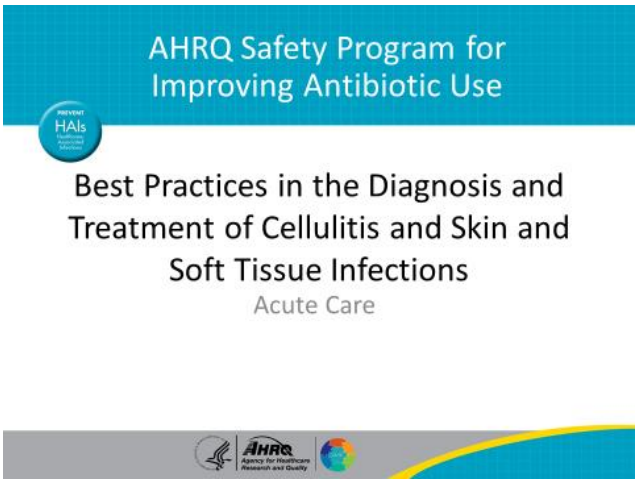
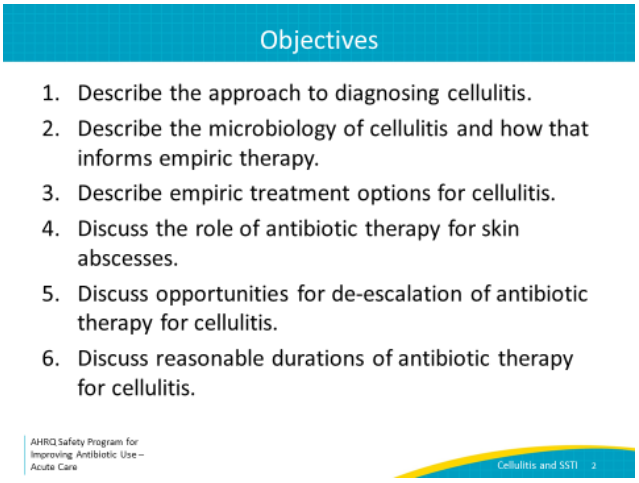
Best Practices in the Diagnosis and Treatment of Cellulitis and Skin and Soft Tissue Infections

Acute Care

Slide Title and Commentary	Slide Number and Slide
Best Practices in the Diagnosis and Treatment of Cellulitis and Skin and Soft Tissue Infections **Acute Care** SAY: This presentation will address best practices in the diagnosis and treatment of cellulitis and skin and soft tissue infections.	**Slide 1** 
Objectives SAY: By the end of this presentation, participants will be able to— • Describe the approach to diagnosing cellulitis • Describe the microbiology of cellulitis and how that informs empiric therapy • Describe empiric treatment options for cellulitis • Discuss the role of antibiotic therapy for skin abscesses • Discuss opportunities for de-escalation of antibiotic therapy for cellulitis • Discuss reasonable durations of antibiotic therapy for cellulitis	**Slide 2** 

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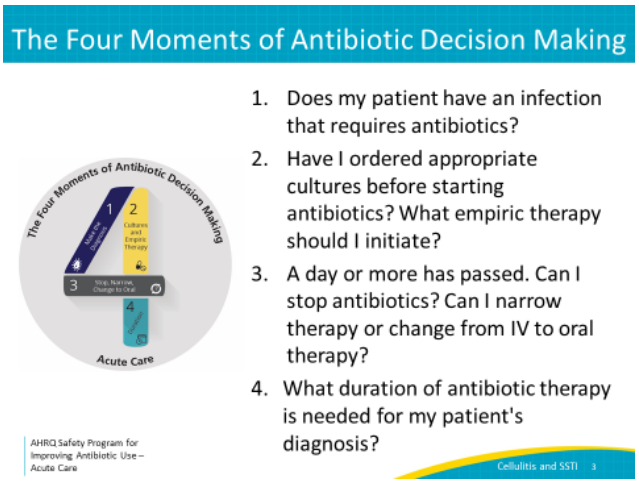
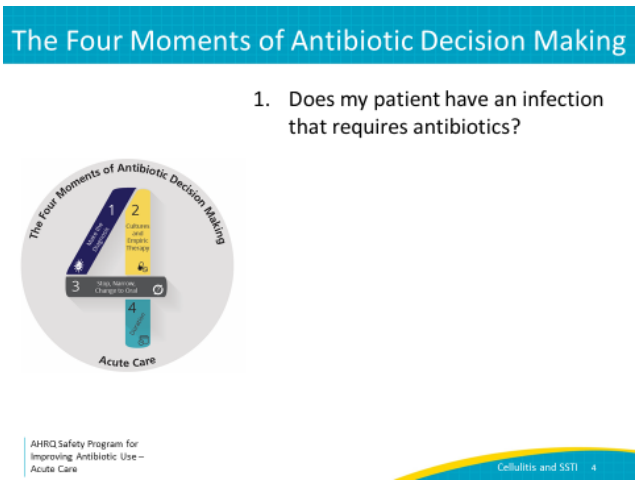
The Four Moments of Antibiotic Decision Making SAY: As we discuss cellulitis and skin and soft tissue infections, we will use the Four Moments of Antibiotic Decision Making framework. As a reminder, Moment 1 asks: Does my patient have an infection that requires antibiotics? Moment 2 consists of two questions and asks: Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate? Moment 3 consists of three questions and asks: A day or more has passed since initiating antibiotics. As I have more clinical and microbiologic data available can I stop antibiotics, can I narrow antibiotics, or can I change from intravenous to oral antibiotics? And finally, Moment 4 asks: What duration of therapy is needed for my patient's diagnosis?	**Slide 3** 
The Four Moments of Antibiotic Decision Making SAY: Moment one is: Does my patient have an infection that requires antibiotics?	**Slide 4** 

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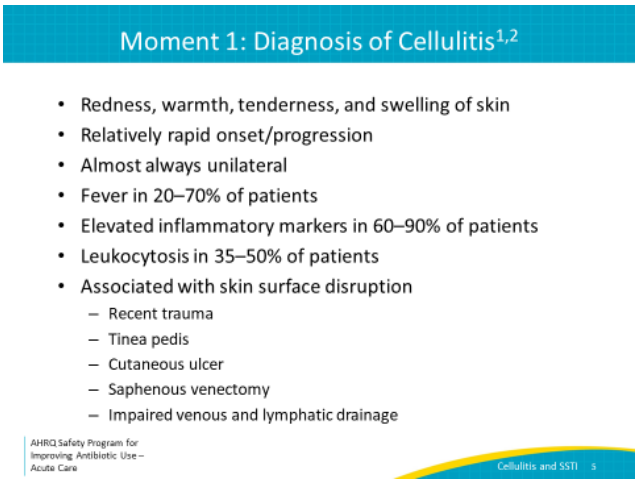
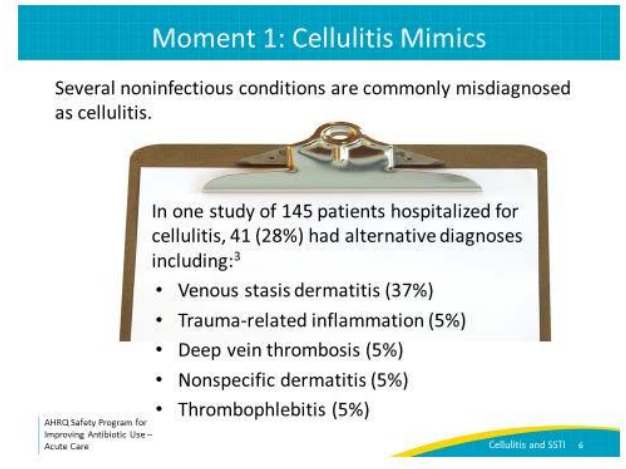
Moment 1: Diagnosis of Cellulitis SAY: Patients with cellulitis present with redness, warmth, tenderness, and swelling of the skin with relatively sudden onset. Cellulitis is almost always unilateral; patients who have bilateral skin findings more likely have chronic venous stasis than infection. Fever is seen in 20–70 percent of patients before or upon presentation, 60–90 percent of patients have elevated inflammatory markers, and 35–50 percent of patients have leukocytosis. Development of cellulitis is generally associated with skin surface disruption due to recent trauma, tinea pedis, cutaneous ulcers, or past saphenous venectomy. In addition, impaired venous and lymphatic drainage can predispose to cellulitis.	**Slide 5** 
Moment 1: Cellulitis Mimics SAY: Several noninfectious conditions can be confused with cellulitis. In one study of 145 patients hospitalized for presumed cellulitis, 41 (28%) had an alternative diagnosis. These included venous stasis dermatitis (37%), trauma-related inflammation (5%), deep vein thrombosis (5%) nonspecific dermatitis, and (5%), thrombophlebitis (5%).	**Slide 6** 

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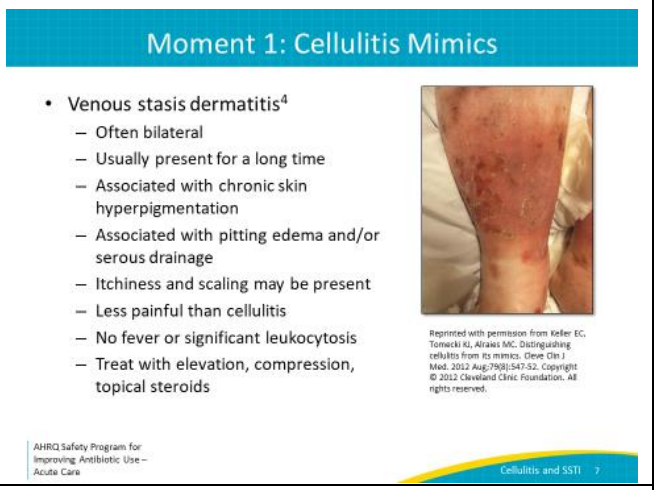
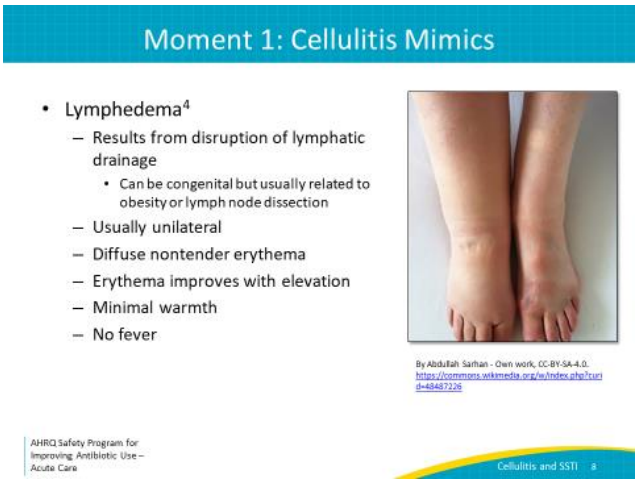
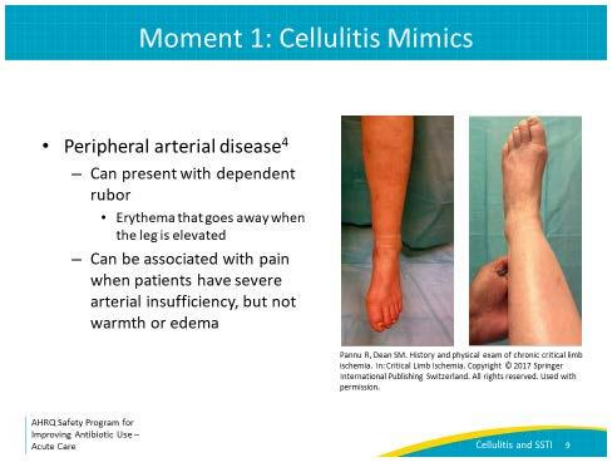
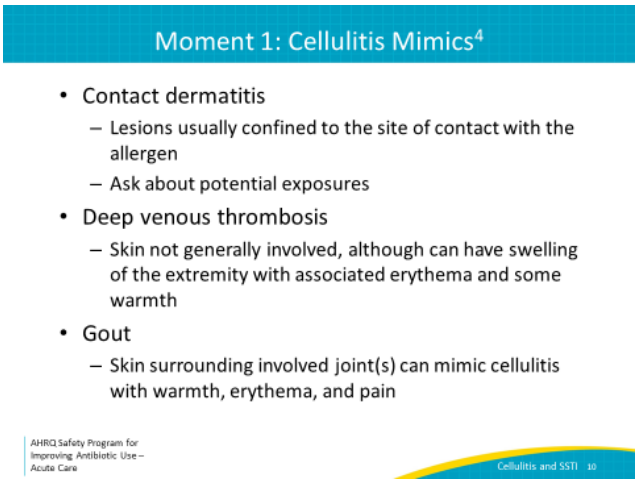
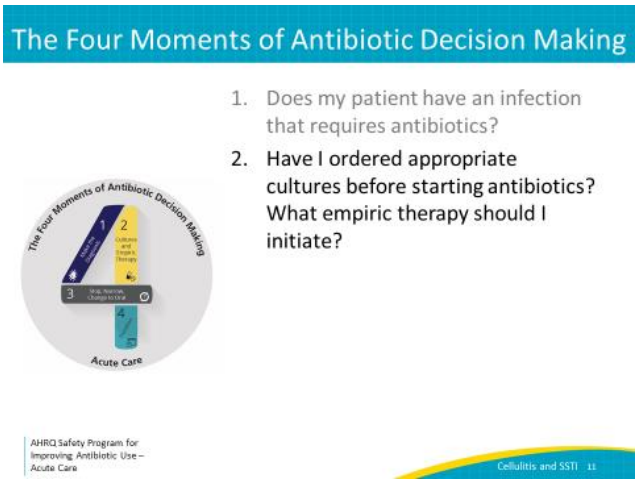
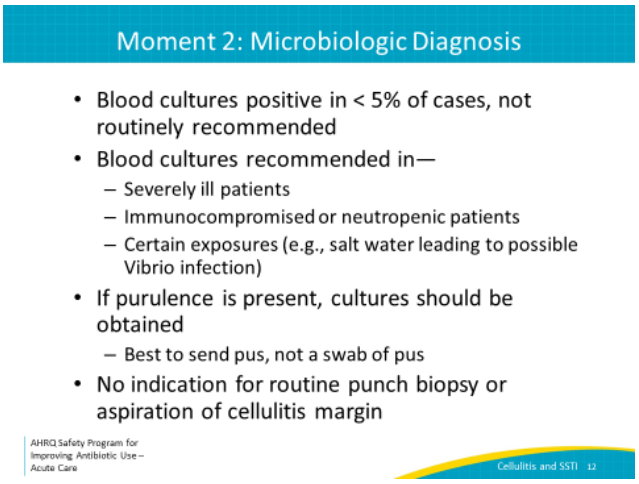
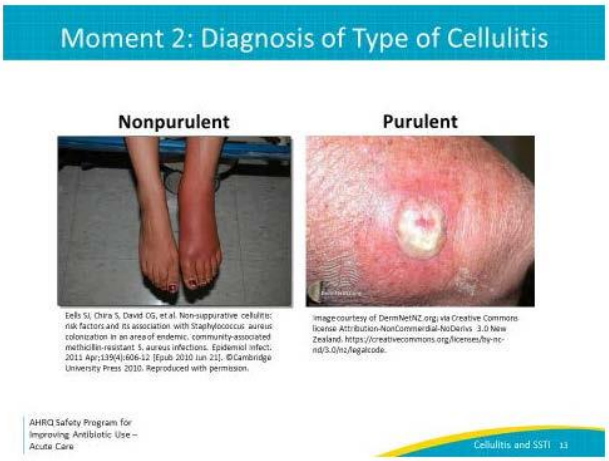
Moment 1: Cellulitis Mimics SAY: Venous stasis dermatitis can be distinguished from cellulitis in several ways. It is often bilateral; usually present for a long period of time; and associated with chronic skin hyperpigmentation, itchiness, scaling, pitting edema, and/or serous drainage. Patients may have pain, but it is less intense than with cellulitis and should not be associated with fever or significant leukocytosis. Venous stasis dermatitis can be treated with elevation of the extremity, compression, and topical steroids.	**Slide 7** 
Moment 1: Cellulitis Mimics SAY: Lymphedema results from disruption of lymphatic drainage. It can be congenital but is usually related to obesity or lymph node dissection. It is usually unilateral (distal to the lymphatic disruption) and associated with diffuse nontender erythema that improves with elevation. There is minimal associated warmth. Fevers should not be present. Both venous stasis and lymphedema can predispose to cellulitis so the history and physical exam is important. Ask if there has been an acute change in symptoms that suggests a new process, new fever, or increased warmth, tenderness and erythema. Examine the extremity for evidence of new superficial cutaneous edema and/or shiny and smooth skin. These symptoms and signs suggest cellulitis.	**Slide 8** 

Slide Title and Commentary	Slide Number and Slide
Moment 1: Cellulitis Mimics SAY: Patients with peripheral arterial disease can present with dependent rubor, defined as erythema that can be bright or dusky red that goes away when the leg is elevated. Dependent rubor can be associated with pain when patients have severe arterial insufficiency, but is not associated with warmth or edema.	**Slide 9** 
Moment 1: Cellulitis Mimics Other noninfectious syndromes that can be confused with cellulitis are listed on this slide. Patients with contact dermatitis can have lesions that looks like cellulitis, but lesions are confined to the site of contact with the allergen. Patients will often be able to identify potential exposures such as bandages or lotions. The skin is generally not involved in patients with deep venous thrombosis, although they can have swelling of the extremity with associated erythema and some warmth. The skin surrounding the affected joint(s) in patients with gout can mimic cellulitis with warmth, erythema, and pain.	**Slide 10** 

Slide Title and Commentary	Slide Number and Slide
The Four Moments of Antibiotic Decision Making SAY: Moment two is: Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate?	**Slide 11** 
Moment 2: Microbiologic Diagnosis SAY: In patients with cellulitis, blood cultures are positive in less than 5 percent of cases and thus not routinely recommended. Blood cultures should be obtained in severely ill patients, immunocompromised or neutropenic patients, and patients with certain exposures (for example, salt water leading to possible *Vibrio* infection). Wound cultures should be obtained if purulence is present. It is best to send the actual pus, not a swab of pus, so that a Gram stain can be performed and to optimize the yield of cultures. There is no indication for aspiration of the cellulitis margin. Punch biopsy can be considered for unusual skin findings particularly in immunocompromised hosts but not for routine cellulitis cases.	**Slide 12** 

Slide Title and Commentary	Slide Number and Slide
Moment 2: Diagnosis of Type of Cellulitis SAY: It is important to assess whether the patient has nonpurulent cellulitis, in which there <u>is no</u> evidence of fluid collection, phlegmon or abscess OR purulent cellulitis in which there <u>is</u> evidence of a fluid collection, phlegmon, or abscess associated with the cellulitis.	**Slide 13** 

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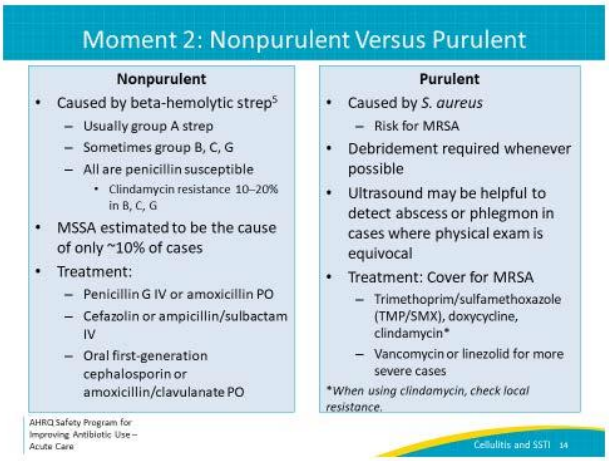
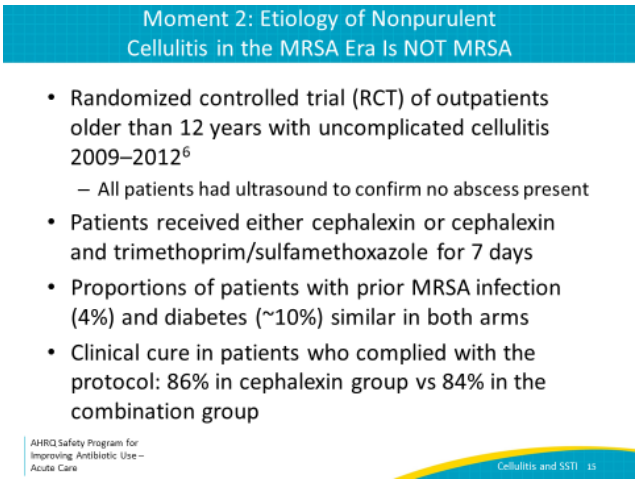
Moment 2: Purulent Versus Nonpurulent SAY: The microbiologic etiology of cellulitis can be predicted by the type of cellulitis. Nonpurulent cellulitis is primarily caused by beta-hemolytic strep—usually group A streptococcus, but sometimes group B, C, or G streptococcus. All beta-hemolytic streptococci are penicillin susceptible; however, clindamycin resistance occurs in 10–20 percent of B, C, and G streptococcal infections. Methicillin-susceptible *Streptococcus aureus* or MSSA is estimated to be the cause of nonpurulent cellulitis in only about 10 percent of cases. Because MSSA is such an uncommon cause of nonpurulent cellulitis, some treat these infections with regimens that do not cover *S. aureus* such as intravenous or IV penicillin if they require IV therapy, or oral amoxicillin. In the United States, many clinicians elect to cover for MSSA using IV cefazolin or ampicillin/sulbactam, or an oral first-generation cephalosporin or amoxicillin/clavulanate. Purulent cellulitis is primarily caused by *S. aureus*, including MRSA. Debridement of any associated abscess should occur whenever possible; ultrasound may be helpful to detect abscess or phlegmon in cases where physical exam is equivocal. Empiric treatment should include coverage for MRSA. Oral options include trimethoprim/sulfamethoxazole, doxycycline, and clindamycin, although if using clindamycin it is important to assess local susceptibility data given recent large increases in resistance in many areas. More severe cases should be treated with IV therapy such as vancomycin or linezolid. It is important to use linezolid judiciously to prevent increases in resistance, particularly now that it is more accessible from a cost standpoint.	**Slide 14** 

Slide Title and Commentary	Slide Number and Slide
Moment 2: Etiology of Nonpurulent Cellulitis in the MRSA Era Is NOT MRSA SAY: A common clinical concern is whether nonpurulent cellulitis is caused by MRSA, given the increase in MRSA skin and soft tissue infections seen in the early 2000s. A 2017 randomized controlled trial in 500 outpatients older than 12 years with uncomplicated, nonpurulent cellulitis compared a regimen without MRSA activity to one with MRSA activity. Patients received either cephalexin or cephalexin and trimethoprim/sulfamethoxazole for 7 days. All patients had ultrasounds of the lesion to confirm no abscess was present. The proportions of patients with prior MRSA infection (4%) and diabetes (~10%) were comparable in both arms. Clinical cure rates in patients who complied with the protocol were similar: 86 percent in the cephalexin only group versus 84 percent in the cephalexin plus trim/sulfa group. The finding that clinical cure was high with therapy directed only at beta-hemolytic strep and MSSA, and that additional MRSA coverage offered no benefit, is highly suggestive that the addition of MRSA coverage is not needed in patients with nonpurulent cellulitis.	**Slide 15** 

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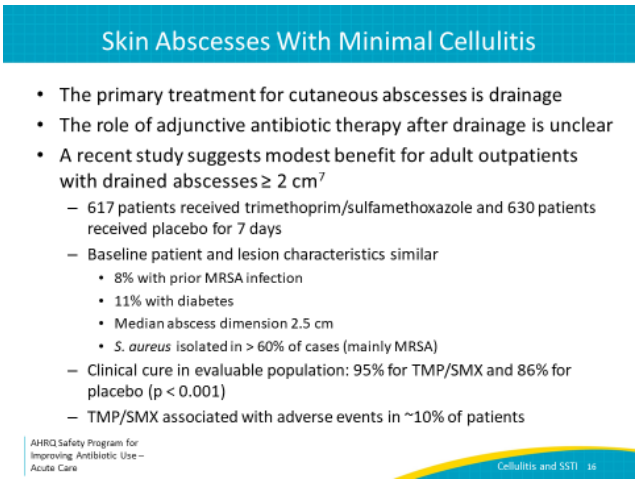
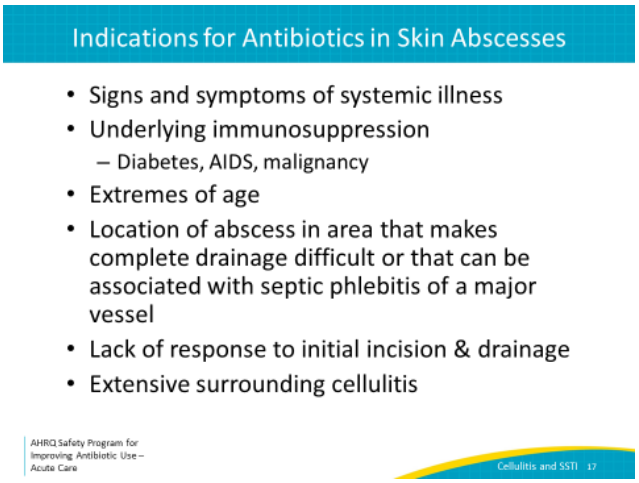
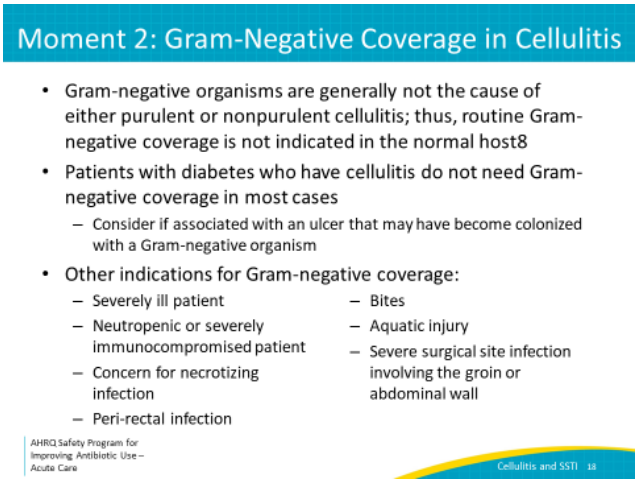
Skin Abscesses With Minimal Cellulitis SAY: Another clinical concern is the role of antibiotics in treatment of skin abscesses with minimal associated cellulitis. The primary treatment for cutaneous abscesses is drainage, and the role of adjunctive antibiotic therapy after drainage has been uncertain. A recent study suggests a modest benefit of antibiotic therapy for adult outpatients with drained abscesses at least 2 cm in diameter. In the study, 617 patients received trimethoprim/sulfamethoxazole and 630 patients received placebo for 7 days. Baseline patient and lesion characteristics were similar—8 percent had prior methicillin-resistant *S. aureus* or MRSA infection, 11 percent had diabetes, the median abscess diameter was 2.5 cm, and *S. aureus was* isolated in more than 60 percent of cases (predominantly MRSA). Clinical cure in the evaluable population was 95 percent for trim/sulfa and 86 percent for placebo with a p-value of < 0.001. However, trim/sulfa was associated with adverse events in approximately 10 percent of patients. Overall, clinical cure was high in both groups. Clinicians should weigh the higher proportion of cure with antibiotics with the potential for antibiotic side effects when making the decision about prescribing antibiotics for patients with uncomplicated skin abscesses.	**Slide 16** 

Slide Title and Commentary	Slide Number and Slide
Indications for Antibiotics in Skin Abscesses SAY: There are certain patients and conditions in which antibiotics should be strongly considered in patients with skin abscesses. These include patients with signs and symptoms of systemic illness; underlying immunosuppression, including diabetes, AIDS, and active malignancy; extremes of age; location of abscess in areas that makes complete drainage difficult or that can be associated with septic phlebitis of a major vessel; lack of response to initial incision and drainage, or I&D; and more extensive surrounding cellulitis. Note that many patients admitted to the hospital for these infections will meet these criteria.	**Slide 17** 
Moment 2: Gram-Negative Coverage in Cellulitis SAY: Gram-negative organisms are generally not the cause of either purulent or nonpurulent cellulitis; thus, routine Gram-negative coverage is not needed in the normal host with cellulitis. Patients with diabetes who have cellulitis also do not need Gram-negative coverage in most cases. For patients with cellulitis associated with a diabetic ulcer, several publications have shown that Gram-positive organisms are the most common colonizing organisms with the exceptions of longstanding ulcers and/or prior receipt of multiple antibiotic courses. Gram-negative coverage can be considered in these patients. Other indications for Gram-negative coverage include critically ill patients, neutropenic or severely immunocompromised patients, concern for necrotizing infection, peri-rectal infections, bites, cellulitis associated with aquatic injuries, and severe surgical site infections involving the groin or abdominal wall.	**Slide 18** 

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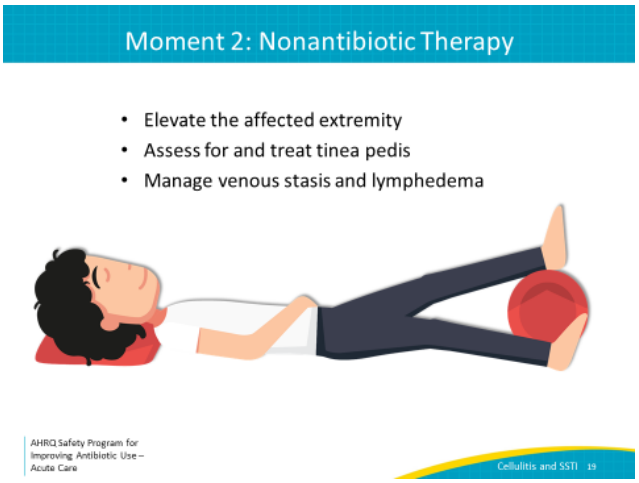
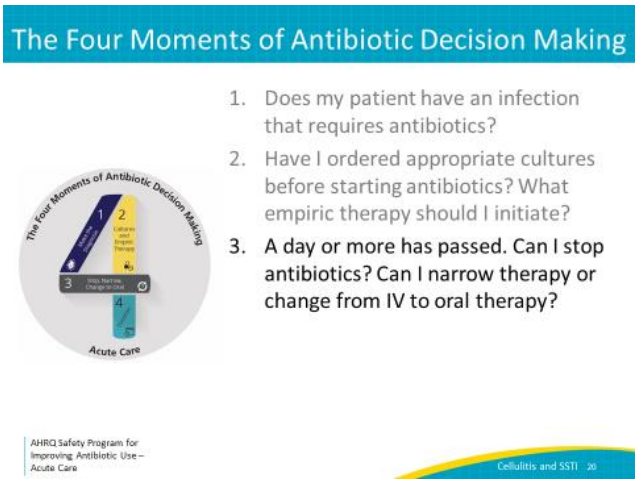
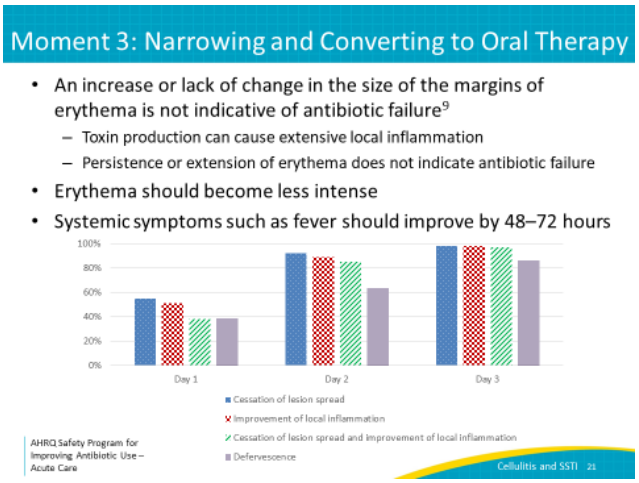
Moment 2: Nonantibiotic Therapy SAY: We often forget that successful treatment of cellulitis requires more than just antibiotics. Most importantly, patients must elevate the affected extremity. In addition, it is important to assess for and treat tinea pedis, if it is found. If the cellulitis is associated with venous stasis or lymphedema, these conditions must be managed at the same time.	**Slide 19** 
The Four Moments of Antibiotic Decision Making SAY: Moment 3 occurs after a day or more has passed. Ask yourself: Can I stop antibiotics? Can I narrow therapy or change from IV to oral therapy?	**Slide 20** 

Slide Title and Commentary	Slide Number and Slide
Moment 3: Narrowing and Converting to Oral Therapy SAY: When deciding whether to narrow or stop therapy for cellulitis, you should assess whether the patient is improving. It is important not to equate an increase or lack of change in the size of margins of erythema after a few doses of antibiotics with antibiotic failure. Toxin production can cause extensive local inflammation, and its persistence or extension over the first 2 days of therapy does not, by itself, indicate antibiotic failure. However, the erythema should become less intense and systemic symptoms such as fever should improve in 48 to72 hours. The graph on the slide shows the results of a study of the natural history of cellulitis on days 1, 2, and 3 of antibiotic therapy (moving left to right). The blue bars show the proportions of patients with cessation of lesion spread. The red bars show improvement in local inflammation. The green bars show both cessation of lesion spread and improvement in inflammation. The purple bars show defervescence. Note that only about half of patients have cessation of lesion spread on day 1 of therapy. This proportion increases to more than 90 percent by day 2–3. Similar findings can be noted for improvement of local inflammation. But, when these variables are combined in the third green bar, overall improvement is generally not seen until day 3 of therapy. Finally, note that many patients remain febrile until day 3.	**Slide 21** 

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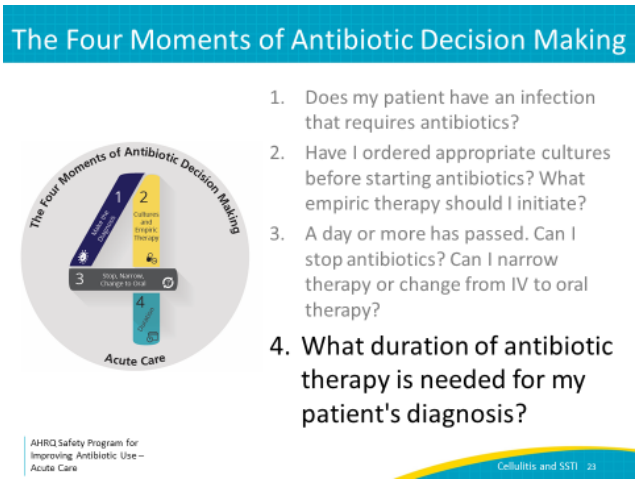
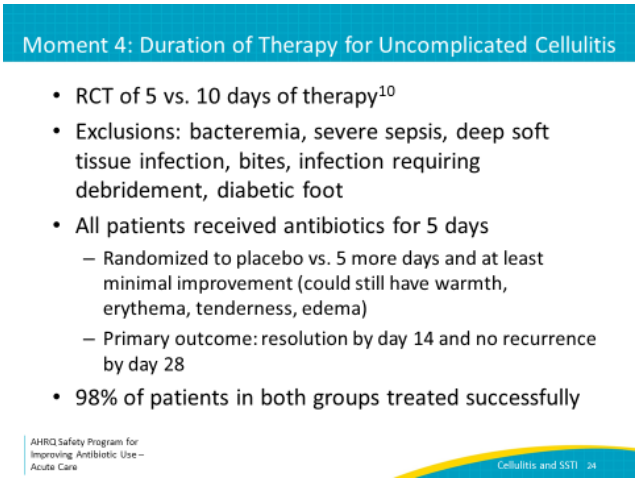
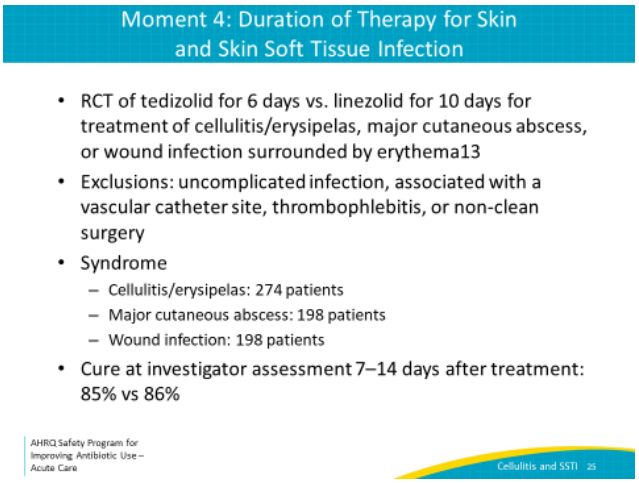
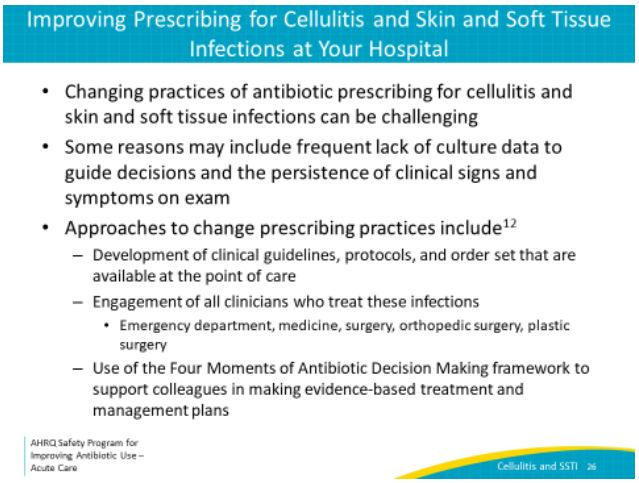
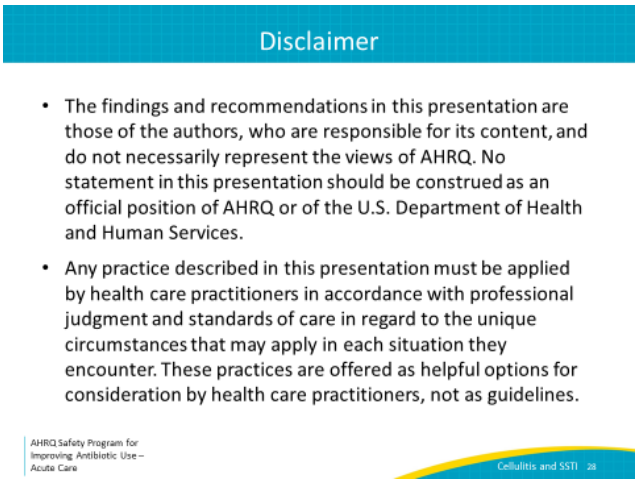
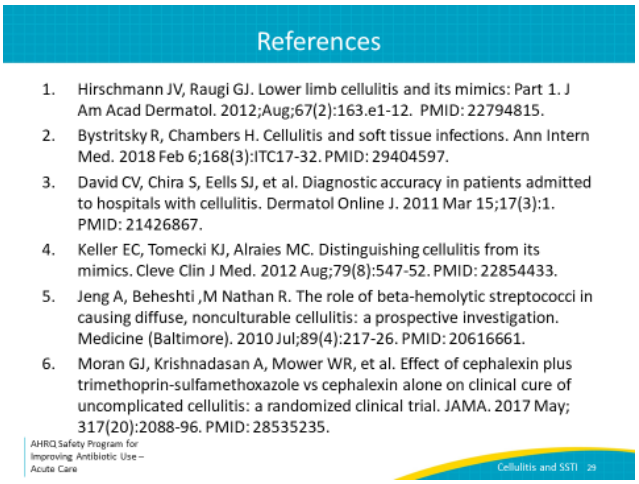
Moment 3: Narrowing and Converting to Oral Therapy SAY: If patients are demonstrating improvement by day 3, most can be converted to oral therapy and have therapy narrowed if initial broad-spectrum therapy was started. For example, therapy specifically directed at Gram-negative organisms can be stopped unless there is evidence of Gram-negative infection. If vancomycin was started, it can usually be switched to an oral agent based on the cellulitis type as described previously. Potential regimens for nonpurulent cellulitis are an oral beta-lactam or, for patients with severe penicillin allergy, clindamycin. For patients with purulent cellulitis and culture data, convert to oral therapy based on these results. For patients without culture data, convert to TMP/SMX or doxycycline. If clindamycin susceptibilities are high in your area or you know that the organism is susceptible, it can be considered as an option for MRSA treatment, although it is more associated with *Clostridioides difficile* infection than other options. Linezolid can be considered for more severe infections but as we discussed previously, widespread use will likely lead to a rise in resistance so it should be used judiciously. You should consider extending IV therapy in obese patients if there is concern that adequate tissue levels cannot be obtained. If a patient is not improving by day 3, it is important to reassess. Consider imaging to assess for a new or persistent abscess and/or a change in antibiotic therapy.	**Slide 22** 

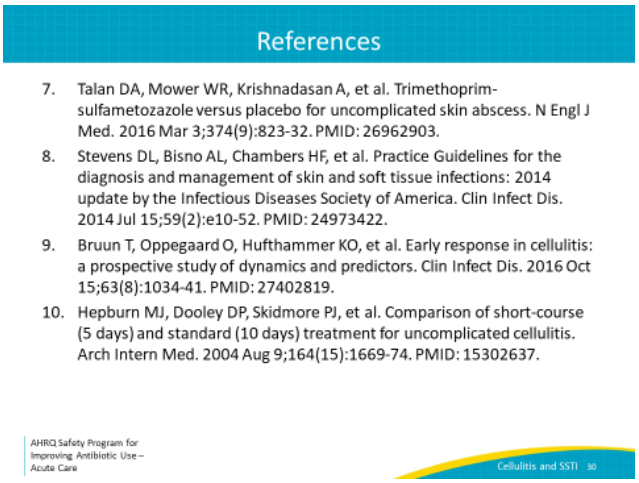
Slide Title and Commentary	Slide Number and Slide
The Four Moments of Antibiotic Decision Making SAY: The last moment you must consider is: What duration of antibiotic therapy is needed for your patient's diagnosis?	**Slide 23** 
Moment 4: Duration of Therapy for Uncomplicated Cellulitis SAY: Most cases of cellulitis can be treated with 5–7 days of antibiotics. This recommendation is supported by evidence from clinical trials showing that shorter course therapy is as effective as longer courses. For example, a randomized controlled trial compared 5 versus 10 days of therapy. Patients with bacteremia, severe sepsis, deep soft tissue infection, bites, infection requiring debridement, or diabetic foot infection were excluded. All patients received antibiotics for 5 days and then were randomized to placebo versus 5 more days of therapy. Of note, patients could still have warmth, erythema, tenderness, and edema at the time of randomization, but it had to be improving. The primary outcome was resolution by day 14 and no recurrence by day 28. Ninety-eight percent of patients in both groups were treated successfully.	**Slide 24** 

Slide Title and Commentary	Slide Number and Slide
Moment 4: Duration of Therapy for Acute Bacterial Skin and Skin Structure Infection SAY: Another randomized controlled trial included patients with more severe infections including cellulitis/erysipelas, major cutaneous abscess, or wound infection surrounded by erythema. Patients received either tedizolid once a day for 6 days or linezolid twice a day for 10 days. Exclusions included uncomplicated infection, associated with a vascular catheter site, thrombophlebitis, or nonclean surgery. Two hundred seventy-four patients had cellulitis/erysipelas, 198 had major cutaneous abscess, and 198 had wound infection with comparable numbers in each arm of the study Cure at investigator assessment 7–14 days after treatment was the same in both groups: 85 percent versus 86 percent. This study is supportive of use of a 5–7 day course of therapy for cellulitis and other skin structure infections with source control. While tedizolid and linezolid were the agents studied, it would be reasonable to extrapolate the findings of this study to patients who receive other agents. Most cases of cellulitis or cutaneous abscesses can be treated with a total of 5–7 days.	**Slide 25** 

Slide Title and Commentary	Slide Number and Slide
Improving Prescribing for Cellulitis and Skin and Soft Tissue Infections at Your Hospital SAY: It is not uncommon for clinicians to prescribe broader-than-necessary antibiotic regimens for longer-than-needed durations for patients with cellulitis and skin and soft tissue infections. These infections often don't have associated culture data to make prescribing decisions easier and, as we have discussed, their physical manifestations such as erythema may take a few days to resolve. We have seen data in this presentation that should provide reassurance to clinicians to modify longstanding prescribing practices. Developing or modifying clinical guidelines for these infections, and making sure guidelines, treatment algorithms, and orders sets are available at the point of care is critical to prompt prescribing changes. Further, it is helpful to expand the discussion of management of cellulitis and skin and soft tissue infections across all disciplines that care for these patients such as the emergency department, medicine, surgery, orthopedic surgery, and plastic surgery. Finally, using the Four Moments of Antibiotic Decision Making framework, support colleagues in making evidence-based decisions about antibiotic and management plans for these infections.	**Slide 26** 

Slide Title and Commentary	Slide Number and Slide
Take-Home Messages SAY: To summarize this discussion, first make the right diagnosis! Cellulitis is generally of sudden onset, unilateral, and associated with significant warmth, erythema, fever, and evidence of inflammation (e.g., elevated WBC and inflammatory markers). Consider mimics of cellulitis before giving antibiotics to all patients with "red" extremities. Distinguish between nonpurulent and purulent cellulitis and treat based on the expected microbiology of these different syndromes. Patients should be improving by day 3 but may have some residual signs and symptoms. Lack of complete resolution does NOT mean that antibiotics are not working. Five- to seven-day courses of therapy work for most cases of cellulitis. There are many opportunities for stewardship in improving empiric therapy for cellulitis and avoiding prolonged courses of therapy. Think about areas for improvement in your practice and in your hospital.	**Slide 27** 

Slide Title and Commentary	Slide Number and Slide
Disclaimer SAY: The findings and recommendations in this presentation are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this presentation should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services. Any practice described in this presentation must be applied by health care practitioners in accordance with professional judgment and standards of care in regard to the unique circumstances that may apply in each situation they encounter. These practices are offered as helpful options for consideration by health care practitioners, not as guidelines.	**Slide 28** 
References	**Slide 29** 

Slide Title and Commentary	Slide Number and Slide
References	**Slide 30** 
References	**Slide 31**