused by MRSA at baseline were excluded from the study.

File TM et al. *Clin Infect Dis.* 2010; 51:1395-1405; by permission of Oxford University Press.

Activity of Various Cephalosporins Against Gram-positive Organisms

Cephalosporin (generation)						
	1st	2nd	3rd	3rd	4th	5th
Representative	Cefazolin	Cefamandole	Ceftriaxone	Ceftazidime	Cefepime	Ceftobiprole
Relative bactericidal activity						
Gram-positive cocci						
MSSA	+++	+++	+++	+	+++	+++
MRSA	0	0	NA	0	0	+++
MRCoNS*	0	0	0	0	0	+++
Streptococcus spp.	+++	+++	+++	+++	+++	+++
PRSP**	NA	NA	++	+	++±	+++

Methicillin-resistant coagulase negative *Staphylococcus
****Penicillin-resistant *S. Pneumoniae***

Adapted from Deresinski SC. *Diagn Microbiol Infect Dis.* 2008; 61(1):82-5.

Activity of Various Cephalosporins Against Gram-negative Organisms

Cephalosporin (generation)						
	1st	2nd	3rd	3rd	4th	5th
Representative	Cefazolin	Cefamandole	Ceftriaxone	Ceftazidime	Cefepime	Ceftobiprole
Relative bactericidal activity						
Gram-negative bacilli						
Enterobacter cloacae	0	+	NA	+	++±	++±
Escherichia coli	++	++	+++	+++	+++	+++
Proteus vulgaris	0	+++	NA	+++	+++	+++
Pseudomonas aeruginosa	0	0	0	++	+++	+++
Serratia spp.	0	++	0	+++	+++	+++
Haemophilus influenzae	+	++	+++	+++	+++	+++

Adapted from Deresinski SC. *Diagn Microbiol Infect Dis.* 2008; 61(1):82-5.

Proportion of patients who experienced clinical cure and microbiological eradication at the test-of-cure visit [*n/N* (%)]

Outcome/population	Ceftobiprole	Ceftriaxone ± Linezolid	95% CI
Clinical cure			
CE patients	200/231 (86.6)	208/238 (87.4)	(−6.9 - 5.3)
ITT patients	240/314 (76.4)	257/324 (79.3)	(−9.3 - 3.6)
Patients receiving i.v. therapy only	77/103 (74.8)	73/101 (72.3)	(−9.6 - 14.6)
Switch to oral therapy	123/128 (96.1)	135/137 (98.5)	(−6.4 - 1.5)
Patients requiring antistaphylococcal therapy	17/21 (81.0)	25/34 (73.5)	(−15.0 - 29.8)
Microbiological eradication			
ME patients	60/68 (88.2)	69/76 (90.8)	(−12.6 - 7.5)
Microbiological ITT	70/87 (80.5)	79/97 (81.4)	(−12.4 - 10.4)

Adapted from Nicholson et al. *Int J Antimicrob Agents*. 2012; 39(3):240-6.

Nemonoxacin vs. Levofloxacin for CAP

Clinical response at Test of Cure or End of Treatment visit

Population	No. of patients (%)			Difference in clinical-cure rates between treatment groups	
	Nemonoxacin		Levofloxacin 500 mg	Nemonoxacin 750 mg-levofloxacin 500 mg	Nemonoxacin 500 mg-levofloxacin 500 mg
	750 mg	500 mg			
Eval-ITT	71 (89.9)	67 (87.0)	72 (91.1)	−10.4 to 7.9	−13.9 to 5.7
Eval-PPc	66 (91.7)	64 (87.7)	65 (90.3)	−8.0 to 10.8	−12.8 to 7.6
ITT	66 (91.7)	64 (87.7)	65 (90.3)	−10.5 to 15.7	−18.6 to 9.1
PPc	66 (83.5)	64 (78.0)	65 (82.3)	−12.1 to 14.6	−18.7 to 9.1

Adapted from van Rensburg et al. *Antimicrob Agents Chemother. 2010 (54); 10:4098-106.*

Nemonoxacin vs. Levofloxacin for CAP

Baseline pathogen (n)	Bacteriological success/organisms isolated at baseline (%)			MIC range baseline (μg/ml)	
	Nemonoxacin		Levofloxacin 500 mg/day		
	750 mg/day	500 mg/day		Nemonoxacin	Levofloxacin
Typical pathogens					
H. influenzae (17)	5/6 (83.3)	4/4 (100.0)	7/7 (100.0)	≤0.008-0.06	≤0.008-0.03
S. pneumoniae (14)	5/5 (100.0)	3/4 (75.0)	5/5 (100.0)	0.06-0.12	0.5-1.0
S. aureus (4)	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)	0.03-0.06	0.12-0.5
Atypical pathogens					
M. pneumoniae (93)	26/29 (89.7)	25/31 (80.6)	31/33 (93.9)		
C. pneumoniae (23)	8/8 (100.0)	8/8 (100.0)	6/7 (85.7)		
L. pneumophila (8)	3/3 (100.0)	2/2 (100.0)	3/3 (100.0)		

Adapted from van Rensburg et al. *Antimicrob Agents Chemother. 2010 (54); 10:4098-106.*

Tedizolid vs. Linezolid for ABSSSI (ESTABLISH-1)

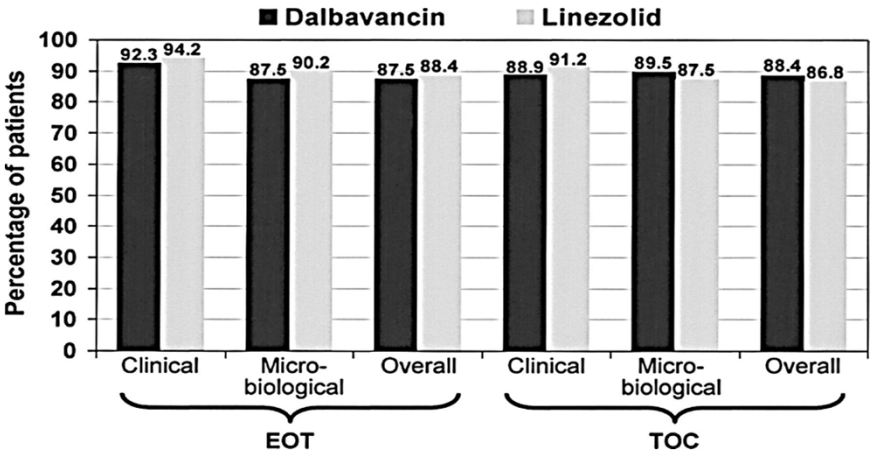
Analysis of intent-to-treat (ITT) and Clinically Evaluable at End-of-treatment (EOT)

	Clinical Success Rate n(%)		Absolute Difference % (95% CI)
	Tedizolid (n=332)	Linezolid (n=335)	
Treatment Response at 48-72 hr Assessment (Intent-to-treat) (≥20% Decrease in lesion area, no fever criteria)	259 (78)	255 (76.1)	1.9 (-4.5 – 8.3)
Decrease in lesion area, no fever criteria	289 (87)	286 (85.4)	1.6 (-3.5 – 7.0)
Sustained treatment response at EOT (Intent-to-treat)	268 (80.7)	271 (80.9)	-0.2 (-6.5 – 5.8)
Clinically Evaluable at EOT (n=273) / (n=286)	239 (87.5)	294 (87.8)	0.4 (-5.8 – 6.0)

Adapted from Prokocimer et al. *JAMA*. 2013; 309(6):559-69.

Dalbavancin vs. Linezolid

Summary of response end points in the evaluable populations illustrating clinical, microbiological, and overall (combined clinical/microbiological) success at end-of-therapy (EOT) and test-of-cure (TOC) visits.



Jauregui et al. *Clin Infect Dis.* 2005; 41;1407-15; by permission of Oxford University Press.

Drug*	Indication	Pros	Cons
Ceftaroline	ABSSSI, CABP	Covers indications/all pathogens as sole therapy	i.v. only, twice-daily dosing, $$
Daptomycin	ABSSSI	Broad Gram (+), No Gram (-), Once-daily dosing	i.v. only, $$$
Linezolid	ABSSSI, CABP	Available i.v./oral. Broad Gram (+), no Gram (-) for pneumonia	$$$, some DDIs with MAOI, risk toxicity >2 weeks
Telavancin	ABSSSI	Broad, Once-daily, no TDM required	FDA boxed warning renal toxicity, teratogen, i.v. only, $$
Tigecycline	ABSSSI, CABP	Covers all pathogens as sole therapy	FDA boxed warning ↑ mortality, i.v. only, $$$
Ceftobiprole	ABSSSI, CABP	Similar to ceftaroline plus Pseudomonas?	Similar to ceftaroline ???
Cethromycin	CAP	Oral. Once-daily	Data limited to OP Tx
Dalbavancin	ABSSSI	Broad Gram (+), weekly dosing, no TDM required	i.v. only, No Gram (-)
Nemonoxacin	CAP	Broad coverage, oral, evades FQ Resistance?	Broad→collateral damage like FQs???

***Black text: FDA approved; Red text: Phase 3 investigational drug**