Ask the Expert: Strategies for Optimizing Antimicrobial Use in ABSSSI and CABP

Presented as a Live Webinar
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1:00 p.m. – 2:00 p.m. EDT

Planned and conducted by ASHP Advantage.

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Be sure to view the webinar system requirements for Windows, Mac, iOS, and Android prior to the activity.

Activity Faculty

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John Esterly, Pharm.D., BCPS (AQ-ID), is Assistant Professor of Pharmacy Practice at Chicago State University College of Pharmacy (CSU-COP) and Infectious Diseases Pharmacist at Northwestern Memorial Hospital in Chicago, Illinois. In these roles Dr. Esterly practices as a clinical pharmacist, specializing in the area of infectious diseases. He is also an integral member of the Antimicrobial Stewardship Program at Northwestern Memorial Hospital.

Dr. Esterly received his Doctor of Pharmacy degree from the University of Illinois-Chicago College of Pharmacy. He completed a pharmacy practice residency with comprehensive pharmacy services at Mercy Hospital and Medical Center in Chicago, Illinois. Dr. Esterly then completed a two-year infectious diseases pharmacotherapy fellowship with the Midwestern University Chicago College of Pharmacy in conjunction with Northwestern Memorial Hospital and Rush University Medical Center in Chicago, Illinois. He is a board certified pharmacotherapy specialist with added qualifications in infectious diseases.

Dr. Esterly’s research interests include antimicrobial resistance, pharmacokinetics and pharmacodynamics of antimicrobials, and antimicrobial stewardship related outcomes. His work has been presented at several national meetings and has been published in peer-reviewed journals. He also serves as a peer reviewer for both infectious diseases and pharmacy medical journals.

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- John Esterly, Pharm.D., BCPS (AQ-ID)
- Erika L. Thomas, M.B.A., B.S.Pharm.
- Susan R. Dombrowski, M.S., B.S.Pharm.

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Activity Overview

This activity will focus factors integral to optimizing use of antimicrobials for acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). Evidence based guidelines and recommendations will be reviewed, and guidance for incorporating antimicrobial stewardship principles into decision making processes for selecting therapies for both empiric and targeted therapies will be emphasized. Particular emphasis will be placed on delineating the role of newer antibiotics that have gained FDA approval for ABSSSI and CABP since the most recent version of consensus treatment guidelines have been published.

The content for this live webinar is based on questions raised by participants in a recent educational symposium on this topic. Time for questions and answers from the webinar audience will be provided at the end of the presentation.

Learning Objectives

At the conclusion of this application-based educational activity, participants should be able to

- Compare and contrast at least one new FDA approved agent to current guideline endorsed therapies for ABSSSI and for CABP.
- Choose a first-line therapy and an alternative therapy recommendation for ABSSSI and CABP that are suitable for an institutional clinical pathway.

Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU) of continuing pharmacy education credit (ACPE activity #0204-0000-14-463-L01-P).

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Additional Educational Opportunities on this Topic

- **Web-based activity "Applying Antimicrobial Stewardship Principles to the Treatment of CABP and ABSSSI: Complying with CMS Criteria and Clinical Guidelines" (2 hours CPE)**
- **Informational podcasts featuring interviews with the faculty**
- **e-Newsletters featuring tips for incorporating information from these activities into practice, and updates on emerging information on the treatment of CABP and ABSSSI**
- **A web-based activity based on today's webinar (please note that individuals who claim CPE credit for the live webinar are ineligible to claim credit for the web-based activity)**

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Ask the Expert: Strategies for Optimizing Antimicrobial Use in ABSSSI and CABP

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Forest Laboratories, Inc.
This educational symposium is planned and conducted by ASHP Advantage and supported by an educational grant from Forest Research Institute, a subsidiary of Forest Laboratories, Inc.

Relevant Guidelines - ABSSSI, CABP

- **Stevens DL, Bisno AL, Chambers 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

**Update in progress!

Clarification of Definition for CABP

- According to FDA guidance for the study of CABP, definitions should exclude patients with:
  - Viral pneumonia
  - Aspiration pneumonia
  - Hospital-acquired bacterial pneumonia (HAP) and ventilator-associated bacterial pneumonia (VAP)
  - Prior receipt of antibacterials
  - Bronchial obstruction or a history of post-obstructive pneumonia NOT COPD
  - Primary or metastatic lung cancer
  - Cystic fibrosis, *Pneumocystis jiroveci* , active tuberculosis

U.S. Department of Health and Human Services. Guidance for industry. Community-acquired bacterial pneumonia: developing drugs for treatment. January 2014. (URL in ref list).

Centers for Medicare & Medicaid Services (CMS) Measures for Pneumonia

Which of the following statements about the time of initiation of antibiotic therapy after hospital arrival is correct regarding CMS reimbursement tied to pneumonia?

a. Antibiotics must start within 4 hours
b. Antibiotics must start within 6 hours
c. Antibiotics must start within 8 hours
d. There is no longer a mandate to start therapy on a specific timeline

What Does CMS Care About?

Set Measure ID#	Measure Short Name
PN-3a	Blood Cultures Performed Within 24 Hours Prior to or 24 Hours After Hospital Arrival for Patients Who Were Transferred or Admitted to the ICU Within 24 Hours of Hospital Arrival
PN-3b	Blood Cultures Performed in the Emergency Department Prior to Initial Antibiotic Received in Hospital
~~PN-5c~~	~~Initial Antibiotic Within 6 hours of Arrival~~
PN-6	Initial Antibiotic Selection for Community-acquired pneumonia (CAP) in Immunocompetent Patient
PN-6a	Initial Antibiotic Selection for CAP in Immunocompetent – ICU Patient
PN-6b	Initial Antibiotic Selection for CAP Immunocompetent – Non ICU Patient

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

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How Does CMS Evaluate You?

- Blood cultures
  - Within 24 hours for all ICU patients
  - For patients admitted through the Emergency Department before initiation of antibiotics
- Guideline concordant antibiotic therapy
- 30-day risk-standardized measures
  - Mortality
  - 30-day readmission
    - "Higher than expected" readmissions can lead to reduced reimbursement rates

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

Empiric Antibiotic Treatment?

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

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

Pneumonia antibiotic consensus recommendations. In: Centers for Medicare & Medicaid Services. The Joint Commission. Specifications manual for national hospital inpatient quality measures. (URL in ref list).

How to Decide Who Gets What?

- Pneumonia severity scoring guides treatment location and pathogen risk
  - CURB-65 criteria/scores, PORT index
- Risk factors requiring *Pseudomonas* coverage for CABP
  - *Bronchiectasis*
  - Structural lung disease + either multiple antibiotic exposures or chronic steroid use within past 3 months
- Healthcare-associated pneumonia qualifiers
  - Hospitalization within 90 days, nursing home/long-term care, recent antibiotics or IV chemo or wound care, visited hemodialysis clinic past 30 days

Mandell L et al. *Clin Infect Dis.* 2007; 44(suppl 2):S27-S72; American Thoracic Society, Infectious Diseases Society of America *Am J Respir Crit Care Med* 2005; 171:388-416.; Centers for Medicare & Medicaid Services. The Joint Commission. Specifications manual for national hospital inpatient quality measures. (URL in ref list).

How Can Antimicrobial Stewardship Efforts Be Complementary to CMS Measures?

- Ensure appropriate use per guidelines
  - Implementation of CAP order sets!
- Avoid overuse of antibiotics
  - CMS allows "outs" for unsure diagnosis, antibiotic use within initial 24 hours for a different indication, transfer from other acute care facilities, immune-compromising conditions or therapies, study enrollment, comfort care patients
- Define need for anti-pseudomonal therapy
  - Differentiate CAP vs. HCAP

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

Pneumonia ED Order Set Example

LAB		
If cultures are obtained, they should be collected prior to initiating antibiotics		
Choose Both BC orders for 2 sets		
Blood Culture	Stat, Add On = No	
Blood Culture	Stat, Add On = No	
Respiratory Culture w/Gram Stain	Stat, Once, Specimen type: Sputum	
A viral PCR test should ALWAYS be ordered with a rapid influenza test due to limited sensitivity of the rapid influenza test.		
Influenza Antigen Test, Direct	Stat, Specimen type: Nasopharyngeal	
Influenza A/B & RSV A/B Detection by PCR	Routine, Once, Specimen type: Nasopharyngeal	
The Streptococcal Pneumoniae Antigen test should be ordered in patients with suspected CAP.		
Strept Pneumoniae Antigen Test	Stat, Urine, Once	
Legionella Urine Antigen	Stat, Urine, Once	
CAP - ORAL TREATMENT		
Continue "ZPak" for 4 additional days		
azithromycin (Zithromax)	500 mg, DF: Tab, PO, Once	
or moxifloxacin 400 mg daily x 5 days		
moxifloxacin (Avelox)	400 mg, DF: Tab, PO, Once	
CAP - INPATIENT FLOOR ADMISSION		
Choose Both		
ceftriaxone (Rocephin)	1 g, IVPB, Once	Rate: 300 mL/Hr, Infuse Over: 20 Minutes
azithromycin (Zithromax)	500 mg, IVPB, Once	
or		
moxifloxacin (Avelox)	400 mg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes

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Pneumonia ED Order Set Example

CAP - ICU ADMISSION		
Choose Both		
ceftriaxone (Rocephin)	2 g, IVPB, Once	Rate: 300 mL/Hr, Infuse Over: 20 Minutes
moxifloxacin (Avelox)	400 mg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes
Alternative to ceftriaxone if Beta-lactam allergy		
vancomycin	15 mg/Kg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes
HEALTHCARE ASSOCIATED PNEUMONIA (HCAP)		
Choose ALL 4 antibiotics		
cefepime	2g, IVPB, Once	
vancomycin	15 mg/Kg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes
amikacin	15 mg/Kg, IVPB, Once	
azithromycin (Zithromax)	500 mg, IVPB, Once	
Alternative to cefepime if Beta-lactam allergy		
aztreonam (Azactam)	2 g, IVPB, Once	
LUNG ABSCESS		
Choose both amp-sulbactam and vancomycin		
ampicillin-sulbactam (Unasyn)	3 g, IVPB, Once	
vancomycin	15 mg/Kg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes
Choose moxifloxacin for alternative to amp-sulbactam for Beta-lactam allergy		
moxifloxacin (Avelox)	400 mg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes
SEVERE ACUTE EXACERBATION OF COPD		
azithromycin (Zithromax)	500 mg, IVPB, Once	
or		
moxifloxacin (Avelox)	400 mg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes
INFLUENZA		
For outpatients, efficacy of treatment is only proven if started within 48 hours of symptom onset (Continue BID for 5 days)		
oseltamivir (Tamiflu)	75 mg, DF: Cap, PO, Once	

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De-escalation & Duration of Therapy?

- For how long should azithromycin be continued to provide coverage for atypical pathogens in patients receiving the drug with a beta-lactam antibiotic as empiric treatment of CAP in the absence of microbiologic test results?
- Answer: The addition of azithromycin to provide atypical coverage has not shown been to be beneficial except in critically ill patients with CAP, so clinical improvement and patient stability are key factors in deciding when to discontinue azithromycin (or atypical coverage) in non-critically ill patients with CAP.

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 β-lactam monotherapy, β-lactam + macrolide, or quinolone monotherapy unknown

Slide courtesy of Dr. Neil Davis. 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. Eliakim-Raz N et al. *Cochrane Database Syst Rev.* 2012; 9:CD004418.

De-escalation Strategies

- Definitively confirm diagnosis of pneumonia
  - Radiology, oxygenation, cultures, other supporting labs (e.g., procalcitonin, C-reactive protein)
- Target antibiotics with single-drug therapy when possible
  - Cultures/susceptibilities, PCR, antigen testing results
- Convert to oral therapy when clinically stable
  - Can discharge as soon as able to take medications orally if no other medical problems and a safe transition environment

Mandell L et al. *Clin Infect Dis.* 2007; 44(suppl 2):S27-S72.

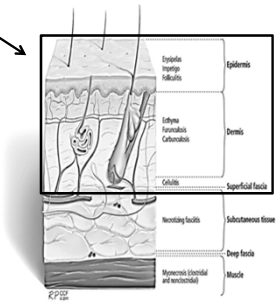
Optimizing Duration of Therapy

- 5 days minimum recommended
  - Afebrile for 48-72 hours before discontinuation of therapy
  - ≤1 CAP-associated sign of clinical instability
  - No sign of extrapulmonary infection
- Shorter courses of therapy → reduced resistance, adverse events, costs for patients and the healthcare system
  - Education!!!

Mandell LA et al. *Clin Infect Dis.* 2007; 44(Suppl 2):S27-72.

ABSSSI Challenges

- Diagnosis
- Severity of infection
- Antibiotic resistance of targeted pathogens
  - Mostly *Staph, Strep* spp.
- All of the above impact:
  - Necessity, selection, and route of antibiotics!!!



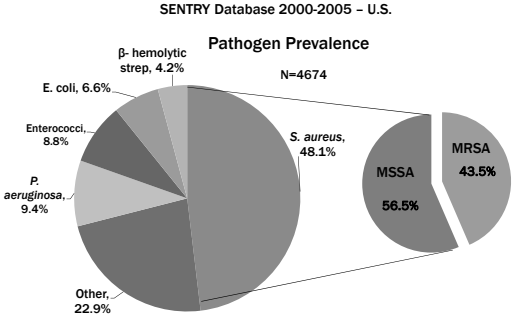
Rajan S. Cleve *Clin J Med.* 2012;79:57-66

See enlargement, p. 16

ABSSSI Follow-up Question

- Question: The rate of CA-MRSA rate is high in my area, so MDs are providing double coverage with a β-lactam (e.g., pip-tazo) + vancomycin as empiric therapy for ABSSSI. How should I address this?
- Answer: Create clinical pathways for clinicians. Stratify initial antibiotic selection and define specific criteria where double-coverage or Gram negative coverage may be appropriate!

Most Common Pathogens in cSSSIs



Slide courtesy of Dr. Neil Davis
Adapted from Sader HS et al. *Int J Antimicrob Agents.* 2007; 30:514-20.

See enlargement, p. 17

Guideline Recommendations - SSTIs

Indication	Agent	Likely Pathogen(s)	Other Considerations
Erysipelas	β-lactam Clindamycin (β-lactam allergy)	S. pyogenes, other β-hemolytic Strep spp.	PO for outpatient, initial IV for inpatient
Cutaneous abscess (furuncle, carbuncle)	None following incision and drainage*	S. aureus	Decolonize with mupirocin for recurrence
Cellulitis (non-purulent)	B-lactam Clindamycin Linezolid B-lactam + either TMP/SMX or Doxycycline/ Minocycline	S. pyogenes, other β-hemolytic Strep spp., MSSA? Role of CA-MRSA unknown	Rarely yields culture. Consider CA-MRSA coverage for non-response to B-lactam or systemic symptoms
Cellulitis (purulent or trauma-related)	Clindamycin TMP/SMX Doxycycline/Minocycline Linezolid	S. aureus	Coverage of B-hem Strep spp. not guideline recommended
Complicated soft-tissue infection requiring hospitalization	Vancomycin Linezolid Daptomycin Clindamycin Telavancin	S. aureus and all β-hemolytic Strep spp.	IV therapy recommended initially

* Consider treatment for multiple sites, rapid spreading, systemic symptoms, comorbidities or immunosuppression, age extremes, difficult to drain, non-response to drainage

Stevens, et al. *Clin Infect Dis*. 2005;41:1373-1406; Liu, et al. *Clin Infect Dis*. 2011;52:e18-55

See enlargement, p. 17

Treatment

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

Slide Courtesy of Dr. Scott Bergman. 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.

Treatment

- Empiric therapy against Gram-negative pathogens (including *P. aeruginosa)* is usually unnecessary except in high-risk patients
  - High local prevalence (your antibiogram?)
  - Previous infection or antibiotic exposure
  - Other infectious exposures (e.g., surgery)
  - Moderate to severe diabetic foot infections
  - Necrotizing infections
  - Immunocompromised hosts

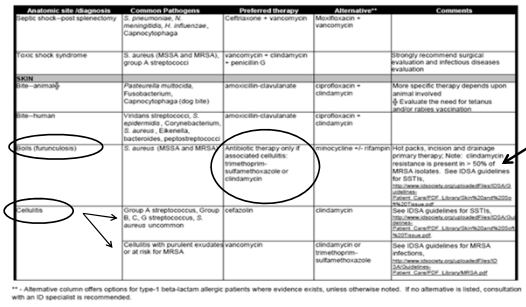
Lipsky BA et al. *Clin Infect Dis*. 2012; 54:e132-73.

Creating Local Pathways

- Initiate contact with your local Infectious Diseases Specialist Physician(s)
- Establish an Antimicrobial Stewardship Committee
- Ask for institutional administrative buy-in!
  - Reduce broad-spectrum antibiotic use
  - Reduce patient collateral harm
  - Reduce (potential) resistance ecology
  - Save healthcare costs

Dellit TH, et al. *Clin Infect Dis* 2007;44:159–77.

Empiric Recommendations/ Clinical Pathway - Skin



Anatomic site /diagnosis	Common Pathogens	Preferred therapy	Alternative**	Comments
Septic shock--post splenectomy	*S. pneumoniae, N. meningitidis, H. influenzae*, Capnocytophaga	Ceftriaxone + vancomycin	Moxifloxacin + vancomycin	
Toxic shock syndrome	S. aureus (MSSA and MRSA), group A streptococci	vancomycin + clindamycin + penicillin G		Strongly recommend surgical evaluation and infectious diseases evaluation
SKIN				
Bite--animals	Pasteurella multocida, Fusobacterium, Capnocytophaga (dog bite)	amoxicillin-clavulanate	ciprofloxacin + clindamycin	More specific therapy depends upon animal involved β Evaluate the need for tetanus and/or rabies vaccination
Bite--human	Viridans streptococci, *S. epidermidis*, Corynebacterium, *S. aureus*, Eikenella, bacteroides, peptostreptococci	amoxicillin-clavulanate	ciprofloxacin + clindamycin	
Boils (furunculosis)	*S. aureus* (MSSA and MRSA)	Antibiotic therapy only if associated cellulitis: trimethoprim-sulfamethoxazole or clindamycin	minocycline +/- rifampin	Hot packs, incision and drainage primary therapy; Note: clindamycin resistance is present in > 50% of MRSA isolates. See IDSA guidelines for SSTIs, http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Skin%20and%20Soft%20Tissue.pdf
Cellulitis	Group A streptococcus, Group B, C, G streptococcus, *S. aureus* uncommon	cefazolin	clindamycin	See IDSA guidelines for SSTIs, http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Skin%20and%20Soft%20Tissue.pdf
	Cellulitis with purulent exudates or at risk for MRSA	vancomycin	clindamycin or trimethoprim-sulfamethoxazole	See IDSA guidelines for MRSA infections, http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/MRSA.pdf

** - Alternative column offers options for type-1 beta-lactam allergic patients where evidence exists, unless otherwise noted. If no alternative is listed, consultation with an ID specialist is recommended.

Northwestern Medicine. Antimicrobial stewardship. URL in ref list.

See enlargement, p. 18

Empiric Recommendations/ Clinical Pathway - Skin

Anatomic site /diagnosis	Common Pathogens	Preferred therapy	Alternative**	Comments
Cellulitis--IV catheter-related	Coagulase-negative staphylococci, *S. aureus* (MSSA and MRSA)	vancomycin		Remove catheter
Decubitus ulcer	Streptococci, enterococci, Enterobacteriaceae, Pseudomonas, bacteroides, *S. aureus* (MSSA and MRSA)	vancomycin + piperacillin/tazobactam		Consider wound care alone (no antibiotic therapy) with no signs of systemic illness, soft tissue abscess, or local cellulitis. With exposed bone, obtain bone biopsy prior to administering antimicrobials to guide therapy.
Diabetic foot ulcer without evidence of infection or exposed bone	skin flora			No antibiotic therapy necessary
Diabetic foot ulcer--mild; small only skin, no inflammation, pulses present	Polymicrobial: *S. aureus* (MSSA and MRSA), streptococci, coliforms, anaerobes, Pseudomonas	amoxicillin-clavulanate	trimethoprim-sulfamethoxazole	See IDSA guidelines for diabetic foot infections, http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Diabetic%20Foot%20Infection.pdf
Diabetic foot ulcer--severe; limb-threatening, skin, subcutaneous, possibly bone, inflammation, fever, neutrophilia		piperacillin/tazobactam +/- vancomycin	clindamycin + ciprofloxacin	Send tissue specimen (bone preferable) for culture prior to starting empiric therapy. See IDSA guidelines for diabetic foot infections, http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Diabetic%20Foot%20Infection.pdf
Infected wound--post operative	Surgery not involving GI tract: *S. aureus* (MSSA and MRSA), group A, B, C, or G streptococci	vancomycin	clindamycin	
	Surgery involving GI tract: *S. aureus* (MSSA and MRSA), coliforms, bacteroides	vancomycin + piperacillin-tazobactam		

Northwestern Medicine. Antimicrobial stewardship. URL in ref list.

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TMP/SMX Dose for ABSSSI?

What dose of trimethoprim/sulfamethoxazole (TMP/SMX) would you choose for an adult patient with a purulent cellulitis?

a. 160/800mg (i.e., 1 DS tablet) PO q 12 hours
b. 160/800mg (i.e., 2 DS tablet) PO q 12 hours
c. 5 mg/kg/day trimethoprim PO in divided doses
d. 10 mg/kg/day trimethoprim PO in divided doses

TMP/SMX Adult Oral Doses for ABSSSI?

- NOT labeled for skin/skin structure infections
- IDSA recommends 160/800mg or 320/1600mg (i.e. 1 or 2 DS tablets) PO q 12 hours
- Weight-based dosing of 5-10 mg/kg/day TMP in divided doses is frequently used in practice for ABSSSI and other non-labeled indications
- Little guidance for obese patients
  - How to calculate an appropriate dosing weight?
  - Maximum dosage limits?

Bactrim and Bactrim DS (sulfamethoxazole and trimethoprim) [Prescribing information]. 2013 Jun Stevens DL et al. *Clin Infect Dis.* 2005; 41:1373-406.

TMP/SMX Dose Comparison Study - ABSSSI

- Prospective, observational cohort study of patients receiving oral monotherapy for MRSA SSTIs
- Compared TMP/SMX doses
  - 1 DS (160/800mg) PO BID vs.
  - 2 DS (320/1600mg) PO BID
- Study compared clinical characteristics of groups and treatment outcomes

Cadena J, et al. *Antimicrob Agents Chemother.* 2011 Dec;55(12):5430-2.

Comparison of select clinical characteristics and outcomes of patients treated with two different doses of TMP/SMX.

Clinical parameter	Result for TMP/SMX twice-daily dose of:		Odds ratio	95% confidence interval	P value
	160/800 mg (n = 170)	320/1600 mg (n = 121)			
Median (range) wt (kg)	77 (44.5-156)	86 (42-141)			0.553
Median (range) BMI (kg/m^2)	28 (16.8-54)	30 (18-58.8)			0.454
No. (%) Abscess	135 (79.4)	102 (84.3)	1.39	0.75–2.57	0.291
No. (%) Receipt of incision and drainage	82 (48.2)	77 (63.6)	1.88	1.17–3.03	0.009
No. (%) with clinical resolution	127 (74.7)	88 (72.7)	0.90	0.53–1.53	0.705

Cadena J, et al. *Antimicrob Agents Chemother.* 2011 Dec;55(12):5430-2.

See enlargement, p. 19

Antibiotic Dosing in Obesity

- Question: What oral dose of trimethoprim/sulfamethoxazole (TMP/SMX) do you use for obese adult patients? How high can you safely go?
- Answer: Some data suggest that excessive oral dose escalation in obese adult patients may not be necessary for treating ABSSSI

Obesity and Treatment Failure?

- 3-year retrospective study of 405 outpatients treated for cellulitis in Hawaii
  - Cephalexin 500 mg PO QID
  - TMP/SMX one DS tablet (160/800mg) PO BID
  - Clindamycin 300mg PO QID
- Primary outcome → treatment success
- Risk factors for treatment failure evaluated via logistic regression analysis

Khawcharoenporn T, Tice A. *Am J Med.* 2010 Oct;123(10):942-50.

Obesity and Treatment Failure?

- 52% of patients in study BMI ≥30 kg/m^2
  - Evenly distributed across groups (p=0.52)
- 44% of patients diagnosed "cellulitis with abscess" (most frequent diagnosis)
- 117 (29%) patients had a positive culture
  - 62% MRSA
  - 20% MSSA
  - 9% β-hemolytic Strep spp.
  - 9% Gram negative spp.

Khawcharoenporn T, Tice A. *Am J Med.* 2010 Oct;123(10):942-50.

Treatment Success Rates Among Patients Treated with Cephalexin, TMP/SMX, and Clindamycin

Characteristic	Cephalexin (n=180)	TMP/SMX (n=152)	Clindamycin (n=40)	p Value
All patients	134 (74%)	138 (91%)	34 (85%)	<0.001*
Obese	67/99 (68%)	65/74 (88%)	19/21 (90%)	0.02*
Moderate severity	21/43 (49%)	45/56 (80%)	9/10 (90%)	0.001*
MRSA positive	6/25 (24%)	36/40 (90%)	5/6 (83%)	<0.001*

*p values displayed represent analysis of cephalexin vs. TMP/SMX (trimethoprim/sulfamethoxazole)

Logistic Regression Analysis of Risk Factors for Treatment Failure

Risk Factor	Adjusted OR (95% CI)	p Value
Therapy not MRSA active	4.22 (2.25-7.92)	<0.001
Severity of cellulitis	3.74 (2.06-6.79)	<0.001
Upper extremity cellulitis	2.06 (1.06-4.01)	0.03
Lack of drainage if abscess	4.38 (1.91-10.05)	<0.001

Khawcharoenporn T, Tice A. *Am J Med.* 2010 Oct;123(10):942-50.

See enlargement, p. 19

MRSA Treatment Options?

- Question: What would be a preferred antimicrobial agent for a pregnant inpatient with MRSA cellulitis?
- Answer: Antimicrobial agents classified pregnancy category B agents are preferred. Make selection based on the severity of infection and local MRSA susceptibilities

MRSA Cellulitis in Pregnancy

Which of the following is a pregnancy category B antibiotic with anti-MRSA activity?

a. Clindamycin
b. Linezolid
c. Telavancin
d. Vancomycin

Pregnancy Categories - MRSA Treatments

Agent	Category	Comments
Clindamycin	B	Endorsed for purulent and non-purulent cellulitis, and cSSTI. Association with C. difficile
Daptomycin	B	Only indicated for cSSTI. Safety not established in children.
Linezolid	C	Side effects include reversible myelosuppression and partially or non-reversible neuropathies with prolonged use (>2 weeks)
Quinupristin-dalfopristin	B	Limited by side effects including severe infusion reactions
Telavancin	C	Indicated for cSSTI. Teratogenic in animals, high incidence of nephrotoxicity in initial studies
Tetracyclines	D	Teratogenic
Trimethoprim/ sulfamethoxazole	C/D*	OK for purulent cellulitis. Lacks adequate strep coverage. Not recommended for 3rd trimester or children <2 months of age
Vancomycin	C	Historical mainstay for most MRSA infections where IV therapy is indicated.
Ceftaroline	B	Newer agent (2012) so not in guidelines. Indicated for ABSSSI but limited data. Most beta-lactams very safe in pregnancy!

*During 3rd trimester

Stevens, et al. *Clin Infect Dis.* 2005;41:1373-1406; Liu, et al. *Clin Infect Dis.* 2011;52:e18-55

See enlargement, p. 20

Role of Topical Agents

Which of the following is recommended in guidelines for the use of topical agents (e.g., mupirocin, chlorhexidine) in adults with MRSA SSTIs?

a. Use with systemic therapy for all MSRA SSTIs
b. Use with systemic therapy only for "severe" MRSA SSTIs
c. Use alone only for abscesses following incision and drainage
d. There is no role for treatment of MRSA SSTIs

Role of Topical Agents

- Question: What is the role of a topical antimicrobial protocol (e.g., mupirocin nasal ointment, chlorhexidine body wash) for MRSA SSTIs?
- Answer: There is minimal evidence supporting the use of topical agents for treatment of MRSA SSTIs (mild infections only). Decolonization with topical agents can be considered in selected situations, but supporting evidence is weak.

Supported Indications – Topical Agents

Indication	Topical Agent(s)	Level of Evidence
Pediatric minor skin infections (impetigo, cuts)	Mupirocin 2% topical ointment	A-III
Neonatal pustulosis	Mupirocin 2% topical ointment	A-III
Decolonization for: Recurrent infection despite wound care/hygiene and/or Ongoing transmission among household or close contacts (symptomatic and asymptomatic)	Nasal Mupirocin 2% ointment BID x 5-10 days and Chlorhexidine skin solution BID for 5-14 days or dilute bleach solution bath for 15 min twice weekly for ~3 months	C-III *Oral antimicrobials are not recommended for decolonization

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

See enlargement, p. 20

Incorporating Newer Agents?

- Question: What is the role of antimicrobial agents recently approved by FDA for CABP and ABSSSI? How should they be positioned on institution formularies?
- Answer: Analysis of efficacy and safety data, followed by cost comparison with other evidence-based treatment options is where to start. This should be coupled with restricted use criteria to optimize use and meet institutional needs.

Ceftaroline fosamil

- Advanced generation cephalosporin
  - Approved in 2010
- FDA-approved indications include:
  - ABSSSI
    - *S. pyogenes, S. agalactiae, S. aureus* (including MRSA), *H. influenzae, E. coli, K. oxytoca* and *K. pneumoniae*
  - 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 Dec

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. 21

Formulary Considerations - Ceftaroline?

- Broadly active against most *Staph* spp., *Strep* spp., and some Gram-negative organisms
- "Non-inferior" for ABSSSI compared with a regimen of vancomycin/aztreonam in 2 RCTs
- Higher clinical response rates at Day 3?!?
  - FDA wants inclusion of this endpoint in all ABSSSI & CABP RCTs
  - Was vancomycin dosing (1 g IV q 12 hours) not optimal as "one-size fits all" in RCTs?

U.S. Department of Health and Human Services. Guidance for industry. Acute bacterial skin and skin structure infections: developing drugs for treatment. January 2014 (URL in ref list).; Friedland HD, et al. *Antimicrob Agents Chemother.* 2012; 56(5):2231-6.

Formulary Considerations - Ceftaroline?

- "Non-inferior" for CABP in 2 RCTs
  - Compared ceftaroline 600 mg IV q 12 hours with regimen of ceftriaxone 1 g IV daily x 5-7 days
- Higher response rates for *S. pneumoniae*?!?
  - 85.5% vs. 68.6% (n=~70 each arm)
  - Post-hoc sub-group analysis so results underpowered
  - Too few multi-drug resistant strains to evaluate
- Too early to be guideline endorsed for either of FDA-approved indications!

File TM et al. *Clin Infect Dis.* 2010; 51:1395-1405. Shorr AF et al. *Diagn Microbiol Infect Dis.* 2013; 75:298-303.

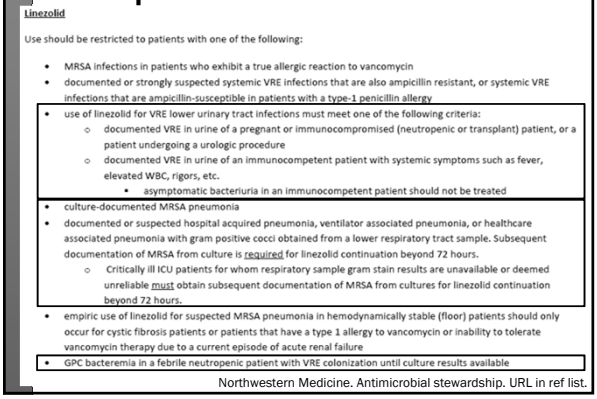
Formulary Considerations - Ceftaroline?

- Pros?
  - Efficacious in RCTs
  - Appears highly effective against pathogens of concern
  - May offer one-drug therapy for mixed infections
  - No therapeutic drug monitoring required
  - Safety data from RCTs are acceptable
  - Better early response rates than alternatives?
- Cons?
  - New drug with limited clinical data/experience
  - Not yet guideline endorsed
  - Only available as IV formulation
  - Expensive compared with generic options
  - Post-marketing safety still being established

Implement Use Restriction Criteria?

- If added to formulary, consider establishing prescribing limitations
  - Use for FDA approved indications only?
  - Use in only specific patient scenarios per institutional policy/protocol?
  - Prescribing only by selected personnel (e.g., ID specialists, intensivists) after consultation?
- Create triggers for automatic pharmacist review for all orders!

Example of Restricted Use Criteria



Linezolid

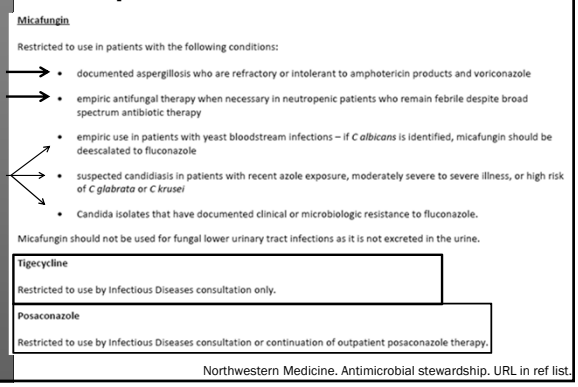
Use should be restricted to patients with one of the following:

- MRSA infections in patients who exhibit a true allergic reaction to vancomycin
- documented or strongly suspected systemic VRE infections that are also ampicillin resistant, or systemic VRE infections that are ampicillin-susceptible in patients with a type-1 penicillin allergy
- use of linezolid for VRE lower urinary tract infections must meet one of the following criteria:
  - documented VRE in urine of a pregnant or immunocompromised (neutropenic or transplant) patient, or a patient undergoing a urologic procedure
  - documented VRE in urine of an immunocompetent patient with systemic symptoms such as fever, elevated WBC, rigors, etc.
    - asymptomatic bacteriuria in an immunocompetent patient should not be treated
- culture-documented MRSA pneumonia
- documented or suspected hospital acquired pneumonia, ventilator associated pneumonia, or healthcare associated pneumonia with gram positive cocci obtained from a lower respiratory tract sample. Subsequent documentation of MRSA from culture is required for linezolid continuation beyond 72 hours.
  - Critically ill ICU patients for whom respiratory sample gram stain results are unavailable or deemed unreliable must obtain subsequent documentation of MRSA from cultures for linezolid continuation beyond 72 hours.
- empiric use of linezolid for suspected MRSA pneumonia in hemodynamically stable (floor) patients should only occur for cystic fibrosis patients or patients that have a type 1 allergy to vancomycin or inability to tolerate vancomycin therapy due to a current episode of acute renal failure
- GPC bacteremia in a febrile neutropenic patient with VRE colonization until culture results available

Northwestern Medicine. Antimicrobial stewardship. URL in ref list.

See enlargement, p. 21

Example of Restricted Use Criteria



Micafungin

Restricted to use in patients with the following conditions:

- documented aspergillosis who are refractory or intolerant to amphotericin products and voriconazole
- empiric antifungal therapy when necessary in neutropenic patients who remain febrile despite broad spectrum antibiotic therapy
- empiric use in patients with yeast bloodstream infections – if *C albicans* is identified, micafungin should be deescalated to fluconazole
- suspected candidiasis in patients with recent azole exposure, moderately severe to severe illness, or high risk of *C glabrata* or *C krusei*
- Candida isolates that have documented clinical or microbiologic resistance to fluconazole.

Micafungin should not be used for fungal lower urinary tract infections as it is not excreted in the urine.

Tigecycline

Restricted to use by Infectious Diseases consultation only.

Posaconazole

Restricted to use by Infectious Diseases consultation or continuation of outpatient posaconazole therapy.

Northwestern Medicine. Antimicrobial stewardship. URL in ref list.

See enlargement, p. 22

Other Antibiotic Stewardship Resources

- Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. (Dellit TH, et al.) *Clin Infect Dis* 2007;44:159–77.
- Centers for Disease Control and Prevention Get Smart for Healthcare campaign (URL in ref list)
- ASHP Advantage antimicrobial stewardship in CABP & ABSSSI initiative (URL in ref list)
- Nebraska Medical Center Antimicrobial Stewardship Program (URL in ref list)
- Northwestern Medicine Antimicrobial Stewardship Program (URL in ref list)
- Antimicrobial Stewardship Certificate programs
  - Society of Infectious Diseases Pharmacists
  - Making a Difference in Infectious Diseases Pharmacotherapy

Conclusion

- Create tools to help facilitate appropriate selection and use of antimicrobials for CABP and ABSSSI to meet CMS requirements
  - Clinical pathways, disease-specific order sets, etc.
- Use stewardship principles to optimize antimicrobial use at your institution
  - Obtain administrative support for AND resources to promote adherence to institutional policies/protocols for use of broad-spectrum and high-cost drugs in treating CABP & ABSSSI
- Consult available resources when help is needed!

What Does CMS Care About?

Set Measure ID#	Measure Short Name
PN-3a	Blood Cultures Performed Within 24 Hours Prior to or 24 Hours After Hospital Arrival for Patients Who Were Transferred or Admitted to the ICU Within 24 Hours of Hospital Arrival
PN-3b	Blood Cultures Performed in the Emergency Department Prior to Initial Antibiotic Received in Hospital
~~PN-5c~~	~~Initial Antibiotic Within 6 hours of Arrival~~
PN-6	Initial Antibiotic Selection for Community-acquired pneumonia (CAP) in Immunocompetent Patient
PN-6a	Initial Antibiotic Selection for CAP in Immunocompetent – ICU Patient
PN-6b	Initial Antibiotic Selection for CAP Immunocompetent – Non ICU Patient

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

Pneumonia ED Order Set Example

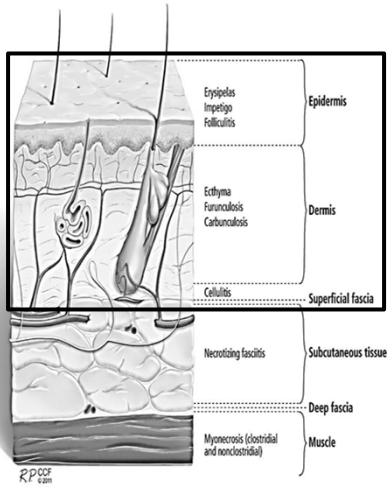
LAB		
If cultures are obtained, they should be collected prior to initiating antibiotics		
Choose Both BC orders for 2 sets		
Blood Culture	Stat, Add On = No	
Blood Culture	Stat, Add On = No	
Respiratory Culture s/Gram Stain	Stat, Once, Specimen type: Sputum	
A viral PCR test should ALWAYS be ordered with a rapid influenza test due to limited sensitivity of the rapid influenza test.		
Influenza Antigen Test, Direct	Stat, Specimen type: Nasopharyngeal	
Influenza A/B & RSV A/B Detection by PCR	Routine, Once, Specimen type: Nasopharyngeal	
The Streptococcal Pneumoniae Antigen test should be ordered in patients with suspected CAP.		
Strept Pneumoniae Antigen Test	Stat, Urine, Once	
Legionella Urine Antigen	Stat, Urine, Once	
CAP - ORAL TREATMENT		
Continue "Z-Pak" for 4 additional days		
azithromycin (Zithromax)	500 mg, DF: Tab, PO, Once	
or moxifloxacin 400 mg daily x 5 days		
moxifloxacin (Avelox)	400 mg, DF: Tab, PO, Once	
CAP - INPATIENT FLOOR ADMISSION		
Choose Both		
ceftriaxone (Rocephin)	1 g, IVPB, Once	Rate: 300 mL/Hr, Infuse Over: 20 Minutes
azithromycin (Zithromax)	500 mg, IVPB, Once	
or		
moxifloxacin (Avelox)	400 mg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes

Pneumonia ED Order Set Example

CAP - ICU ADMISSION		
Choose Both		
ceftriaxone (Rocephin)	2 g, IVPB, Once	Rate: 300 mL/Hr, Infuse Over: 20 Minutes
moxifloxacin (Avelox)	400 mg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes
Alternative to ceftriaxone if Beta-lactam allergy		
vancomycin	15 mg/Kg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes
HEALTH-CARE ASSOCIATED PNEUMONIA (HCAP)		
Choose ALL 4 antibiotics		
cefepime	2g, IVPB, Once	
vancomycin	15 mg/Kg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes
amikacin	15 mg/Kg, IVPB, Once	
azithromycin (Zithromax)	500 mg, IVPB, Once	
Alternative to cefepime if Beta-lactam allergy		
aztreonam (Azactam)	2 g, IVPB, Once	
LUNG ABSCESS		
Choose both amp-sulbactam and vancomycin		
ampicillin-sulbactam (Unasyn)	3 g, IVPB, Once	
vancomycin	15 mg/Kg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes
Choose moxifloxacin for alternative to amp-sulbactam for Beta-lactam allergy		
moxifloxacin (Avelox)	400 mg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes
SEVERE ACUTE EXACERBATION OF COPD		
azithromycin (Zithromax)	500 mg, IVPB, Once	
or		
moxifloxacin (Avelox)	400 mg, IVPB, Once	Rate: 250 mL/Hr, Infuse Over: 60 Minutes
INFLUENZA		
For outpatients, efficacy of treatment is only proven if started within 48 hours of symptom onset (Continue BID for 5 days)		
oseltamivir (Tamiflu)	75 mg, DF: Cap, PO, Once	

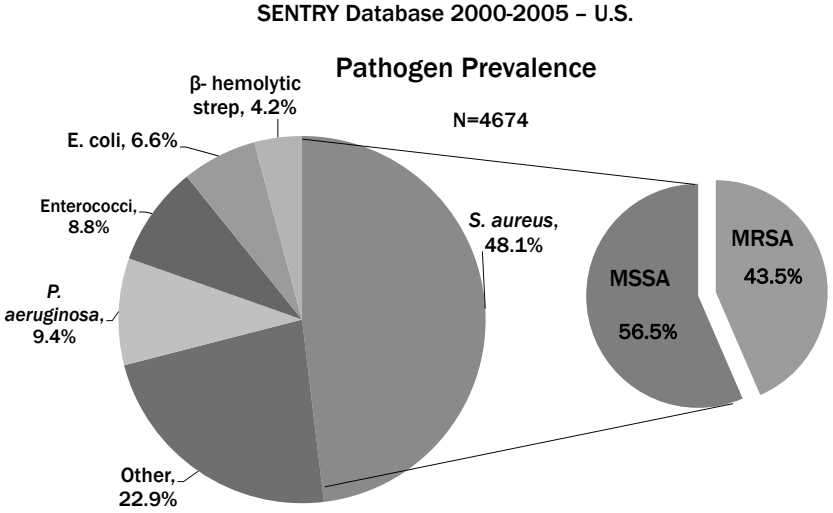
ABSSSI Challenges

- Diagnosis
- Severity of infection
- Antibiotic resistance of targeted pathogens
  - Mostly *Staph, Strep* spp.
- All of the above impact:
  - Necessity, selection, and route of antibiotics!!!



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

Most Common Pathogens in cSSSIs



Slide courtesy of Dr. Neil Davis
Adapted from Sader HS et al. *Int J Antimicrob Agents*. 2007; 30:514-20.

Guideline Recommendations - SSTIs

Indication	Agent	Likely Pathogen(s)	Other Considerations
Erysipelas	β-lactam Clindamycin (β-lactam allergy)	S. pyogenes, other β-hemolytic Strep spp.	PO for outpatient, initial IV for inpatient
Cutaneous abscess (furuncle, carbuncle)	None following incision and drainage*	S. aureus	Decolonize with mupirocin for recurrence
Cellulitis (non-purulent)	B-lactam Clindamycin Linezolid B-lactam + either TMP/SMX or Doxycycline/ Minocycline	S. pyogenes, other β-hemolytic Strep spp., MSSA? Role of CA-MRSA unknown	Rarely yields culture. Consider CA-MRSA coverage for non-response to B-lactam or systemic symptoms
Cellulitis (purulent or trauma-related)	Clindamycin TMP/SMX Doxycycline/Minocycline Linezolid	S. aureus	Coverage of B-hem Strep spp. not guideline recommended
Complicated soft-tissue infection requiring hospitalization	Vancomycin Linezolid Daptomycin Clindamycin Telavancin	S. aureus and all β-hemolytic Strep spp.	IV therapy recommended initially

* Consider treatment for multiple sites, rapid spreading, systemic symptoms, comorbidities or immunosuppression, age extremes, difficult to drain, non-response to drainage

Stevens, et al. *Clin Infect Dis*. 2005;41:1373-1406; Liu, et al. *Clin Infect Dis*. 2011;52:e18-55

Empiric Recommendations/ Clinical Pathway - Skin

Anatomic site /diagnosis	Common Pathogens	Preferred therapy	Alternative**	Comments
Septic shock--post splenectomy	*S. pneumoniae, N. meningitidis, H. influenzae*, Capnocytophaga	Ceftriaxone + vancomycin	Moxifloxacin + vancomycin	
Toxic shock syndrome	S. aureus (MSSA and MRSA), group A streptococci	vancomycin + clindamycin + penicillin G		Strongly recommend surgical evaluation and infectious diseases evaluation
SKIN				
Bite--animal	*Pasteurella multocida*, Fusobacterium, Capnocytophaga (dog bite)	amoxicillin-clavulanate	ciprofloxacin + clindamycin	More specific therapy depends upon animal involved Evaluate the need for tetanus and/or rabies vaccination
Bite--human	Viridans streptococci, *S. epidermidis*, Corynebacterium, *S. aureus*, Eikenella, bacteroides, peptostreptococci	amoxicillin-clavulanate	ciprofloxacin + clindamycin	
Boils (furunculosis)	*S. aureus* (MSSA and MRSA)	Antibiotic therapy only if associated cellulitis: trimethoprim-sulfamethoxazole or clindamycin	minocycline +/- rifampin	Hot packs, incision and drainage primary therapy; Note: clindamycin resistance is present in > 50% of MRSA isolates. See IDSA guidelines for SSTIs, http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Skin%20and%20Soft%20Tissue.pdf
Cellulitis	Group A streptococcus, Group B, C, G streptococcus, *S. aureus* uncommon	cefazolin	clindamycin	See IDSA guidelines for SSTIs, http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Skin%20and%20Soft%20Tissue.pdf.
	Cellulitis with purulent exudates or at risk for MRSA	vancomycin	clindamycin or trimethoprim-sulfamethoxazole	See IDSA guidelines for MRSA infections, http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/MRSA.pdf

** - Alternative column offers options for type-1 beta-lactam allergic patients where evidence exists, unless otherwise noted. If no alternative is listed, consultation with an ID specialist is recommended.

Northwestern Medicine. Antimicrobial stewardship. URL in ref list.

Empiric Recommendations/ Clinical Pathway - Skin

Anatomic site /diagnosis	Common Pathogens	Preferred therapy	Alternative**	Comments
Cellulitis--IV catheter-related	Coagulase-negative staphylococci, *S. aureus* (MSSA and MRSA)	vancomycin		Remove catheter
Decubitus ulcer	Streptococci, enterococci, Enterobacteriaceae, Pseudomonas, bacteroides, *S. aureus* (MSSA and MRSA)	vancomycin + piperacillin/tazobactam		Consider wound care alone (no antibiotic therapy) with no signs of systemic illness, soft tissue abscess, or local cellulitis. With exposed bone, obtain bone biopsy prior to administering antimicrobials to guide therapy.
Diabetic foot ulcer without evidence of infection or exposed bone	skin flora			No antibiotic therapy necessary
Diabetic foot ulcer--mild; small only skin, no inflammation, pulses present	Polymicrobial: *S. aureus* (MSSA and MRSA), streptococci, coliforms, anaerobes, Pseudomonas	amoxicillin-clavulanate	trimethoprim-sulfamethoxazole	See IDSA guidelines for diabetic foot infections, http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Diabetic%20Foot%20Infection.pdf
Diabetic foot ulcer--severe; limb-threatening, skin, subcutaneous, possibly bone, inflammation, fever, neutrophilia		piperacillin/tazobactam +/- vancomycin	clindamycin + ciprofloxacin	Send tissue specimen (bone preferable) for culture prior to starting empiric therapy. See IDSA guidelines for diabetic foot infections, http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Diabetic%20Foot%20Infection.pdf
Infected wound--post operative	Surgery not involving GI tract: *S. aureus* (MSSA and MRSA), group A, B, C, or G streptococci	vancomycin	clindamycin	
	Surgery involving GI tract: *S. aureus* (MSSA and MRSA), coliforms, bacteroides	vancomycin + piperacillin-tazobactam		

Northwestern Medicine. Antimicrobial stewardship. URL in ref list.

Comparison of select clinical characteristics and outcomes of patients treated with two different doses of TMP/SMX.

Clinical parameter	Result for TMP/SMX twice-daily dose of:		Odds ratio	95% confidence interval	P value
	160/800 mg (n = 170)	320/1600 mg (n = 121)			
Median (range) wt (kg)	77 (44.5-156)	86 (42-141)			0.553
Median (range) BMI (kg/m^2)	28 (16.8-54)	30 (18-58.8)			0.454
No. (%) Abscess	135 (79.4)	102 (84.3)	1.39	0.75–2.57	0.291
No. (%) Receipt of incision and drainage	82 (48.2)	77 (63.6)	1.88	1.17–3.03	0.009
No. (%) with clinical resolution	127 (74.7)	88 (72.7)	0.90	0.53–1.53	0.705

Cadena J, et al. *Antimicrob Agents Chemother.* 2011 Dec;55(12):5430-2.

Treatment Success Rates Among Patients Treated with Cephalexin, TMP/SMX, and Clindamycin

Characteristic	Cephalexin (n=180)	TMP/SMX (n=152)	Clindamycin (n=40)	p Value
All patients	134 (74%)	138 (91%)	34 (85%)	<0.001*
Obese	67/99 (68%)	65/74 (88%)	19/21 (90%)	0.02*
Moderate severity	21/43 (49%)	45/56 (80%)	9/10 (90%)	0.001*
MRSA positive	6/25 (24%)	36/40 (90%)	5/6 (83%)	<0.001*

*p values displayed represent analysis of cephalexin vs. TMP/SMX (trimethoprim/sulfamethoxazole)

Logistic Regression Analysis of Risk Factors for Treatment Failure

Risk Factor	Adjusted OR (95% CI)	p Value
Therapy not MRSA active	4.22 (2.25-7.92)	<0.001
Severity of cellulitis	3.74 (2.06-6.79)	<0.001
Upper extremity cellulitis	2.06 (1.06-4.01)	0.03
Lack of drainage if abscess	4.38 (1.91-10.05)	<0.001

Khawcharoenporn T, Tice A. *Am J Med.* 2010 Oct;123(10):942-50.

Pregnancy Categories - MRSA Treatments

Agent	Category	Comments
Clindamycin	B	Endorsed for purulent and non-purulent cellulitis, and cSSTI. Association with C. difficile
Daptomycin	B	Only indicated for cSSTI. Safety not established in children.
Linezolid	C	Side effects include reversible myelosuppression and partially or non-reversible neuropathies with prolonged use (>2 weeks)
Quinupristin-dalfopristin	B	Limited by side effects including severe infusion reactions
Telavancin	C	Indicated for cSSTI. Teratogenic in animals, high incidence of nephrotoxicity in initial studies
Tetracyclines	D	Teratogenic
Trimethoprim/ sulfamethoxazole	C/D*	OK for purulent cellulitis. Lacks adequate strep coverage. Not recommended for 3rd trimester or children <2 months of age
Vancomycin	C	Historical mainstay for most MRSA infections where IV therapy is indicated.
Ceftaroline	B	Newer agent (2012) so not in guidelines. Indicated for ABSSSI but limited data. Most beta-lactams very safe in pregnancy!

*During 3rd trimester

Stevens, et al. *Clin Infect Dis*. 2005;41:1373-1406; Liu, et al. *Clin Infect Dis*. 2011;52:e18-55

Supported Indications – Topical Agents

Indication	Topical Agent(s)	Level of Evidence
Pediatric minor skin infections (impetigo, cuts)	Mupirocin 2% topical ointment	A-III
Neonatal pustulosis	Mupirocin 2% topical ointment	A-III
Decolonization for: Recurrent infection despite wound care/hygiene and/or Ongoing transmission among household or close contacts (symptomatic and asymptomatic)	Nasal Mupirocin 2% ointment BID x 5-10 days and Chlorhexidine skin solution BID for 5-14 days or dilute bleach solution bath for 15 min twice weekly for ~3 months	C-III *Oral antimicrobials are not recommended for decolonization

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

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.

Example of Restricted Use Criteria

Linezolid

Use should be restricted to patients with one of the following:

- MRSA infections in patients who exhibit a true allergic reaction to vancomycin
- documented or strongly suspected systemic VRE infections that are also ampicillin resistant, or systemic VRE infections that are ampicillin-susceptible in patients with a type-1 penicillin allergy
- use of linezolid for VRE lower urinary tract infections must meet one of the following criteria:
  - documented VRE in urine of a pregnant or immunocompromised (neutropenic or transplant) patient, or a patient undergoing a urologic procedure
  - documented VRE in urine of an immunocompetent patient with systemic symptoms such as fever, elevated WBC, rigors, etc.
    - asymptomatic bacteriuria in an immunocompetent patient should not be treated
- culture-documented MRSA pneumonia
- documented or suspected hospital acquired pneumonia, ventilator associated pneumonia, or healthcare associated pneumonia with gram positive cocci obtained from a lower respiratory tract sample. Subsequent documentation of MRSA from culture is required for linezolid continuation beyond 72 hours.
  - Critically ill ICU patients for whom respiratory sample gram stain results are unavailable or deemed unreliable must obtain subsequent documentation of MRSA from cultures for linezolid continuation beyond 72 hours.
- empiric use of linezolid for suspected MRSA pneumonia in hemodynamically stable (floor) patients should only occur for cystic fibrosis patients or patients that have a type 1 allergy to vancomycin or inability to tolerate vancomycin therapy due to a current episode of acute renal failure
- GPC bacteremia in a febrile neutropenic patient with VRE colonization until culture results available

Northwestern Medicine. Antimicrobial stewardship. URL in ref list.

Example of Restricted Use Criteria

Micafungin

Restricted to use in patients with the following conditions:

- documented aspergillosis who are refractory or intolerant to amphotericin products and voriconazole
- empiric antifungal therapy when necessary in neutropenic patients who remain febrile despite broad spectrum antibiotic therapy
- empiric use in patients with yeast bloodstream infections – if *C albicans* is identified, micafungin should be deescalated to fluconazole
- suspected candidiasis in patients with recent azole exposure, moderately severe to severe illness, or high risk of *C glabrata* or *C krusei*
- Candida isolates that have documented clinical or microbiologic resistance to fluconazole.

Micafungin should not be used for fungal lower urinary tract infections as it is not excreted in the urine.

Tigecycline

Restricted to use by Infectious Diseases consultation only.

Posaconazole

Restricted to use by Infectious Diseases consultation or continuation of outpatient posaconazole therapy.

Northwestern Medicine. Antimicrobial stewardship. URL in ref list.

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Other Resources

ASHP Advantage Applying Antimicrobial Stewardship Principles to the Treatment of CABP and ABSSSI initiative (http://www.ashpadvantagemedia.com/id/)

Centers for Disease Control and Prevention Get Smart for Healthcare campaign (http://www.cdc.gov/getsmart/healthcare/)

Nebraska Medical Center antimicrobial stewardship program (http://www.nebraskamed.com/careers/education-programs/asp)

Northwestern Medicine. Antimicrobial stewardship program. http://asp.northwesternmedicine.org/ (website under construction).

Antimicrobial Stewardship Certificate Programs

Society of Infectious Diseases Pharmacists (http://www.sidp.org/Default.aspx?pageId=1442823)

Making a Difference in Infectious Diseases Pharmacotherapy (http://mad-id.org/antimicrobial-stewardship-programs/)

Self-assessment Questions

1. Which of the following is no longer assessed by the Centers for Medicare & Medicaid Services in evaluating hospital care provided to patients with community-acquired pneumonia?
   a. Initial antibiotic within 6 hours of arrival
   b. Initial antibiotic selection in immunocompetent patients
   c. Initial antibiotic selection in immunocompetent ICU patients
   d. Initial antibiotic selection in immunocompetent non-ICU patients

2. Which of the following is the most common pathogen in patients with complicated skin and soft tissue infection?
   a. Beta-hemolytic streptococci
   b. *Pseudomonas aeruginosa*
   c. *Staphylococcus aureus*
   d. *Streptococcus pneumoniae*

3. Which of the following is recommended for a non-pregnant woman with recurrent skin and soft tissue infection caused by methicillin-resistant *Staphylococcus aureus* despite wound care and hygiene measures?
   a. Dilute bleach solution baths and oral trimethoprim-sulfamethoxazole
   b. Mupirocin 2% nasal ointment and chlorhexidine topical solution
   c. Oral clindamycin and mupirocin 2% topical ointment
   d. Intravenous vancomycin and mupirocin 2% topical ointment

Answers

1. a
2. c
3. b

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   Please record the Enrollment Code in the grid below for your records.

4. The title of this activity should now appear in a pop-up box on your screen. Click on the **Go** button or the **activity title.**

5. Complete all required elements. A green ✔ should appear as each required element is completed. You can now claim your credit.

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