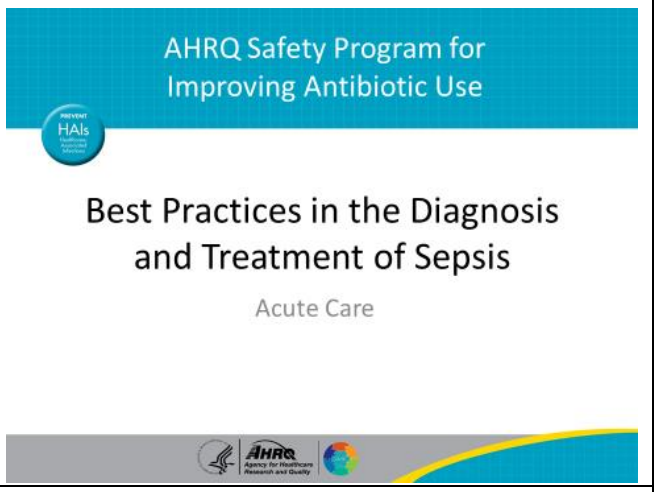
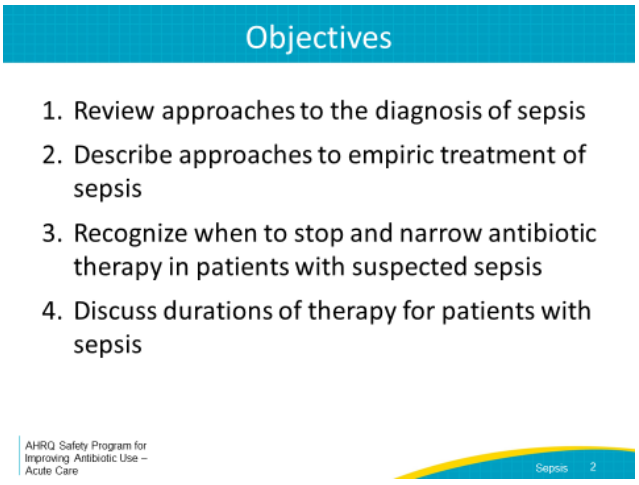
Best Practices in the Diagnosis and Treatment of Sepsis

Acute Care

Slide Title and Commentary	Slide Number and Slide
Best Practices in the Diagnosis and Treatment of Sepsis **Acute Care** SAY: This presentation will address best practices in the diagnosis and treatment of sepsis.	**Slide 1** 
Objectives SAY: The objectives of this presentation are: • Review approaches to the diagnosis of sepsis • Describe approaches to the empiric treatment of sepsis • Recognize when to stop or narrow antibiotic therapy in patients with suspected sepsis • Discuss durations of therapy for patients with sepsis	**Slide 2** 

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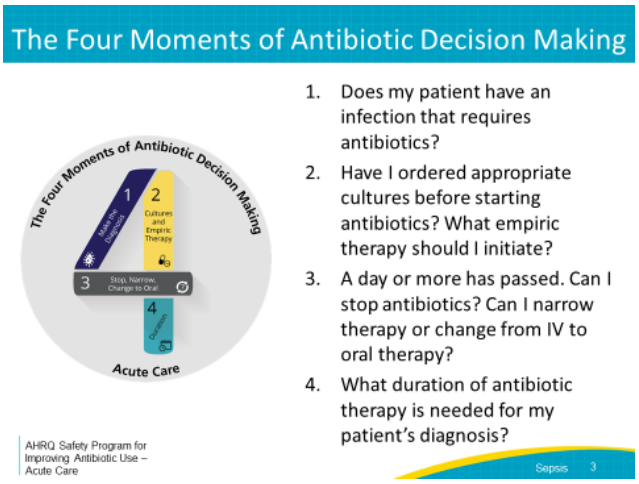
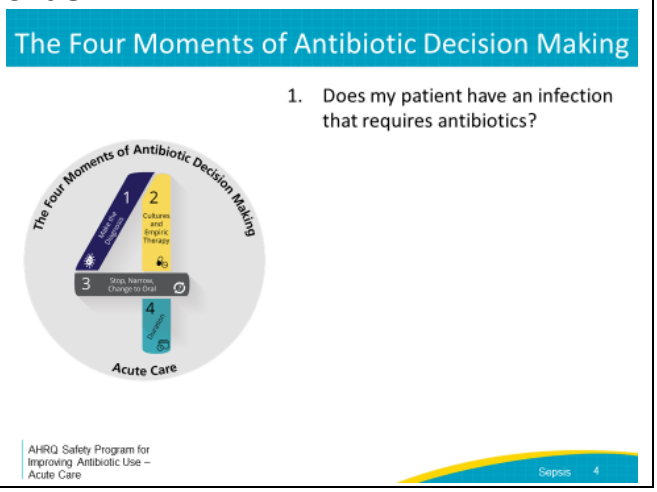
The Four Moments of Antibiotic Decision Making SAY: We will review the diagnosis and management of sepsis using the Four Moments of Antibiotic Decision Making framework. As a reminder, the Four Moments include: Moment 1: Does my patient have an infection that requires antibiotics? Moment 2: Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate? Moment 3: A day or more has passed. Can I stop antibiotics? Can I narrow therapy or change from intravenous to oral therapy? Moment 4: What duration of antibiotic 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** 

Moment 1: Diagnosing Sepsis

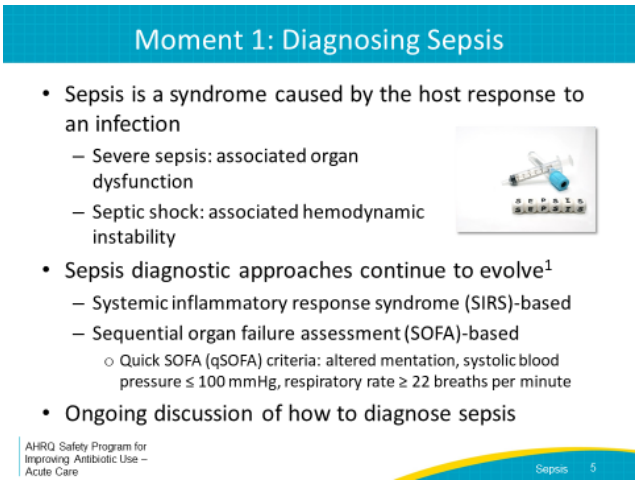
SAY:

Sepsis is a syndrome caused by the host response to an infection. Severe sepsis is defined as sepsis with associated organ dysfunction and septic shock is defined as severe sepsis with hemodynamic instability. In most cases, the infecting pathogen is a bacteria, with Gram-negative bacteria being most often associated with severe sepsis and septic shock, but the signs and symptoms of sepsis can also be induced by nonbacterial organisms.

Because sepsis can present in various ways in different hosts and because as of April 2019 there is no gold standard test for sepsis, developing diagnostic criteria for sepsis has been challenging and is evolving over time. An early diagnostic approach was based on the systemic inflammatory response syndrome, or SIRS, criteria. These criteria are based on abnormalities in temperature, heart rate, respiratory rate, and white blood cell count. In this approach, patients with sepsis are defined as having a suspected source of infection and two or more of the four SIRS criteria. Use of SIRS criteria is considered problematic by some because many patients have abnormalities in these parameters that are unrelated to an infection or have an infection without concomitant sepsis, and some patients with sepsis do not have these criteria despite having evidence of organ dysfunction.

A more recent approach is the use of the sequential organ failure assessment, or SOFA, score, in which organ system function is assessed on a scale of 0 to 4 on the basis of signs and laboratory results. This score performs better than SIRS criteria in identifying patients with sepsis but is more complicated to apply and requires laboratory results to be calculated. A quick SOFA score, or qSOFA, has been proposed as an alternative to more easily identify at-risk patients

Slide 5



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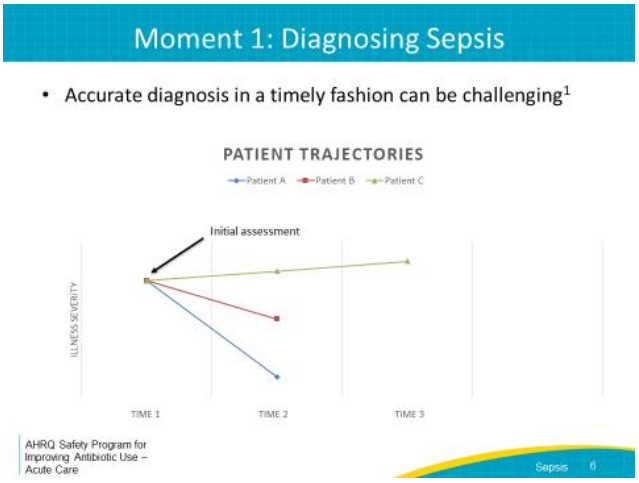
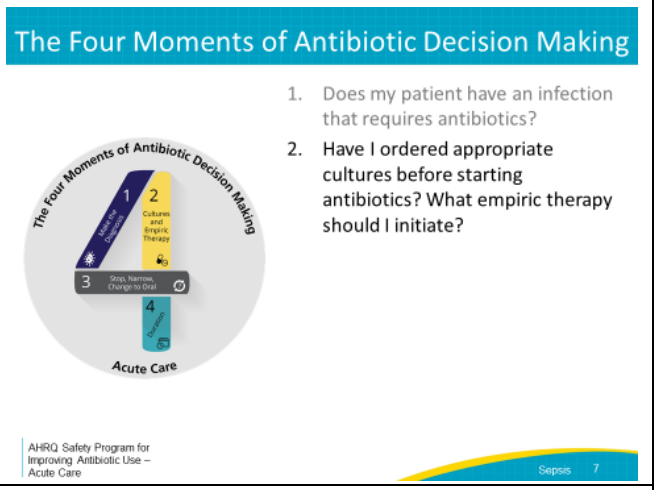
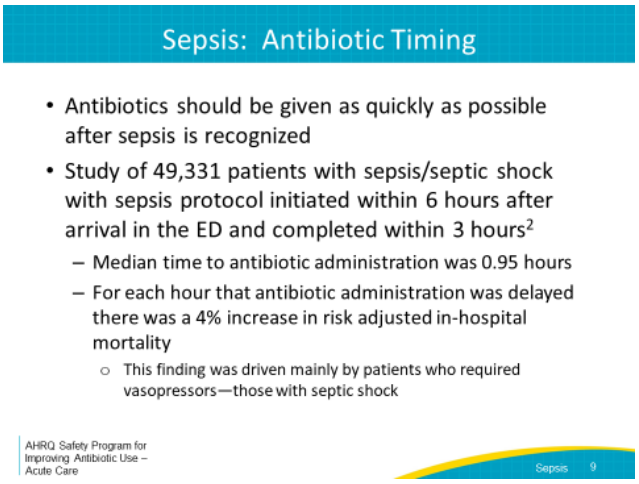
and prompt clinicians to further evaluate for organ dysfunction. qSOFA criteria are a respiratory rate of ≥ 22 breaths per minute, altered mentation, and a systolic blood pressure ≤ 100 mm Hg. As of April 2019, discussion of the most appropriate approach to diagnosis of sepsis in various patient populations is evolving.	
Moment 1: Diagnosing Sepsis SAY: The diagnosis of sepsis is often challenging because a patient is evaluated at one point in time. At the time of assessment, the clinician may not have complete information on the trajectory of illness prior to this point and obviously does not have knowledge of the trajectory of illness in the future. The figure on this slide demonstrates this concept. At the time of evaluation, patient A in blue, patient B in red, and patient C in green appear similar clinically. However, each has a different trajectory after initial assessment, with patient A improving rapidly and patients B and C getting sicker at different rates. As clinicians, we must do our best to identify at-risk patients at the time of assessment and support them aggressively. However, it is also important to follow all of these patients closely over time to assess whether they do or do not actually have an infection and that they are responding to interventions to treat their underlying problem.	**Slide 6** 

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 7** 
Sepsis: Cultures SAY: Patients with suspected sepsis should have blood cultures drawn before antibiotics are administered whenever possible. Remember that two sets of blood cultures (as in two sets of aerobic and anaerobic bottles) should be drawn from different sites and an adequate volume of blood should be obtained—usually 10cc per bottle. If the patient's history and physical exam suggest a source of infection, additional cultures from relevant sites should also be obtained, also ideally before antibiotics are administered.	**Slide 8** 

Slide Title and Commentary	Slide Number and Slide
Sepsis: Antibiotic Timing SAY: Antibiotics should be given as quickly as possible after sepsis is recognized. Let's take a closer look at the data for rapid antibiotic administration. A study evaluated 49,331 patients in New York State with sepsis and septic shock who had a sepsis protocol initiated within 6 hours after arrival in the emergency department with protocol completion within 3 hours. The investigators noted an association between later antibiotic administration and mortality. The median time to antibiotic administration was just under 1 hour. For each hour that antibiotic administration was delayed there was a 4 percent increase in risk adjusted in-hospital mortality. This finding was driven mainly by patients who required vasopressors—those with septic shock.	**Slide 9** 

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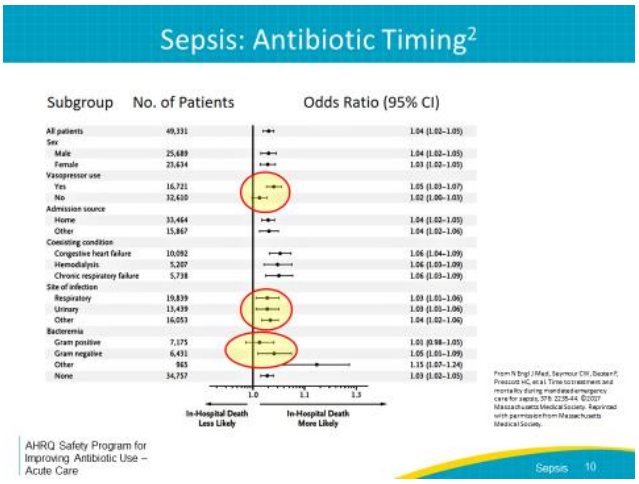
Sepsis: Antibiotic Timing SAY: This is a figure from the New York study. The differential effect of earlier antibiotics in patients requiring vasopressors compared to those who did not is seen in the top red circle. Also of interest on this slide is the finding that the respiratory tract and urinary tract were the most common suspected sources of infection. Finally, 30 percent of patients in the cohort had bacteremia—about evenly divided between Gram-positive and Gram-negative organisms. Early antibiotic administration appears to be of greater importance for Gram-negative bacteremia than Gram-positive bacteremia. This may be related to endotoxin-mediated sepsis seen in Gram-negative organisms, and speaks to the importance of prioritizing administration of an antibiotic with Gram-negative coverage in patients receiving more than one agent. To summarize, once a patient is identified as having severe sepsis or septic shock, an antibiotic should be administered as quickly as possible. The evidence for this recommendation is stronger for increasing severity of illness, with the strongest evidence for patients with septic shock. As clinicians, we must work to ensure that we are not incorrectly identifying patients with noninfectious sources of symptoms as having sepsis so that we avoid unnecessary antibiotic use, and we must ensure that patients who are ill from infections, particularly those with septic shock, receive antibiotics as quickly as possible.	**Slide 10** 

Sepsis: Considerations When Making Empiric Choices

SAY:

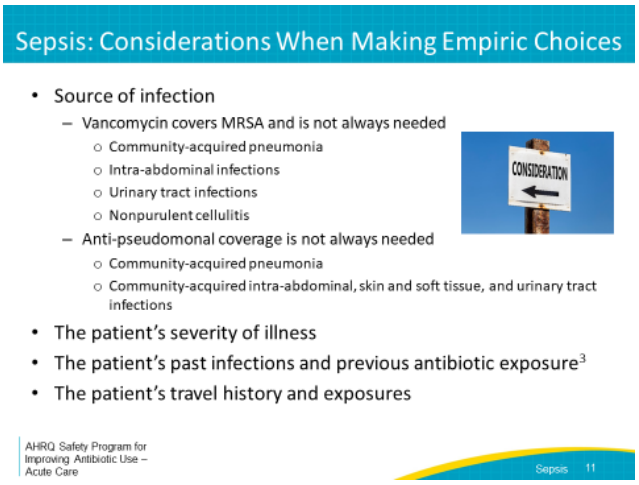
While most patients with septic shock should receive broad spectrum Gram-positive and Gram-negative coverage that includes *Pseudomonas* coverage, from a stewardship perspective, it is important to consider when such coverage may not be needed, on the basis of the suspected source of infection, the previous health status of the patient, and the patient's severity of illness.

Vancomycin specifically provides coverage for methicillin-resistant *Staphylococcus aureus*, or MRSA, and is not always needed. The majority of broad-spectrum agents administered for sepsis have activity against Gram-positive organisms such as methicillin-susceptible *Staphylococcus aureus*, or MSSA, and Streptococcal species. This includes the antibiotics piperacillin/tazobactam, ceftriaxone, cefepime, meropenem, and imipenem/cilastatin. Thus, for most cases of community-acquired pneumonia, intra-abdominal infections, and urinary tract infections, the addition of empiric vancomycin is not needed because MRSA is an uncommon cause of these infections.

Exceptions that provide no Gram-positive coverage include the antibiotics aztreonam, aminoglycosides, and ciprofloxacin. If these agents are used as primary agents because the patient has a severe penicillin allergy, then the addition of vancomycin (or in some cases linezolid) is needed for Gram-positive coverage.

In addition, the majority of community-acquired pneumonia and community-acquired intra-abdominal and urinary tract infections are not caused by *Pseudomonas*; thus, agents such as ceftriaxone, ampicillin/sulbactam, and ertapenem

Slide 11



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can be considered instead—depending on the likely source of infection. Narrower regimens should be considered when you are concerned about infection but the patient is not demonstrating severe illness—for example a patient who has a rapid response to fluids (or does not require fluids at all), has no vasopressor requirement, and/or barely meets the sepsis definition. Most clinicians are likely to err on the side of broad-spectrum therapy when a patient is critically ill. This is very appropriate, but it is important to reconsider this decision during Moment 3. Remember to obtain information about prior antibiotic exposure, as recent exposure to an agent increases the risk that the patient carries an organism that is resistant to that agent. For example in one study of 140 patients with a current *P. aeruginosa* infection resistant to piperacillin-tazobactam, 37 percent of patients had received piperacillin-tazobactam in the previous month. The patient's travel history and exposure history are also important. For example, in a returning traveler from Africa, malaria can present with septic parameters, but would obviously require different diagnostic and treatment considerations.	

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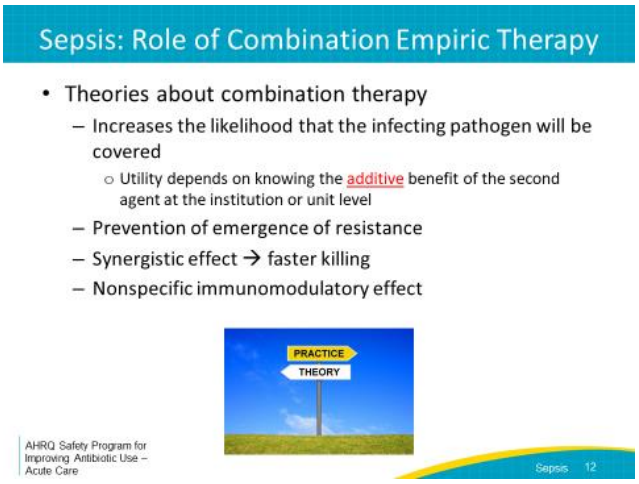
Sepsis: Role of Combination Therapy SAY: An issue that comes up in the management of sepsis is the role of combination Gram-negative therapy. There are several theories about the utility of combination therapy. The most compelling is that it can increase the likelihood that the infecting pathogen will be treated by at least one active antibiotic—this depends on knowing the additive benefit of the second agent. Some additional possibilities are that the addition of a second agent may reduce the risk of emergence of resistance, although this is refuted by a meta-analysis of eight studies that did not find this to be the case; that two agents may produce a synergistic effect leading to faster killing of organisms and more rapid recovery; and that there could be non-specific immunomodulatory effects from non-beta–lactam antibiotics. In the next few slides, we will examine some of these theories.	**Slide 12** 

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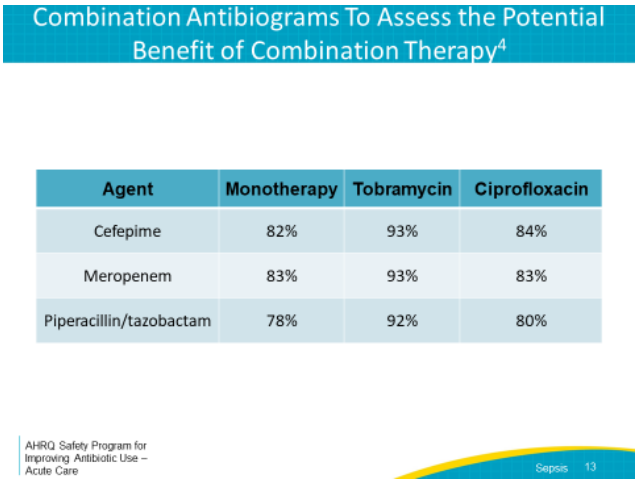
Combination Antibiograms To Assess the Potential Benefit of Combination Therapy SAY: Before making recommendations about possible combination treatment regimens, it is helpful to develop combination antibiograms to determine if the addition of a second agent is likely to enhance coverage. This figure shows the susceptibility profiles of cefepime, meropenem, and piperacillin-tazobactam as monotherapy to a hypothetical Gram-negative organism. Then, for each potential combination agent, an antibiogram is developed that shows the additional proportion of Gram-negative isolates that would be covered by the combination agents, but not the monotherapy agents. Thus, the addition of tobramycin to cefepime captures 11 percent more organisms that were resistant to cefepime but susceptible to tobramycin. In this example, an 11 percent increase in susceptibility, such as would be assumed by adding tobramycin to cefepime, may make a clinical difference for patients and justify combination therapy when patients are ill. However, in the same example, the addition of ciprofloxacin offers little additional coverage and would not be a suitable agent to add. It is important to ensure that a second agent adds coverage before exposing a patient to additional antibiotics and their associated side effects.	**Slide 13** 

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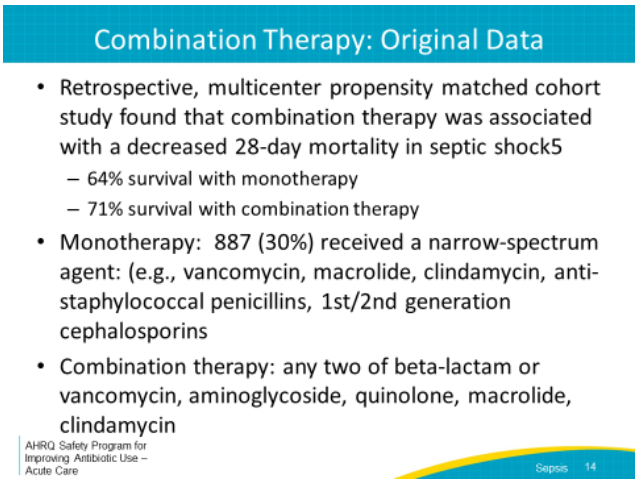
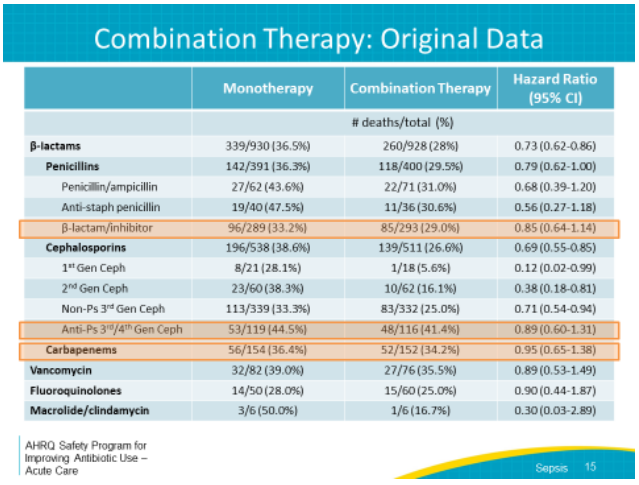
Combination Therapy: Original Data SAY: The idea that combination therapy improves patient outcomes was largely driven by a study published in 2010. This retrospective, multicenter cohort study found that combination therapy was associated with an increased 28-day survival (64% survived in the monotherapy group and 71% survived in the combination therapy group). However, 30 percent of the agents that were considered monotherapy were very narrow and not agents that we would routinely use as monotherapy for empiric treatment of sepsis such as vancomycin, macrolides, clindamycin, anti-staphylococcal penicillins and first- and second-generation cephalosporins. In contrast, combination therapy regimens primarily consisted of a beta-lactam agent plus a second agent with broad Gram negative coverage such as an aminoglycoside (40%) or a quinolone (38%).	**Slide 14** 
Combination Therapy: Original Data SAY: In taking a closer look at the results when stratified by agents, you can see that there was no difference in mortality in patients who received combination therapy vs monotherapy when one of the agents in both arms was a beta-lactam/beta-lactamase combination, an anti-pseudomonal third- or fourth-generation cephalosporin, or a carbapenem, agents that are commonly used to treat patients with septic shock.	**Slide 15** 

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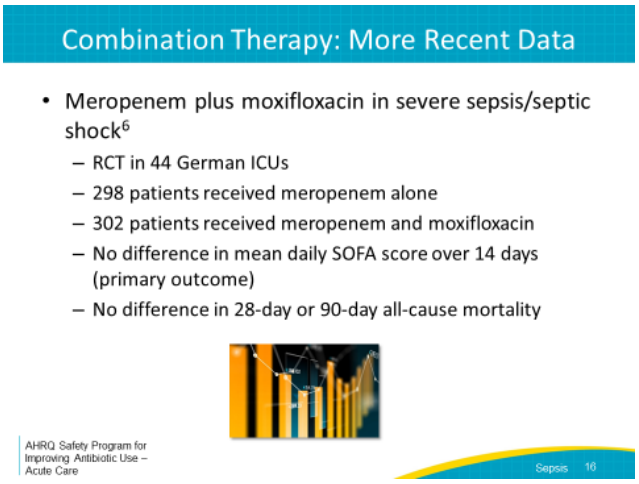
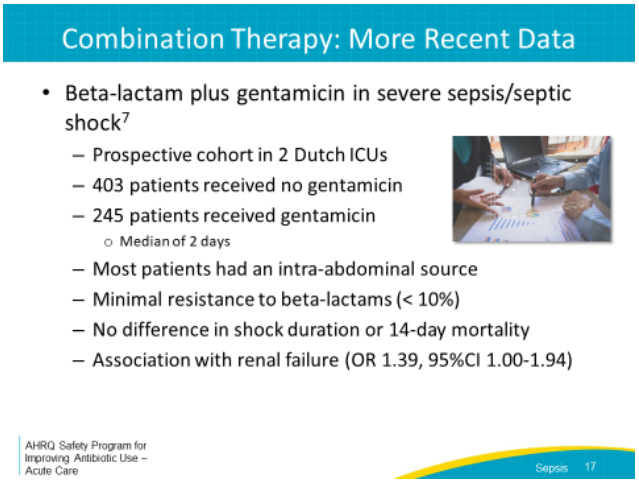
Combination Therapy: More Recent Data SAY: Two more studies call into question the utility of routine administration of combination therapy in severe sepsis and septic shock. In one study, 298 patients receiving meropenem monotherapy were compared to 302 patients receiving meropenem plus moxifloxacin in a randomized controlled trial or RCT conducted in 44 German intensive care units. There was no difference between the arms for the primary outcome--mean daily SOFA score when evaluating 14-day, 28-day, or 90-day all-cause mortality.	**Slide 16** 
Combination Therapy: More Recent Data SAY: In a second prospective cohort study in two Dutch intensive care units, 403 patients who received beta-lactam therapy alone were compared with 245 patients who received a beta-lactam plus gentamicin, the latter for a median of 2 days. Most patients had an intra-abdominal source and there was minimal resistance to beta-lactams (<10%) among organisms ultimately isolated. There was no difference in duration of shock symptoms or 14-day mortality, but administration of gentamicin was slightly associated with development of renal failure.	**Slide 17** 

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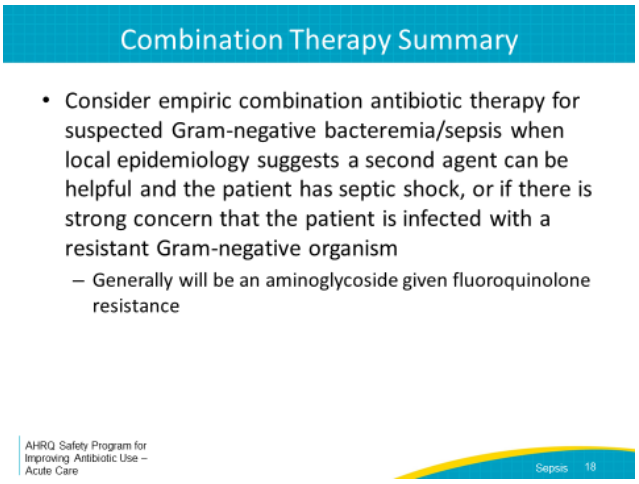
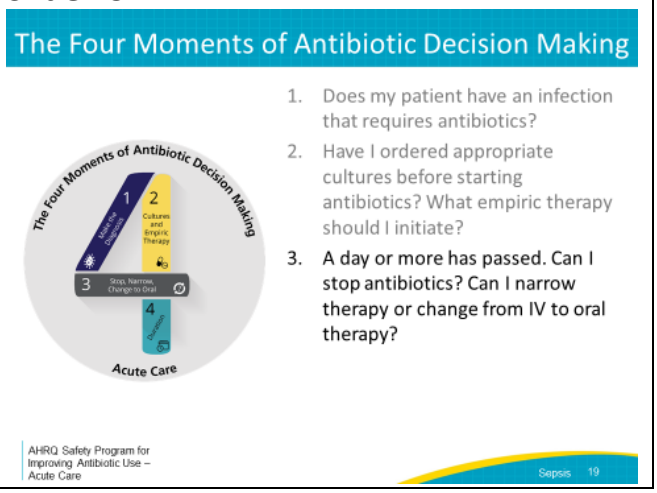
Combination Therapy Summary SAY: To summarize, routine combination therapy is unlikely to prevent emergence of resistance or improve patient outcomes and should generally be avoided. It should be considered in sick patients with suspected Gram-negative bacteremia and/or sepsis, especially in the presence of shock, when local epidemiology suggests a second agent can be helpful or if there are patient risk factors for resistant Gram-negative organisms. In many hospitals, the second agent will be an aminoglycoside given increasing rates of resistance among fluoroquinolones; thus, consider the potential risk of renal dysfunction when making the decision to initiate this therapy.	**Slide 18** 
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 19** 

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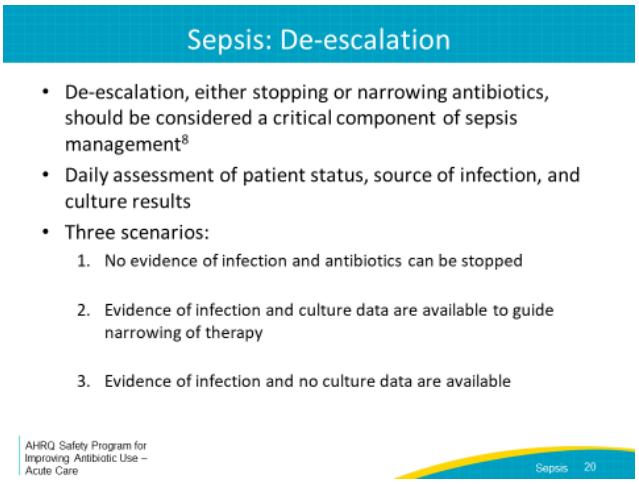
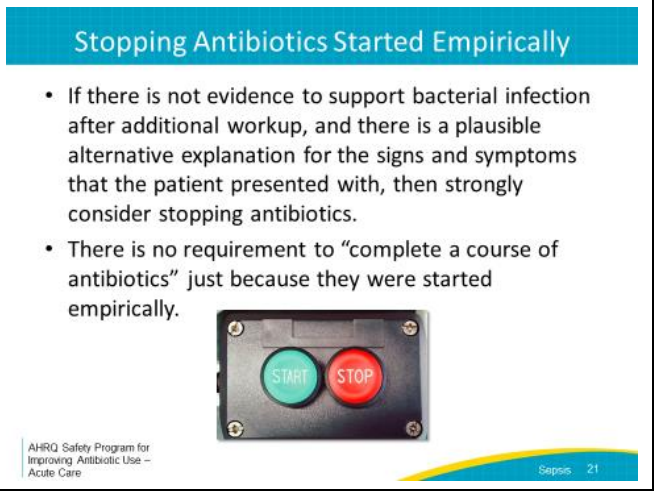
Sepsis: De-escalation SAY: De-escalation, defined as either stopping or narrowing antibiotics, is a critical component of sepsis management. Because of the inherent diagnostic uncertainty associated with the need for early recognition and intervention with sepsis, the need to reassess the patient's response to therapy and initial management strategy is paramount. Opportunities for de-escalation should be assessed on a daily basis based on the patient's clinical status, source of infection, and culture results. There are three potential scenarios at the time of assessment. The patient can have no evidence of infection, in which case the antibiotics that were started empirically can be stopped. The patient can have evidence of an infectious source and culture data are available to guide the narrowing (or expansion) of therapy. Or, the patient can have evidence of an infection and culture data are not available. We will review each scenario in the next few slides.	**Slide 20** 
Stopping Antibiotics Started Empirically SAY: If there is no longer evidence to support a bacterial infection after diagnostic results are available and there is a plausible alternative explanation for the signs and symptoms the patient presented with, then strongly consider stopping antibiotics. Remember, there is no requirement to "complete a course of antibiotics" just because you started them empirically.	**Slide 21** 

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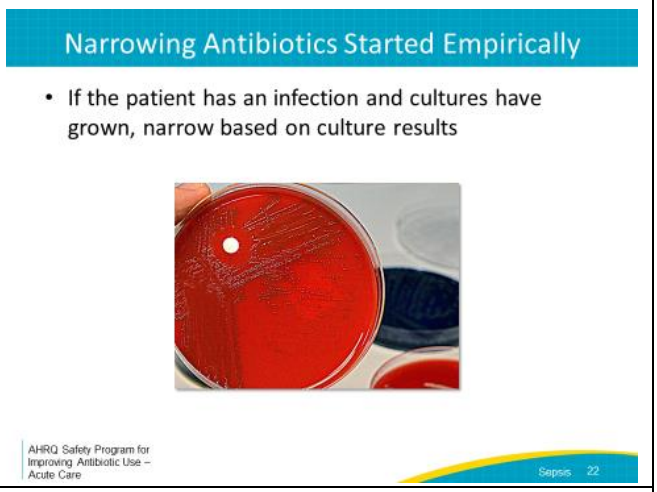
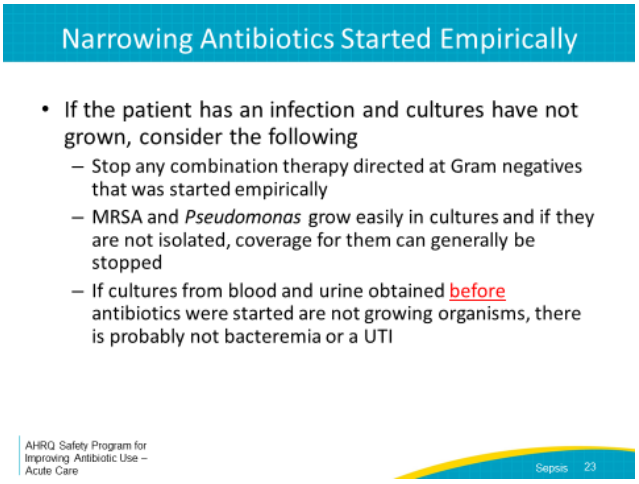
Narrowing Antibiotics Started Empirically SAY: If the patient has an infection and cultures have grown, narrow based on those cultures. Of course, if the culture results show a resistant organism that is not adequately covered, adjust therapy accordingly.	**Slide 22** 
Narrowing Antibiotics Started Empirically SAY: If the patient has an infection and cultures have not grown, consider the following: Stop therapy directed at MRSA or *Pseudomonas* if they are not isolated in cultures. These organisms both grow easily, including in the majority of cases in which the patient has received a dose of antibiotics prior to collection. Stop any second agent directed at Gram-negatives started empirically for similar reasons, such as aminoglycosides or fluoroquinolones, as common Gram-negative organisms such as *E. coli*, *Klebsiella* spp., and *Enterobacter* spp. also grow easily in cultures. If cultures from blood and urine were obtained before antibiotics were started and are not growing organisms, there is probably not bacteremia or a urinary tract infection. If the patient remains ill and you have no culture data to work with, consider further evaluation to assess for alternative nonbacterial processes or occult sources of infection such as intra-abdominal abscess.	**Slide 23** 

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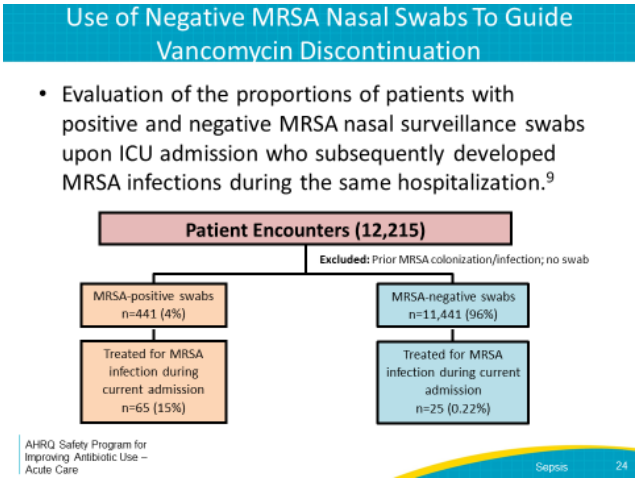
Use of Negative MRSA Nasal Swabs To Guide Vancomycin Discontinuation SAY: Negative MRSA nasal surveillance swabs may be helpful in guiding decisions about de-escalating vancomycin. In a study conducted in six ICUs at a tertiary-care hospital over an 18-month period in which 12,215 patients had nasal swabs upon ICU admission, 15 percent of the 441 patients with positive nasal swabs had an MRSA infection during the same hospitalization, but only 0.22 percent of the 11,441 patients with negative MRSA nasal swabs had an MRSA infection during the same hospitalization. The negative predictive value, defined as the ability of a negative nasal swab to predict correctly no subsequent MRSA infection was calculated for all patients in the cohort who received vancomycin, indicating that the treating clinician was concerned for possible MRSA infection. In this group of patients, the negative predictive value was 99.4 percent. A negative MRSA nasal swab was helpful in identifying patients with low risk of MRSA infection in whom empiric vancomycin therapy could be stopped and in whom the subsequent initiation of vancomycin therapy during an ICU admission could be avoided.	**Slide 24** 

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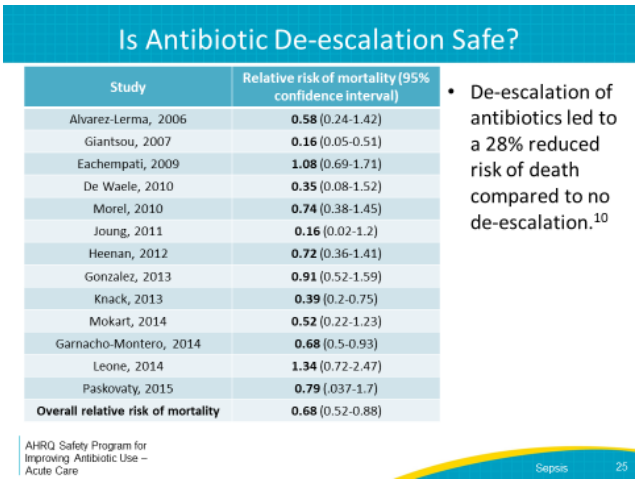
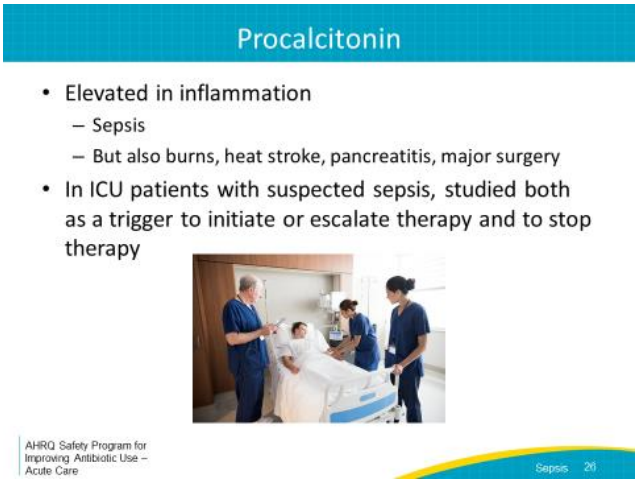
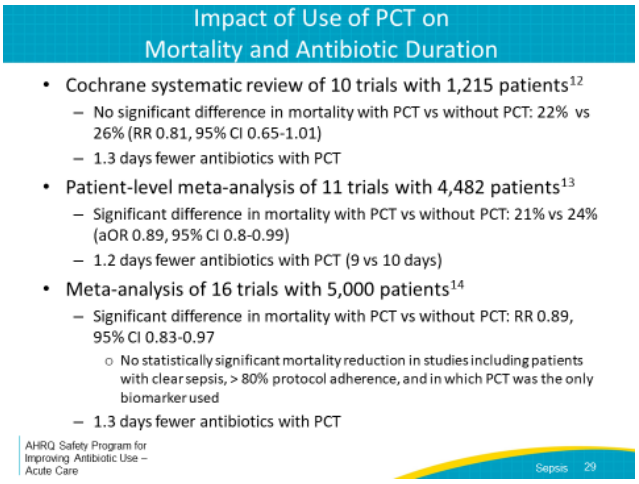
Evidence that De-escalation Is Safe SAY: These are the results from a meta-analysis reviewing the results of 13 studies showing that narrowing or de-escalation of antibiotic therapy is safe. The patients included in these studies were severely ill and did not have worse outcomes after the decision was made to de-escalate therapy, and were spared from potential adverse events associated with broad-spectrum antibiotic use. This meta-analysis shows that not only is descalation safe, patients who undergo antibiotic de-escalation have a 28 percent reduced risk of death compared to patients who remain on broad-spectrum antibiotic therapy. Remember: just because antibiotics are broader spectrum does not mean they will be more effective for treating a patient's infection.	**Slide 25** 
Procalcitonin SAY: Some advocate for the use of procalcitonin or PCT to guide antibiotic decision making in patients with sepsis. Procalcitonin is a precursor of calcitonin and is elevated in inflammation. This inflammation can be from a bacterial infection leading to sepsis, but it can also be due to non-infectious conditions such as burns, heat stroke, pancreatitis, or major surgery. Viral infections do not lead to an increase in procalcitonin levels. In intensive care unit patients with suspected sepsis, procalcitonin has been studied both as a trigger to initiate or escalate therapy and to stop therapy.	**Slide 26** 

Slide Title and Commentary	Slide Number and Slide
PCT-Guided Antibiotic Initiation/Escalation SAY: Procalcitonin does not appear to be of benefit guiding the decision to initiate or escalate antibiotic therapy in intensive care unit patients. In a randomized, controlled trial of 1,200 adult intensive care unit patients who received treatment according to guidelines (control) or according to daily procalcitonin levels and an algorithm to start or broaden antibiotics, there was no difference in 28-day mortality, but there was an increase in length of stay and duration of ventilation as well as increased broad-spectrum antibiotic use in the procalcitonin group.	**Slide 27** PCT-Guided Antibiotic Initiation/Escalation • RCT of 1,200 adult ICU patients who received treatment according to guidelines (control) or according to daily PCT and escalation algorithm[11] • No difference in 28-day mortality (32% vs 32%) • LOS increased by 1 day and ventilation by 5% in PCT group • Significant increases in meropenem, piperacillin/tazobactam and ciprofloxacin use AHRQ Safety Program for Improving Antibiotic Use – Acute Care Sepsis 27
PCT-Guided Antibiotic De-escalation SAY: Next let's consider use of procalcitonin to assist with de-escalation and stopping antibiotics in critically ill patients. There have been several clinical trials with different sizes, populations, and procalcitonin algorithms. Most algorithms have recommended antibiotic discontinuation if the procalcitonin level drops below 0.5 mcg/L or by 80 percent from the peak level. Many studies have had poor algorithm compliance, suggesting that the rules may be difficult to implement at the bedside. Also, several trials included both procalcitonin and C-reactive protein in the intervention group. The vast majority of studies have been performed at sites outside of the United States.	**Slide 28** PCT-Guided Antibiotic De-escalation • Several studies with different sizes, populations, and PCT algorithms • Common limitations – Poor algorithm compliance – Use of PCT plus C-reactive protein – Very limited data from U.S. sites  AHRQ Safety Program for Improving Antibiotic Use – Acute Care Sepsis 28

Slide Title and Commentary	Slide Number and Slide
Impact of Use of Procalcitonin on Mortality and Antibiotic Duration in Critically Ill Patients SAY: Given variable results of clinical trials, several meta-analyses have been performed to address the question of whether procalcitonin use to inform antibiotic de-escalation in intensive care unit patients reduces mortality and antibiotic use. Let's review the results of three of the most recent ones. A Cochrane systematic review of 10 trials with 1,215 subjects did not find significant differences in mortality, but noted that patients in the procalcitonin arms received 1.3 days fewer antibiotics. A patient-level meta-analysis of 11 trials with 4,482 patients found decreased mortality in the procalcitonin arm, although the mortality difference was small—21 percent with procalcitonin vs 24 percent without. Patients in the procalcitonin arm received 1.2 days fewer antibiotics, although overall antibiotic durations were long—9 days versus 10 days. Finally, a meta-analysis of 16 trials with 5,000 patients showed almost identical results to the patient-level meta-analysis in the previous study we discussed. However, subgroup analyses showed no mortality reduction in studies in which patients had sepsis, in studies that had greater than 80 percent protocol adherence, or in studies in which PCT was the only biomarker used. The results of this subgroup analysis suggest that the mortality benefit seen in these meta-analyses may not be related to procalcitonin use.	**Slide 29** 

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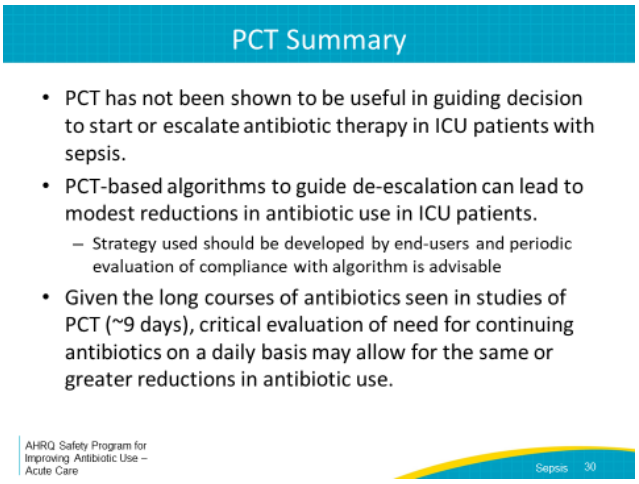
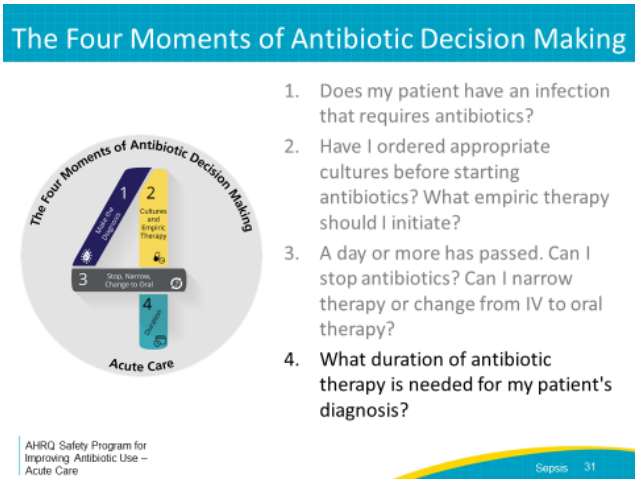
Procalcitonin Summary SAY: To summarize, procalcitonin has not been shown to be useful in guiding the decision to start or escalate antibiotic therapy in ICU patients with sepsis. Procalcitonin-based algorithms in patients being treated for sepsis can be useful in achieving modest reductions in antibiotic use; however, the strategy used should be developed by end-users and periodic evaluation of compliance with available algorithms is advisable. Given the long courses of antibiotics used in studies of procalcitonin (~9 days), regular and thoughtful evaluation of the need for continuing antibiotics on a daily basis in patients diagnosed with sepsis may allow for the same or greater reductions in use. This can be achieved using a daily antibiotic time-out.	**Slide 30** 
The Four Moments of Antibiotic Decision Making SAY: The last moment that should be considered is: What duration of antibiotic therapy is needed for your patient's diagnosis?	**Slide 31** 

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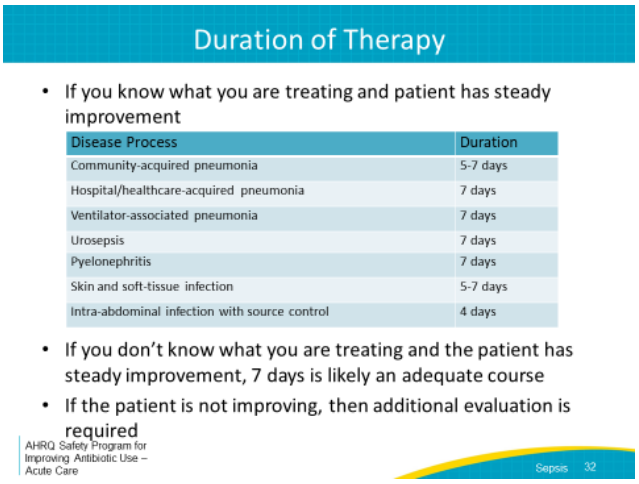
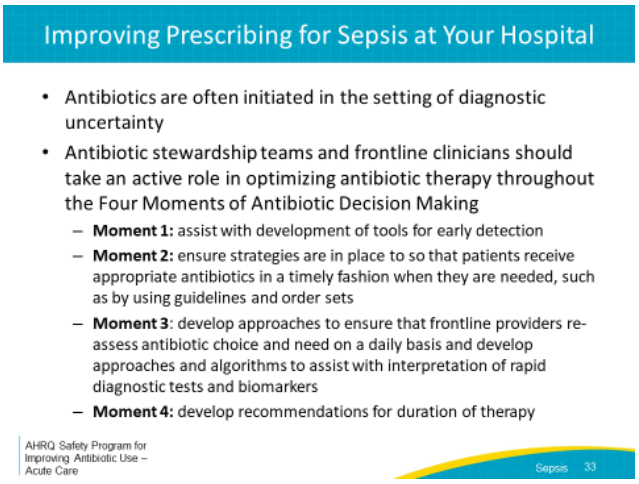
Duration of Therapy SAY: Let's consider some different situations with regard to duration of therapy. If you know what you are treating and a patient has steady improvement, then standard durations of therapy that have been discussed throughout the AHRQ Safety Program shown on this table should be used in most cases. If you don't know what you are treating and the patient has steady improvement, then based on the table, 7 days is likely an adequate course of therapy. If the patient is not improving, then additional evaluation is required.	**Slide 32** 
Improving Prescribing for Sepsis at Your Hospital As we have discussed, antibiotics are often initiated in patients with suspected sepsis in the setting of diagnostic uncertainty. Antibiotic stewardship teams and frontline clinicians should take an active role in facilitating appropriate antibiotic therapy for sepsis across the Four Moments of Antibiotic Decision Making. Stewardship teams and frontline clinicians should be at the table when tools are designed and implemented to ensure early diagnosis and appropriate treatment of sepsis. Stewardship teams should work with relevant front-line clinicians to develop guidelines and order sets for use at the point of care to assist prescribers with initial antibiotic choice and ensure that patients who need antibiotics receive them in a timely fashion. Stewardship teams and frontline clinicians should develop approaches to ensure that the choice of and need for antibiotics is reassessed on a daily basis and that rapid diagnostics and biomarkers are interpreted appropriately. Finally, stewardship teams and front-line providers should develop recommendations for determining appropriate duration of therapy.	**Slide 33** 

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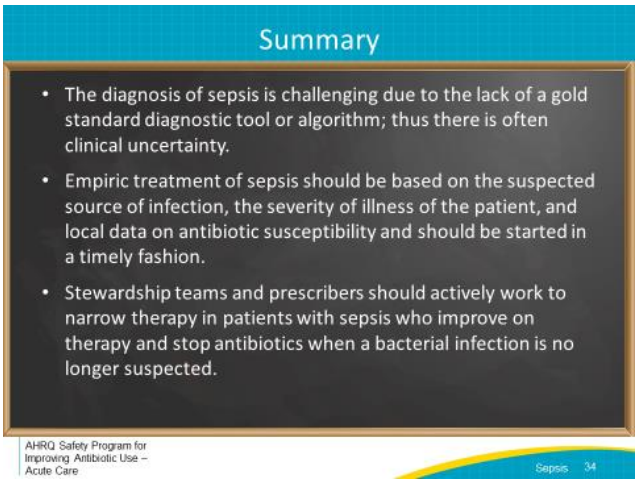
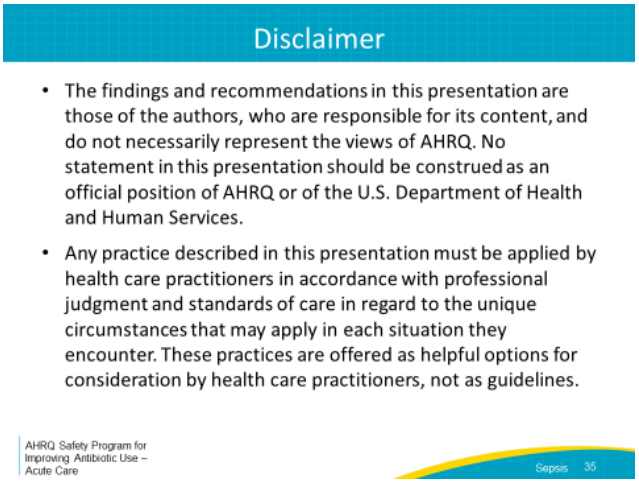
Summary SAY: The diagnosis of sepsis is challenging due to the lack of a gold standard diagnostic tool or algorithm; thus, there is often clinical uncertainty, and this uncertainty may occur in the setting of rapid patient decompensation due to critical illness. Empiric treatment of sepsis should be based on the suspected source of infection, the severity of illness of the patient, and local data on antibiotic susceptibility and should be started in a timely fashion. Stewardship teams and prescribers should actively work to narrow therapy in patients with sepsis who improve on therapy and stop antibiotics when infection is no longer suspected.	**Slide 34** 
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 35** 

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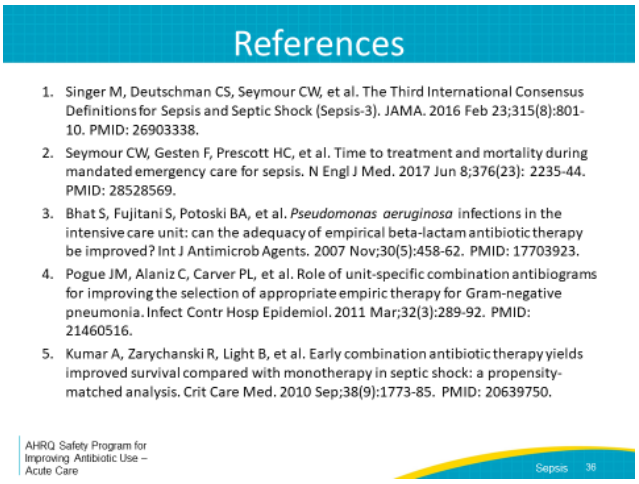
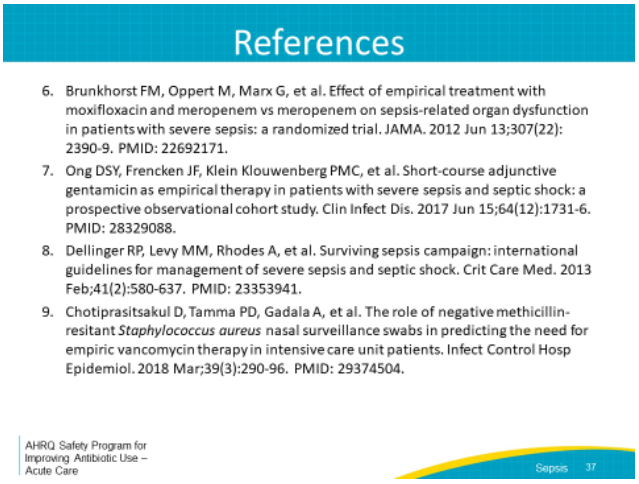
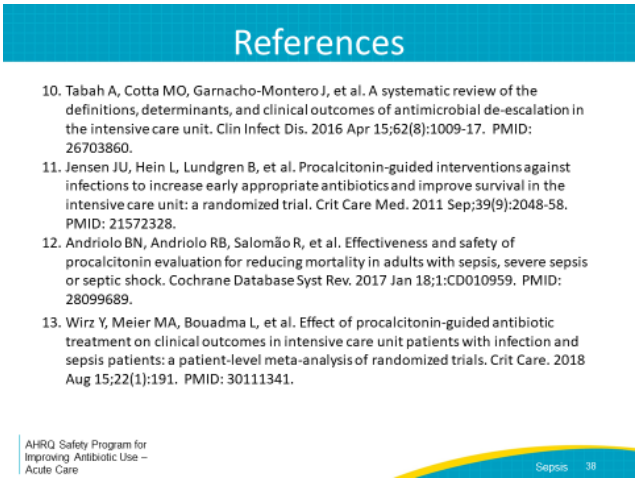
References	**Slide 36** 
References	**Slide 37** 
References	**Slide 38** 

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