

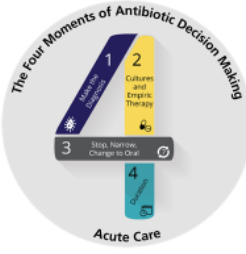
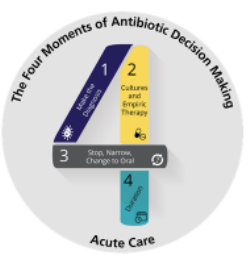
AHRQ Safety Program for Improving Antibiotic Use



Best Practices in the Diagnosis and Treatment of Sepsis Acute Care

Slide Title and Commentary	Slide Number and Slide
<p>Best Practices in the Diagnosis and Treatment of Sepsis Acute Care</p> <p>SAY:</p> <p>This presentation will address best practices in the diagnosis and treatment of sepsis.</p>	<p>Slide 1</p>
<p>Objectives</p> <p>SAY:</p> <p>The objectives of this presentation are:</p> <ul style="list-style-type: none"> • 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 	<p>Slide 2</p> <p>1. Review approaches to the diagnosis of sepsis</p> <p>2. Describe approaches to empiric treatment of sepsis</p> <p>3. Recognize when to stop and narrow antibiotic therapy in patients with suspected sepsis</p> <p>4. Discuss durations of therapy for patients with sepsis</p> <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 2</p>



Slide Title and Commentary	Slide Number and Slide
<p>The Four Moments of Antibiotic Decision Making</p> <p>SAY:</p> <p>We will review the diagnosis and management of sepsis using the Four Moments of Antibiotic Decision Making framework.</p> <p>As a reminder, the Four Moments include:</p> <p>Moment 1: Does my patient have an infection that requires antibiotics?</p> <p>Moment 2: Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate?</p> <p>Moment 3: A day or more has passed. Can I stop antibiotics? Can I narrow therapy or change from intravenous to oral therapy?</p> <p>Moment 4: What duration of antibiotic therapy is needed for my patient’s diagnosis?</p>	<p>Slide 3</p> <p>The Four Moments of Antibiotic Decision Making</p>  <ol style="list-style-type: none"> 1. Does my patient have an infection that requires antibiotics? 2. Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate? 3. A day or more has passed. Can I stop antibiotics? Can I narrow therapy or change from IV to oral therapy? 4. What duration of antibiotic therapy is needed for my patient’s diagnosis? <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 3</p>
<p>The Four Moments of Antibiotic Decision-Making</p> <p>SAY:</p> <p>Moment one is: Does my patient have an infection that requires antibiotics?</p>	<p>Slide 4</p> <p>The Four Moments of Antibiotic Decision Making</p>  <ol style="list-style-type: none"> 1. Does my patient have an infection that requires antibiotics? <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 4</p>

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

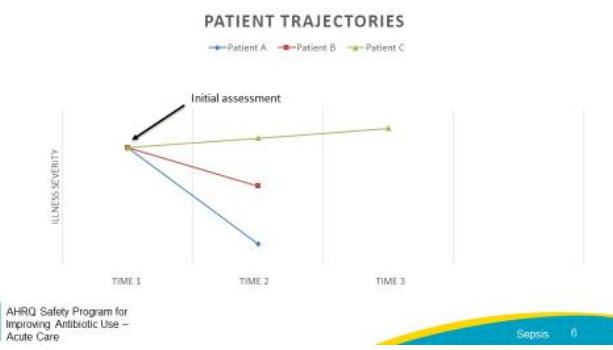
Moment 1: Diagnosing Sepsis

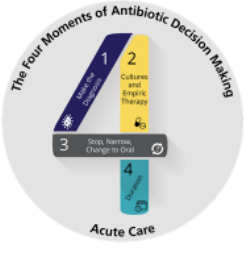

- Sepsis is a syndrome caused by the host response to an infection
 - Severe sepsis: associated organ dysfunction
 - Septic shock: associated hemodynamic instability
- Sepsis diagnostic approaches continue to evolve¹
 - Systemic inflammatory response syndrome (SIRS)-based
 - Sequential organ failure assessment (SOFA)-based
 - Quick SOFA (qSOFA) criteria: altered mentation, systolic blood pressure \leq 100 mmHg, respiratory rate \geq 22 breaths per minute
- Ongoing discussion of how to diagnose sepsis



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Sepsis 5

Slide Title and Commentary	Slide Number and Slide
<p>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.</p>	
<p>Moment 1: Diagnosing Sepsis SAY:</p> <p>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.</p>	<p>Slide 6</p> <p>Moment 1: Diagnosing Sepsis</p> <ul style="list-style-type: none"> Accurate diagnosis in a timely fashion can be challenging¹  <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 6</p>

Slide Title and Commentary	Slide Number and Slide
<p>The Four Moments of Antibiotic Decision Making</p> <p>SAY:</p> <p>Moment two is: Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate?</p>	<p>Slide 7</p> <p>The Four Moments of Antibiotic Decision Making</p>  <ol style="list-style-type: none"> 1. Does my patient have an infection that requires antibiotics? 2. Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate? <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 7</p>
<p>Sepsis: Cultures</p> <p>SAY:</p> <p>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.</p>	<p>Slide 8</p> <p>Sepsis: Cultures</p> <ul style="list-style-type: none"> • Blood cultures before antibiotics • Obtain cultures from other suspected sites of infection  <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 8</p>

Slide Title and Commentary	Slide Number and Slide
<p>Sepsis: Antibiotic Timing</p> <p>SAY:</p> <p>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.</p> <p>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.</p>	<p>Slide 9</p> <p style="text-align: center;">Sepsis: Antibiotic Timing</p> <ul style="list-style-type: none"> • Antibiotics should be given as quickly as possible after sepsis is recognized • Study of 49,331 patients with sepsis/septic shock with sepsis protocol initiated within 6 hours after arrival in the ED and completed within 3 hours² <ul style="list-style-type: none"> – Median time to antibiotic administration was 0.95 hours – For each hour that antibiotic administration was delayed there was a 4% increase in risk adjusted in-hospital mortality <ul style="list-style-type: none"> ○ This finding was driven mainly by patients who required vasopressors—those with septic shock <p><small>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</small></p> <p style="text-align: right;"><small>Sepsis 9</small></p>

Slide Title and Commentary

Sepsis: Antibiotic Timing

SAY:

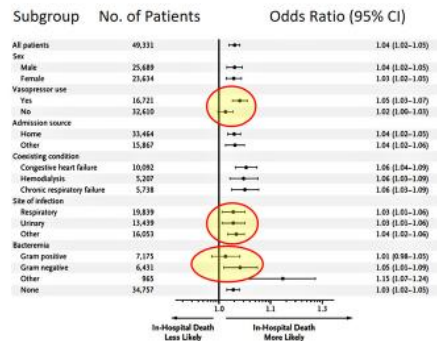
This is a figure from the New York study. The differential effect of earlier antibiotics in patients requiring vasopressors compared to those who did not is seen in the top red circle. Also of interest on this slide is the finding that the respiratory tract and urinary tract were the most common suspected 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 Number and Slide

Slide 10

Sepsis: Antibiotic Timing²



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Sepsis 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

Sepsis: Considerations When Making Empiric Choices


- Source of infection
 - Vancomycin covers MRSA and is not always needed
 - Community-acquired pneumonia
 - Intra-abdominal infections
 - Urinary tract infections
 - Nonpurulent cellulitis
 - Anti-pseudomonal coverage is not always needed
 - Community-acquired pneumonia
 - Community-acquired intra-abdominal, skin and soft tissue, and urinary tract infections
- The patient's severity of illness
- The patient's past infections and previous antibiotic exposure³
- The patient's travel history and exposures



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Sepsis 11

Slide Title and Commentary	Slide Number and Slide
<p>can be considered instead—depending on the likely source of infection.</p> <p>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.</p> <p>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 <i>P. aeruginosa</i> infection resistant to piperacillin-tazobactam, 37 percent of patients had received piperacillin-tazobactam in the previous month.</p> <p>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.</p>	

Slide Title and Commentary	Slide Number and Slide
<p>Sepsis: Role of Combination Therapy</p> <p>SAY:</p> <p>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.</p>	<p>Slide 12</p> <p>Sepsis: Role of Combination Empiric Therapy</p> <ul style="list-style-type: none"> • Theories about combination therapy <ul style="list-style-type: none"> – Increases the likelihood that the infecting pathogen will be covered <ul style="list-style-type: none"> ◦ Utility depends on knowing the additive benefit of the second agent at the institution or unit level – Prevention of emergence of resistance – Synergistic effect → faster killing – Nonspecific immunomodulatory effect <div style="text-align: center;">  </div> <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p style="text-align: right;">Sepsis 12</p>

Slide Title and Commentary	Slide Number and Slide																
<p>Combination Antibiograms To Assess the Potential Benefit of Combination Therapy</p> <p>SAY:</p> <p>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.</p> <p>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.</p>	<p>Slide 13</p> <p>Combination Antibiograms To Assess the Potential Benefit of Combination Therapy⁴</p> <table border="1" data-bbox="883 422 1446 594"> <thead> <tr> <th>Agent</th> <th>Monotherapy</th> <th>Tobramycin</th> <th>Ciprofloxacin</th> </tr> </thead> <tbody> <tr> <td>Cefepime</td> <td>82%</td> <td>93%</td> <td>84%</td> </tr> <tr> <td>Meropenem</td> <td>83%</td> <td>93%</td> <td>83%</td> </tr> <tr> <td>Piperacillin/tazobactam</td> <td>78%</td> <td>92%</td> <td>80%</td> </tr> </tbody> </table> <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 13</p>	Agent	Monotherapy	Tobramycin	Ciprofloxacin	Cefepime	82%	93%	84%	Meropenem	83%	93%	83%	Piperacillin/tazobactam	78%	92%	80%
Agent	Monotherapy	Tobramycin	Ciprofloxacin														
Cefepime	82%	93%	84%														
Meropenem	83%	93%	83%														
Piperacillin/tazobactam	78%	92%	80%														

Slide Title and Commentary

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 Number and Slide

Slide 14

Combination Therapy: Original Data

- Retrospective, multicenter propensity matched cohort study found that combination therapy was associated with a decreased 28-day mortality in septic shock⁵
 - 64% survival with monotherapy
 - 71% survival with combination therapy
- Monotherapy: 887 (30%) received a narrow-spectrum agent: (e.g., vancomycin, macrolide, clindamycin, anti-staphylococcal penicillins, 1st/2nd generation cephalosporins)
- Combination therapy: any two of beta-lactam or vancomycin, aminoglycoside, quinolone, macrolide, clindamycin

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Sepsis 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

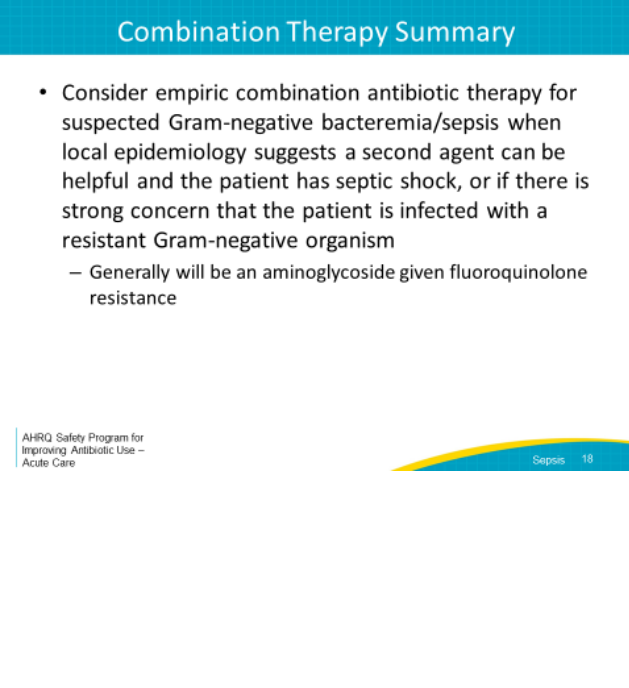
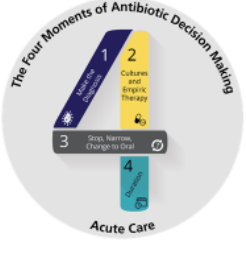
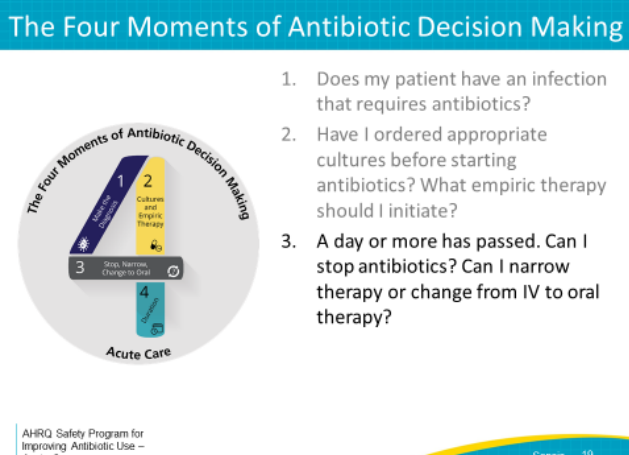
Combination Therapy: Original Data


	Monotherapy	Combination Therapy	Hazard Ratio (95% CI)
# deaths/total (%)			
β-lactams	339/930 (36.5%)	260/928 (28%)	0.73 (0.62-0.86)
Penicillins	142/391 (36.3%)	118/400 (29.5%)	0.79 (0.62-1.00)
Penicillin/ampicillin	27/62 (43.6%)	22/71 (31.0%)	0.68 (0.39-1.20)
Anti-staph penicillin	19/40 (47.5%)	11/36 (30.6%)	0.56 (0.27-1.18)
β-lactam/inhibitor	96/289 (33.2%)	85/293 (29.0%)	0.85 (0.64-1.14)
Cephalosporins	196/538 (38.6%)	139/511 (26.6%)	0.69 (0.55-0.85)
1 st Gen Ceph	8/21 (28.1%)	1/18 (5.6%)	0.12 (0.02-0.99)
2 nd Gen Ceph	23/60 (38.3%)	10/62 (16.1%)	0.38 (0.18-0.81)
Non-Ps 3 rd Gen Ceph	113/339 (33.3%)	83/332 (25.0%)	0.71 (0.54-0.94)
Anti-Ps 3 rd /4 th Gen Ceph	53/119 (44.5%)	48/116 (41.4%)	0.89 (0.60-1.31)
Carbapenems	56/154 (36.4%)	52/152 (34.2%)	0.95 (0.65-1.38)
Vancomycin	32/82 (39.0%)	27/76 (35.5%)	0.89 (0.53-1.49)
Fluoroquinolones	14/50 (28.0%)	15/60 (25.0%)	0.90 (0.44-1.87)
Macrolide/clindamycin	3/6 (50.0%)	1/6 (16.7%)	0.30 (0.03-2.89)


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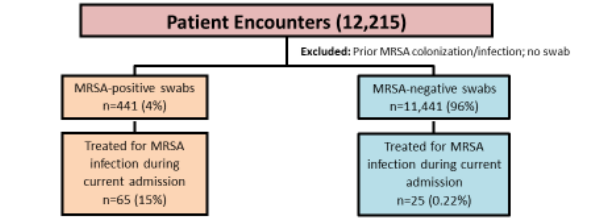
Sepsis 15

Slide Title and Commentary	Slide Number and Slide
<p>Combination Therapy: More Recent Data</p> <p>SAY:</p> <p>Two more studies call into question the utility of routine administration of combination therapy in severe sepsis and septic shock.</p> <p>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.</p>	<p>Slide 16</p> <p>Combination Therapy: More Recent Data</p> <ul style="list-style-type: none"> Meropenem plus moxifloxacin in severe sepsis/septic shock⁶ <ul style="list-style-type: none"> RCT in 44 German ICUs 298 patients received meropenem alone 302 patients received meropenem and moxifloxacin No difference in mean daily SOFA score over 14 days (primary outcome) No difference in 28-day or 90-day all-cause mortality  <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p>
<p>Combination Therapy: More Recent Data</p> <p>SAY:</p> <p>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.</p>	<p>Slide 17</p> <p>Combination Therapy: More Recent Data</p> <ul style="list-style-type: none"> Beta-lactam plus gentamicin in severe sepsis/septic shock⁷ <ul style="list-style-type: none"> Prospective cohort in 2 Dutch ICUs 403 patients received no gentamicin 245 patients received gentamicin <ul style="list-style-type: none"> Median of 2 days Most patients had an intra-abdominal source Minimal resistance to beta-lactams (< 10%) No difference in shock duration or 14-day mortality Association with renal failure (OR 1.39, 95%CI 1.00-1.94)  <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p>

Slide Title and Commentary	Slide Number and Slide
<p>Combination Therapy Summary</p> <p>SAY:</p> <p>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.</p> <p>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.</p>	<p>Slide 18</p> <p>Combination Therapy Summary</p> <ul style="list-style-type: none"> Consider empiric combination antibiotic therapy for suspected Gram-negative bacteremia/sepsis when local epidemiology suggests a second agent can be helpful and the patient has septic shock, or if there is strong concern that the patient is infected with a resistant Gram-negative organism <ul style="list-style-type: none"> Generally will be an aminoglycoside given fluoroquinolone resistance 
<p>The Four Moments of Antibiotic Decision Making</p> <p>SAY:</p> <p>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?</p>	<p>Slide 19</p> <p>The Four Moments of Antibiotic Decision Making</p>  <ol style="list-style-type: none"> Does my patient have an infection that requires antibiotics? Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate? A day or more has passed. Can I stop antibiotics? Can I narrow therapy or change from IV to oral therapy? 

Slide Title and Commentary	Slide Number and Slide
<p>Sepsis: De-escalation</p> <p>SAY:</p> <p>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.</p> <p>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.</p>	<p>Slide 20</p> <p>Sepsis: De-escalation</p> <ul style="list-style-type: none"> De-escalation, either stopping or narrowing antibiotics, should be considered a critical component of sepsis management⁸ Daily assessment of patient status, source of infection, and culture results Three scenarios: <ol style="list-style-type: none"> No evidence of infection and antibiotics can be stopped Evidence of infection and culture data are available to guide narrowing of therapy Evidence of infection and no culture data are available <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 20</p>
<p>Stopping Antibiotics Started Empirically</p> <p>SAY:</p> <p>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.</p>	<p>Slide 21</p> <p>Stopping Antibiotics Started Empirically</p> <ul style="list-style-type: none"> If there is not evidence to support bacterial infection after additional workup, and there is a plausible alternative explanation for the signs and symptoms that the patient presented with, then strongly consider stopping antibiotics. There is no requirement to “complete a course of antibiotics” just because they were started empirically.  <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 21</p>

Slide Title and Commentary	Slide Number and Slide
<p>Narrowing Antibiotics Started Empirically</p> <p>SAY:</p> <p>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.</p>	<p>Slide 22</p> <p>Narrowing Antibiotics Started Empirically</p> <ul style="list-style-type: none"> If the patient has an infection and cultures have grown, narrow based on culture results  <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 22</p>
<p>Narrowing Antibiotics Started Empirically</p> <p>SAY:</p> <p>If the patient has an infection and cultures have not grown, consider the following: Stop therapy directed at MRSA or <i>Pseudomonas</i> 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 <i>E. coli</i>, <i>Klebsiella</i> spp., and <i>Enterobacter</i> spp. also grow easily in cultures.</p> <p>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.</p> <p>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.</p>	<p>Slide 23</p> <p>Narrowing Antibiotics Started Empirically</p> <ul style="list-style-type: none"> If the patient has an infection and cultures have not grown, consider the following <ul style="list-style-type: none"> Stop any combination therapy directed at Gram negatives that was started empirically MRSA and <i>Pseudomonas</i> grow easily in cultures and if they are not isolated, coverage for them can generally be stopped If cultures from blood and urine obtained before antibiotics were started are not growing organisms, there is probably not bacteremia or a UTI <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 23</p>

Slide Title and Commentary	Slide Number and Slide
<p>Use of Negative MRSA Nasal Swabs To Guide Vancomycin Discontinuation</p> <p>SAY:</p> <p>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.</p>	<p>Slide 24</p> <p>Use of Negative MRSA Nasal Swabs To Guide Vancomycin Discontinuation</p> <ul style="list-style-type: none"> Evaluation of the proportions of patients with positive and negative MRSA nasal surveillance swabs upon ICU admission who subsequently developed MRSA infections during the same hospitalization.⁹  <pre> graph TD A["Patient Encounters (12,215)"] --> B["MRSA-positive swabs n=441 (4%)"] A --> C["MRSA-negative swabs n=11,441 (96%)"] A --- D["Excluded: Prior MRSA colonization/infection; no swab"] B --> E["Treated for MRSA infection during current admission n=65 (15%)"] C --> F["Treated for MRSA infection during current admission n=25 (0.22%)"] </pre> <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 24</p>

Slide Title and Commentary	Slide Number and Slide
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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

Is Antibiotic De-escalation Safe?

Study	Relative risk of mortality (95% confidence interval)
Alvarez-Lerma, 2006	0.58 (0.24-1.42)
Giantsou, 2007	0.16 (0.05-0.51)
Eachempati, 2009	1.08 (0.69-1.71)
De Waele, 2010	0.35 (0.08-1.52)
Morel, 2010	0.74 (0.38-1.45)
Joung, 2011	0.16 (0.02-1.2)
Heenan, 2012	0.72 (0.36-1.41)
Gonzalez, 2013	0.91 (0.52-1.59)
Knack, 2013	0.39 (0.2-0.75)
Mokart, 2014	0.52 (0.22-1.23)
Garnacho-Montero, 2014	0.68 (0.5-0.93)
Leone, 2014	1.34 (0.72-2.47)
Paskovaty, 2015	0.79 (.037-1.7)
Overall relative risk of mortality	0.68 (0.52-0.88)

- De-escalation of antibiotics led to a 28% reduced risk of death compared to no de-escalation.¹⁰

AHRQ Safety Program for Improving Antibiotic Use – Acute Care Sepsis 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.

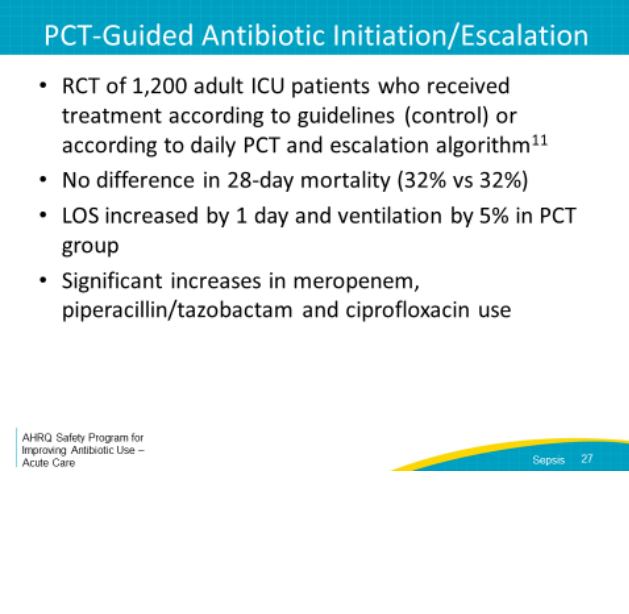
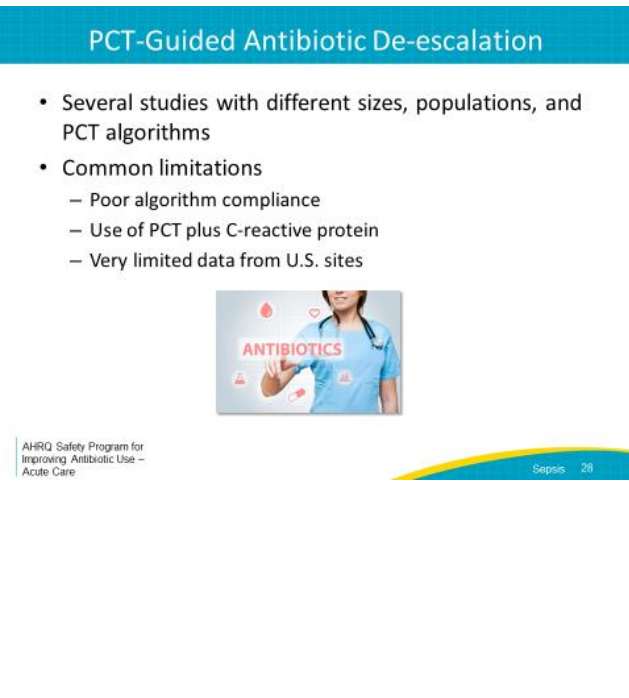
Slide 26

Procalcitonin

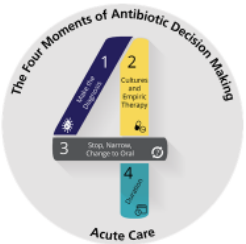
- Elevated in inflammation
 - Sepsis
 - But also burns, heat stroke, pancreatitis, major surgery
- In ICU patients with suspected sepsis, studied both as a trigger to initiate or escalate therapy and to stop therapy



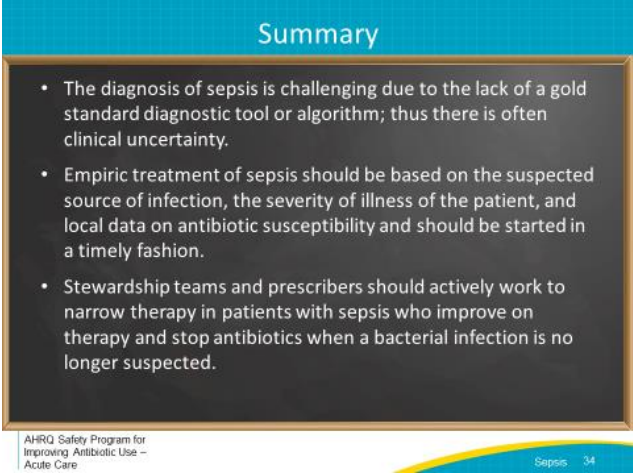
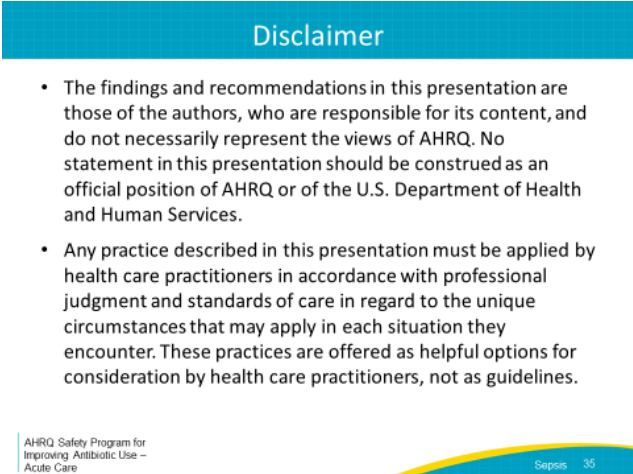
AHRQ Safety Program for Improving Antibiotic Use – Acute Care Sepsis 26

Slide Title and Commentary	Slide Number and Slide
<p>PCT-Guided Antibiotic Initiation/Escalation</p> <p>SAY:</p> <p>Procalcitonin does not appear to be of benefit guiding the decision to initiate or escalate antibiotic therapy in intensive care unit patients.</p> <p>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.</p>	<p>Slide 27</p> <p>PCT-Guided Antibiotic Initiation/Escalation</p> <ul style="list-style-type: none"> • RCT of 1,200 adult ICU patients who received treatment according to guidelines (control) or according to daily PCT and escalation algorithm¹¹ • 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 
<p>PCT-Guided Antibiotic De-escalation</p> <p>SAY:</p> <p>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.</p>	<p>Slide 28</p> <p>PCT-Guided Antibiotic De-escalation</p> <ul style="list-style-type: none"> • Several studies with different sizes, populations, and PCT algorithms • Common limitations <ul style="list-style-type: none"> – Poor algorithm compliance – Use of PCT plus C-reactive protein – Very limited data from U.S. sites 

Slide Title and Commentary	Slide Number and Slide
<p>Impact of Use of Procalcitonin on Mortality and Antibiotic Duration in Critically Ill Patients</p> <p>SAY:</p> <p>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.</p> <p>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.</p>	<p>Slide 29</p> <p>Impact of Use of PCT on Mortality and Antibiotic Duration</p> <ul style="list-style-type: none"> • Cochrane systematic review of 10 trials with 1,215 patients¹² <ul style="list-style-type: none"> – No significant difference in mortality with PCT vs without PCT: 22% vs 26% (RR 0.81, 95% CI 0.65-1.01) – 1.3 days fewer antibiotics with PCT • Patient-level meta-analysis of 11 trials with 4,482 patients¹³ <ul style="list-style-type: none"> – Significant difference in mortality with PCT vs without PCT: 21% vs 24% (aOR 0.89, 95% CI 0.8-0.99) – 1.2 days fewer antibiotics with PCT (9 vs 10 days) • Meta-analysis of 16 trials with 5,000 patients¹⁴ <ul style="list-style-type: none"> – Significant difference in mortality with PCT vs without PCT: RR 0.89, 95% CI 0.83-0.97 <ul style="list-style-type: none"> ○ No statistically significant mortality reduction in studies including patients with clear sepsis, > 80% protocol adherence, and in which PCT was the only biomarker used – 1.3 days fewer antibiotics with PCT <p><small>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</small></p> <p style="text-align: right;"><small>Sepsis 29</small></p>

Slide Title and Commentary	Slide Number and Slide
<p>Procalcitonin Summary</p> <p>SAY:</p> <p>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.</p>	<p>Slide 30</p> <p>PCT Summary</p> <ul style="list-style-type: none"> • PCT has not been shown to be useful in guiding decision to start or escalate antibiotic therapy in ICU patients with sepsis. • PCT-based algorithms to guide de-escalation can lead to modest reductions in antibiotic use in ICU patients. <ul style="list-style-type: none"> – Strategy used should be developed by end-users and periodic evaluation of compliance with algorithm is advisable • Given the long courses of antibiotics seen in studies of PCT (~9 days), critical evaluation of need for continuing antibiotics on a daily basis may allow for the same or greater reductions in antibiotic use. <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care Sepsis 30</p>
<p>The Four Moments of Antibiotic Decision Making</p> <p>SAY:</p> <p>The last moment that should be considered is: What duration of antibiotic therapy is needed for your patient's diagnosis?</p>	<p>Slide 31</p> <p>The Four Moments of Antibiotic Decision Making</p>  <ol style="list-style-type: none"> 1. Does my patient have an infection that requires antibiotics? 2. Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate? 3. A day or more has passed. Can I stop antibiotics? Can I narrow therapy or change from IV to oral therapy? 4. What duration of antibiotic therapy is needed for my patient's diagnosis? <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care Sepsis 31</p>

Slide Title and Commentary	Slide Number and Slide																
<p>Duration of Therapy</p> <p>SAY:</p> <p>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.</p>	<p>Slide 32</p> <p>Duration of Therapy</p> <ul style="list-style-type: none"> If you know what you are treating and patient has steady improvement <table border="1"> <thead> <tr> <th>Disease Process</th> <th>Duration</th> </tr> </thead> <tbody> <tr> <td>Community-acquired pneumonia</td> <td>5-7 days</td> </tr> <tr> <td>Hospital/healthcare-acquired pneumonia</td> <td>7 days</td> </tr> <tr> <td>Ventilator-associated pneumonia</td> <td>7 days</td> </tr> <tr> <td>Urosepsis</td> <td>7 days</td> </tr> <tr> <td>Pyelonephritis</td> <td>7 days</td> </tr> <tr> <td>Skin and soft-tissue infection</td> <td>5-7 days</td> </tr> <tr> <td>Intra-abdominal infection with source control</td> <td>4 days</td> </tr> </tbody> </table> <ul style="list-style-type: none"> If you don’t know what you are treating and the patient has steady improvement, 7 days is likely an adequate course If the patient is not improving, then additional evaluation is required <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 32</p>	Disease Process	Duration	Community-acquired pneumonia	5-7 days	Hospital/healthcare-acquired pneumonia	7 days	Ventilator-associated pneumonia	7 days	Urosepsis	7 days	Pyelonephritis	7 days	Skin and soft-tissue infection	5-7 days	Intra-abdominal infection with source control	4 days
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<p>Improving Prescribing for Sepsis at Your Hospital</p> <p>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.</p> <p>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.</p>	<p>Slide 33</p> <p>Improving Prescribing for Sepsis at Your Hospital</p> <ul style="list-style-type: none"> Antibiotics are often initiated in the setting of diagnostic uncertainty Antibiotic stewardship teams and frontline clinicians should take an active role in optimizing antibiotic therapy throughout the Four Moments of Antibiotic Decision Making <ul style="list-style-type: none"> Moment 1: assist with development of tools for early detection Moment 2: ensure strategies are in place to so that patients receive appropriate antibiotics in a timely fashion when they are needed, such as by using guidelines and order sets Moment 3: develop approaches to ensure that frontline providers re-assess antibiotic choice and need on a daily basis and develop approaches and algorithms to assist with interpretation of rapid diagnostic tests and biomarkers Moment 4: develop recommendations for duration of therapy <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p>Sepsis 33</p>																

Slide Title and Commentary	Slide Number and Slide
<p>Summary</p> <p>SAY:</p> <p>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.</p>	<p>Slide 34</p>  <ul style="list-style-type: none"> • The diagnosis of sepsis is challenging due to the lack of a gold standard diagnostic tool or algorithm; thus there is often clinical uncertainty. • 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 a bacterial infection is no longer suspected.
<p>Disclaimer</p> <p>SAY:</p> <p>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.</p> <p>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.</p>	<p>Slide 35</p>  <ul style="list-style-type: none"> • 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 Title and Commentary	Slide Number and Slide
References	<p>Slide 36</p> <p style="text-align: center;">References</p> <ol style="list-style-type: none"> 1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). <i>JAMA</i>. 2016 Feb 23;315(8):801-10. PMID: 26903338. 2. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. <i>N Engl J Med</i>. 2017 Jun 8;376(23): 2235-44. PMID: 28528569. 3. Bhat S, Fujitani S, Potoski BA, et al. <i>Pseudomonas aeruginosa</i> infections in the intensive care unit: can the adequacy of empirical beta-lactam antibiotic therapy be improved? <i>Int J Antimicrob Agents</i>. 2007 Nov;30(5):458-62. PMID: 17703923. 4. Pogue JM, Alaniz C, Carver PL, et al. Role of unit-specific combination antibiograms for improving the selection of appropriate empiric therapy for Gram-negative pneumonia. <i>Infect Contr Hosp Epidemiol</i>. 2011 Mar;32(3):289-92. PMID: 21460516. 5. Kumar A, Zarychanski R, Light B, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. <i>Crit Care Med</i>. 2010 Sep;38(9):1773-85. PMID: 20639750. <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care Sepsis 36</p>
References	<p>Slide 37</p> <p style="text-align: center;">References</p> <ol style="list-style-type: none"> 6. Brunkhorst FM, Oppert M, Marx G, et al. Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial. <i>JAMA</i>. 2012 Jun 13;307(22): 2390-9. PMID: 22692171. 7. Ong DSY, Frencken JF, Klein Klouwenberg PMC, et al. Short-course adjunctive gentamicin as empirical therapy in patients with severe sepsis and septic shock: a prospective observational cohort study. <i>Clin Infect Dis</i>. 2017 Jun 15;64(12):1731-6. PMID: 28329088. 8. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. <i>Crit Care Med</i>. 2013 Feb;41(2):580-637. PMID: 23353941. 9. Chotiprasitsakul D, Tamma PD, Gadala A, et al. The role of negative methicillin-resistant <i>Staphylococcus aureus</i> nasal surveillance swabs in predicting the need for empiric vancomycin therapy in intensive care unit patients. <i>Infect Control Hosp Epidemiol</i>. 2018 Mar;39(3):290-96. PMID: 29374504. <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care Sepsis 37</p>
References	<p>Slide 38</p> <p style="text-align: center;">References</p> <ol style="list-style-type: none"> 10. Tabah A, Cotta MO, Garnacho-Montero J, et al. A systematic review of the definitions, determinants, and clinical outcomes of antimicrobial de-escalation in the intensive care unit. <i>Clin Infect Dis</i>. 2016 Apr 15;62(8):1009-17. PMID: 26703860. 11. Jensen JU, Hein L, Lundgren B, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. <i>Crit Care Med</i>. 2011 Sep;39(9):2048-58. PMID: 21572328. 12. Andriolo BN, Andriolo RB, Salomão R, et al. Effectiveness and safety of procalcitonin evaluation for reducing mortality in adults with sepsis, severe sepsis or septic shock. <i>Cochrane Database Syst Rev</i>. 2017 Jan 18;1:CD010959. PMID: 28099689. 13. Wirz Y, Meier MA, Bouadma L, et al. Effect of procalcitonin-guided antibiotic treatment on clinical outcomes in intensive care unit patients with infection and sepsis patients: a patient-level meta-analysis of randomized trials. <i>Crit Care</i>. 2018 Aug 15;22(1):191. PMID: 30111341. <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care Sepsis 38</p>

Slide Title and Commentary	Slide Number and Slide
<p>References</p>	<p>Slide 39</p> <p style="text-align: center;">References</p> <p>14. Pepper DJ, Sun J, Rhee C, et al. Procalcitonin-guided antibiotic discontinuation and mortality in critically ill adults: a systematic review and meta-analysis. <i>Chest</i>. 2019 Feb 14. pii: S0012-3692(19)30154-0. PMID: 30772386.</p> <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p style="text-align: right;">Sepsis 39</p>