Emergency Medicine Curriculum Utilizing the Flipped Classroom Method: Infectious Disease and Immunology

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ABSTRACT:

**Audience:** This curriculum was designed to educate emergency medicine (EM) residents, PGY-1 to PGY-3, as well as medical students and attending physicians.

**Introduction:** Infectious disease-related problems are a common reason for emergency department visits. In 2015, infectious diseases were responsible for 3% of all emergency department visits.¹ Residents must be proficient in the differential diagnosis and management of the wide variety of infectious disease and immunologic emergencies that may present to an emergency department. To address these specific curricular needs, we developed a flipped classroom case-based small group discussion series for emergency medicine learners. The flipped classroom curricular model emphasizes self-directed learning activities, followed by facilitated small group discussions pertaining to the topic reviewed. The active learning fostered by this curriculum increases faculty and learner engagement and interaction time typically absent in traditional lecture-based formats.²⁻⁴ The application of knowledge through case studies, personal interaction with content experts, and integrated questions are effective learning strategies for emergency medicine residents.⁵⁻⁶ For these reasons, we created this 18-month flipped-classroom with the goal of improving our residency education program which can be generalized to other EM residency programs.⁶⁻⁷,⁸ While our immunology curriculum is based on the ABEM EM model curriculum, the infectious disease curriculum does not strictly follow the ABEM model because many of these topics are covered elsewhere in the resident didactic curriculum. As such, this curriculum focused on topics that education faculty determined to be the most common and essential for EM resident education.

**Objectives:** We aim to teach the presentation and management of infectious disease and immunological emergencies through the creation of a flipped classroom design. The topics include sepsis, sexually
transmitted infections (STIs), tropical diseases, angioedema and anaphylaxis, transplant-related emergencies, and collagen vascular diseases. This unique, innovative curriculum utilizes resources chosen by education faculty and resident learners, study questions, real-life experiences, and small group discussions in place of traditional lectures. The goal of our curriculum is to encourage self-directed learning, improve understanding and knowledge retention, and improve the educational experience of our residents.

**Methods:** The educational strategies used in this curriculum include: small group modules authored by education faculty and content experts based on the core emergency medicine content as outlined in the ABEM model curriculum. The question and answer format of the Socratic method, with an emphasis on an open learning environment, encouraged active participation. Small groups also focus on the synthesis and application of knowledge through the discussion of real-life experiences. The use of pre-reading assignments and encouragement for residents to find their own free open access medical education (FOAM) resources allows learners to work at their own pace and maximize autonomy.

**Topics:** Emergency medicine, flipped classroom, medical education, infectious disease and immunology emergencies, pedagogy, teaching.
USER GUIDE

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Learner Audience:
Medical students, interns, junior residents, senior residents, attending physicians and faculty members

Length of Curriculum:
The infectious disease and immunology emergencies module consists of six 45-60-minute small group sessions.

Topics:
Emergency medicine, flipped classroom, medical education, infectious disease and immunology emergencies, pedagogy, teaching

Objectives:
Each chapter within our curriculum has individual objectives as outlined in the appendices; however, educational objectives for the overall curriculum include:

1. Sepsis
   a. Define both systemic inflammatory response syndrome (SIRS) and quick sepsis related organ failure assessment (qSOFA) and how they are used to screen patients with possible sepsis.
   b. Understand the most recent Surviving Sepsis guidelines.
   c. List the most common causes of sepsis.
   d. Review the workup and diagnosis of sepsis.
   e. Discuss the management of a patient with suspected sepsis and common complications.

2. Sexually Transmitted Infections
   a. Discuss the most common sexually transmitted infections (STIs) managed in the ED.
   b. Describe the appropriate workup, treatment, and disposition of patients with cervicitis and pelvic inflammatory disease (PID).
   c. Discuss the state-specific guidelines for mandatory health department reporting and STIs.
   d. Discuss the evaluation and management of infections in patients with human immunodeficiency virus (HIV).
   e. Review acquired immunodeficiency syndrome (AIDS) defining illnesses.

3. Tropical Diseases
   a. List some common pathogens and diseases affecting travelers returning from foreign destinations.
   b. Describe the typical presentation to the emergency department for malarial disease.
   c. Discuss the risk factors for contracting malaria.
   d. Describe the clinical presentation of dengue fever and discuss the appropriate workup.
   e. Discuss the clinical manifestation of enteric fever and explore treatment objectives.

4. Angioedema and Anaphylaxis
   a. Describe the types of angioedema and hypersensitivity reactions.
   b. Differentiate angioedema from histaminergic edema and anaphylaxis.
   c. Discuss criteria regarding management of the airway in patients with angioedema and anaphylaxis.
   d. Review pharmacotherapy of angioedema and anaphylaxis.
   e. Discuss appropriate disposition of angioedema and anaphylaxis.

5. Transplant-Related Emergencies
   a. Review the presentation of common transplant complications in patients with lung, kidney, and pancreas transplants.
   b. Discuss the diagnosis and management of complications in solid organ transplant patients.
   c. Distinguish features of infection from rejection in patients with renal transplants.

6. Collagen Vascular Diseases
   a. Review common presentations of collagen vascular disease-related problems.
b. Discuss the diagnosis and workup of complications of common collagen vascular diseases including systemic lupus erythematosus, dermatomyositis, and ankylosing spondylitis.

c. Discuss the basic strategies for treatment of collagen vascular diseases.

d. Discuss appropriate dispositions for patients presenting with collagen vascular diseases and associated complications.

Brief introduction:
The flipped classroom learning approach is becoming more commonly recognized as a preferred curricular model for mature learners, specifically those in medical education. This particular model is a natural fit for the hands-on, experiential emergency medicine learner. The active learning fostered by this curriculum increases faculty and learner engagement and interaction time, which is typically absent in traditional lecture-based formats. Education literature shows that resident learners prefer learning activities that involve small group discussion, are case- or skill-based, and emphasize the application of newly obtained knowledge. This educational model also provides a clear channel for the incorporation of evidence-based medicine and increases opportunities for educator-learner conversations. A successful flipped classroom curriculum fosters learner accountability and provides robust opportunities for formal assessment in various emergency medicine milestones. For these reasons, we developed a flipped classroom curriculum. This infectious disease and immunology emergencies curriculum is one of several content blocks in our overall didactic curriculum.

Problem identification, general and targeted needs assessment:
Traditional lecture-based didactics may not be the most effective or preferred method for emergency medicine resident education. Previously, we used a traditional lecture format in our residency curriculum despite overwhelming evidence favoring a more hands-on, “flipped classroom” approach. From the perspective of resident learners, the chance to remain fully engaged through the asking of questions developed from personal experiences, in addition to also learning from the experiences of others, provides a manner of learning that makes a topic more difficult to forget. Infectious disease and immunology emergencies are identified as an important aspect of an emergency medicine curriculum as outlined in the ABEM Model EM curriculum. This topic makes up a significant portion of the content that will appear on the emergency medicine in-training exam. Because of this, we decided that infectious disease and immunology emergencies warranted a dedicated content block within our flipped classroom curriculum. We grouped immunologic emergencies, such as anaphylaxis, transplant-related emergencies, and collagen vascular disease with infectious disease to create the immunology content block.

Both educators and learners benefit from an interactive and collaborative classroom, leading to the creation and implementation of this proposed curricular model at our emergency medicine residency program. This weekly small group curriculum has now replaced three hours of traditional lecture-based didactics. Learners divide into small groups of about 20 participants. Each group is led a faculty facilitator, with the option for senior residents to facilitate discussion. Since implementation, residents and educators are engaging in new, valuable flipped classroom learning communities. Through the curriculum, we continually seek to foster self-directed learning and increased collaboration between resident learners and education faculty members. This ensures that resident time will be maximized and learning will be more efficient and effective, therefore providing a potential positive impact on patient care and physician wellness. Currently, minimal flipped classroom curricular materials dedicated to the core content of emergency medicine exist.

Goals of the curriculum:
We aim to teach the presentation and management of infectious disease and immunology emergencies through the creation of a flipped classroom design. The topics include sepsis, sexually transmitted infections, tropical diseases, angioedema and anaphylaxis, transplant-related emergencies, and collagen vascular diseases. This unique, innovative curriculum utilizes resources chosen by education faculty and resident learners, study questions, real-life experiences, and small group discussions in place of traditional lectures. In doing so, a goal of the curriculum is to encourage self-directed learning, improve understanding and knowledge retention, and improve the educational experience of our residents.

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   c. Discuss the basic strategies for treatment of collagen vascular diseases.
   d. Discuss appropriate dispositions for patients presenting with collagen vascular diseases and associated complications.

Educational Strategies:
(See curriculum chart) Please refer to the curriculum chart of linked objectives and educational strategies.

Evaluation and Feedback:
This curriculum was literature-based and specifically designed to maximize active learning using the flipped classroom learning model. We overcame initial challenges and skepticism from both educators and learners to execute a successful, novel curricular model. Both resident learners and faculty educators have provided an overwhelming amount of positive feedback. Additionally, a survey was administered to each resident prior to initiation of the curricular innovation, and repeated at the conclusion of the first 18-month cycle. Learners and educators were enthusiastic about the conference structure and expressed a preference for it rather than the previous, lecture-based didactics. More recently during the second 18-month cycle of the flipped classroom curriculum, students were surveyed on their perceived quality of instruction of the various program components. In comparing varying conference activities over the last year, a majority of residents (60.9%) preferred small group discussions to formal grand rounds lectures. This curriculum has been delivered to two cohorts of learners, the content having been delivered twice in three years with about 50 residents per cycle. On the most recent iteration, residents evaluated the teaching methods as effective, with an average rating of more than 4.6 out of 5 (4 being agree, 5 being strongly agree). The curriculum is critically evaluated and updated by education faculty members in order to ensure educational material remains current and consistent with the emergency medicine core content.

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Educational resources are available within each individual appendix of this neurologic emergencies curriculum module; however, a complete list of resources and educational materials are listed below.
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| Topic | Recommended Educational Strategy | Educational Content | Objectives | Learners | Timing, Resources Needed | Recommended Assessment, Milestones Addressed |
|-------|----------------------------------|----------------------|------------|----------|--------------------------|---------------------------------------------|
| Sepsis | “Flipped” classroom discussion of pre-reading material, case discussions, and discussion questions. Encourage participants to share clinical experiences to enhance discussion. 45 minutes for case and content discussion. | Pathophysiology, diagnosis, and management of sepsis in the Emergency Department. | 1. Define both systemic inflammatory response syndrome (SIRS) and quick sepsis related organ failure assessment (qSOFA) and how they are used to screen patients with possible sepsis. 2. Understand the most recent Surviving Sepsis guidelines. 3. List the most common causes of sepsis. 4. Review the workup and diagnosis of sepsis. 5. Discuss the management of a patient with suspected sepsis and common complications. | PGY-1 PGY-2 PGY-3 Medical Students Faculty | Equipment: projector and screen preferable (instructor can pull up web images during session). Tables and space promoting small group discussion. Instructors: 1-2 faculty members or content experts. Predetermined senior resident discussion leader (optional). Timing: small group discussions involve no more than 15 learners and last about 45 minutes. | Milestone: Emergency stabilization (PC1), diagnostic studies (PC3), differential diagnosis (PC4), pharmacology (PC5), medical knowledge (MK). Assessment: Faculty evaluation of resident participation during small group activities. Evaluation: Resident evaluation of small group session content and facilitators. Yearly program evaluation of overall small group component. |
| Topic                      | Recommended Educational Strategy                                                                 | Educational Content                                                                                                                                                                                                 | Objectives                                                                                                                                                                                                 | Learners                            | Timing, Resources Needed (Space, Instructors, Equipment, Citations of JETem pubs or other literature) | Recommended Assessment, Milestones Addressed                                                                 |
|---------------------------|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sexually Transmitted Infections | “Flipped” classroom discussion of pre-reading material, case discussions, and discussion questions. Encourage participants to share clinical experiences to enhance discussion. 45 minutes for case and content discussion. | Pathophysiology, diagnosis, and management of commonly encountered sexually transmitted infections in the Emergency Department.                                                                                       | 1. Discuss the most common sexually transmitted infections (STIs) managed in the emergency department (ED).                                                                                               | PGY-1 PGY-2 PGY-3 Medical Students Faculty | Equipment: projector and screen preferable (instructor can pull up web images during session). Tables and space promoting small group discussion. Instructors: 1-2 faculty members or content experts. Predetermined senior resident discussion leader (optional). Timing: small group discussions involve no more than 15 learners and last about 45 minutes. | Milestone: Performance of Focused History and Physical Exam (PC2), Diagnostic Studies (PC3), Diagnosis (PC4), Pharmacotherapy (PC5), Disposition (PC7), Medical Knowledge (MK). Assessment: Faculty evaluation of resident participation during small group activities. Evaluation: Resident evaluation of small group session content and facilitators. Yearly program evaluation of overall small group component. |

Ostro B, et al. Emergency Medicine Curriculum Utilizing the Flipped Classroom Method: Infectious Disease and Immunology. JETem 2019. 4(3):C1-S5. [https://doi.org/10.21980/J8DD1T](https://doi.org/10.21980/J8DD1T)
| Topic               | Recommended Educational Strategy                                                                 | Educational Content                                                                 | Objectives                                                                 | Learners                        | Timing, Resources Needed (Space, Instructors, Equipment, Citations of JETem pubs or other literature) | Recommended Assessment, Milestones Addressed |
|---------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------|---------------------------------------------------------------------------------|---------------------------------------------|
| Tropical Diseases   | “Flipped” classroom discussion of pre-reading material, case discussions, and discussion questions. Encourage participants to share clinical experiences to enhance discussion. 45 minutes for case and content discussion. | Pathophysiology, diagnosis, and management of commonly encountered tropical diseases in the Emergency Department. | 1. List some common pathogens and diseases affecting travelers returning from foreign destinations. 2. Describe the typical presentation to the emergency department (ED) for malarial disease. 3. Discuss the risk factors for contracting malaria. 4. Review the treatment of malaria. 5. Describe the clinical presentations of dengue fever and discuss the appropriate workup. 6. Discuss the clinical manifestation of enteric fever and explore treatment objectives. | PGY-1 PGY-2 PGY-3 Medical Students Faculty | Equipment: projector and screen preferable (instructor can pull up web images during session). Tables and space promoting small group discussion. Instructors: 1-2 faculty members or content experts. Predetermined senior resident discussion leader (optional). Timing: small group discussions involve no more than 15 learners and last about 45 minutes. | Milestone: Performance of Focused History and Physical Exam (PC2), Diagnostic Studies (PC3), Diagnosis (PC4), Pharmacotherapy (PC5), Disposition (PC7), Medical Knowledge (MK). Assessment: Faculty evaluation of resident participation during small group activities. Evaluation: Resident evaluation of small group session content and facilitators. Yearly program evaluation of overall small group component. |
| Topic                              | Recommended Educational Strategy                                                                 | Educational Content                                                                                                                                                                                                 | Objectives                                                                                                                                                                                                 | Learners                                    | Timing, Resources Needed (Space, Instructors, Equipment, Citations of JETem pubs or other literature)                                                                 | Recommended Assessment, Milestones Addressed                                                                                                                                 |
|----------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anaphylaxis and Angioedema       | “Flipped” classroom discussion of pre-reading material, case discussions, and discussion questions. Encourage participants to share clinical experiences to enhance discussion. 45 minutes for case and content discussion. | Pathophysiology, diagnosis, and management of anaphylaxis and angioedema in the Emergency Department.                                                                                                                                                                         | 1. Review types of angioedema and hypersensitivity reactions. 2. Differentiate angioedema from histaminergic edema and anaphylaxis. 3. Discuss criteria regarding management of the airway in patients with angioedema or anaphylaxis. 4. Review pharmacotherapy of angioedema and anaphylaxis. 5. Discuss appropriate disposition of angioedema and anaphylaxis. | PGY-1 PGY-2 PGY-3 Medical Students Faculty | Equipment: projector and screen preferable (instructor can pull up web images during session). Tables and space promoting small group discussion. Instructors: 1-2 faculty members or content experts. Predetermined senior resident discussion leader (optional). Timing: small group discussions involve no more than 15 learners and last about 45 minutes. | Milestone: Emergency Stabilization (PC1), Performance of Focused History and Physical Exam (PC2), Diagnostic Studies (PC3), Diagnosis (PC4), Pharmacotherapy (PC5), Observation and Reassessment (PC6), Disposition (PC7), Airway Management (PC10), Medical Knowledge (MK). Assessment: Faculty evaluation of resident participation during small group activities. Evaluation: Resident evaluation of small group session content and facilitators. Yearly program evaluation of overall small group component. |
## Transplant-Related Emergencies

**Recommended Educational Strategy**

"Flipped" classroom discussion of pre-reading material, case discussions, and discussion questions.

Encourage participants to share clinical experiences to enhance discussion.

45 minutes for case and content discussion.

**Educational Content**

Pathophysiology, diagnosis, and management of common transplant-related emergencies in the Emergency Department.

**Objectives**

1. Review the presentations of common transplant complications in patients with lung, kidney, and pancreas transplants.
2. Discuss the diagnosis and management of complications in solid organ transplant patients.
3. Distinguish features of infection from rejection in patients with renal transplants.

**Learners**

PGY-1
PGY-2
PGY-3
Medical Students
Faculty

**Timing, Resources Needed (Space, Instructors, Equipment, Citations of JETem pubs or other literature)**

Equipment: projector and screen preferable (instructor can pull up web images during session). Tables and space promoting small group discussion.

Instructors: 1-2 faculty members or content experts. Predetermined senior resident discussion leader (optional).

Timing: small group discussions involve no more than 15 learners and last about 45 minutes.

**Recommended Assessment, Milestones Addressed**

Milestone: Performance of Focused History and Physical Exam (PC2), Diagnostic Studies (PC3), Diagnosis (PC4), Pharmacotherapy (PC5), Disposition (PC7), Medical Knowledge (MK).

Assessment: Faculty evaluation of resident participation during small group activities.

Evaluation: Resident evaluation of small group session content and facilitators. Yearly program evaluation of overall small group component.
| Topic                        | Recommended Educational Strategy                                                                 | Educational Content                                                                                   | Objectives                                                                                                                                                                                                 | Learners                      | Timing, Resources Needed (Space, Instructors, Equipment, Citations of JETem pubs or other literature) | Recommended Assessment, Milestones Addressed |
|------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|--------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Collagen Vascular Diseases   | “Flipped” classroom discussion of pre-reading material, case discussions, and discussion questions. Encourage participants to share clinical experiences to enhance discussion. 45 minutes for case and content discussion. | Pathophysiology, diagnosis, and management of common collagen vascular disease emergencies in the Emergency Department. | 1. Review common presentations of collagen vascular disease-related problems. 2. Discuss the diagnosis and workup of complications of common collagen vascular diseases including systemic lupus erythematosus, dermatomyositis, and ankylosing spondylitis. 3. Discuss the basic strategies for treatment of collagen vascular diseases. 4. Discuss appropriate dispositions for patients presenting with collagen vascular diseases and associated complications. | PGY-1 PGY-2 PGY-3 Medical Students Faculty | Equipment: projector and screen preferable (instructor can pull up web images during session). Tables and space promoting small group discussion. Instructors: 1-2 faculty members or content experts. Predetermined senior resident discussion leader (optional). Timing: small group discussions involve no more than 15 learners and last about 45 minutes. | Milestone: Performance of Focused History and Physical Exam (PC2), Diagnostic Studies (PC3), Diagnosis (PC4), Pharmacotherapy (PC5), Disposition (PC7), Medical Knowledge (MK). Assessment: Faculty evaluation of resident participation during small group activities. Evaluation: Resident evaluation of small group session content and facilitators. Yearly program evaluation of overall small group component. |
Appendix A:
Sepsis

Objectives

By the end of this small group session, the learner will be able to:
1. Define both systemic inflammatory response syndrome (SIRS) and quick sepsis-related organ failure assessment (qSOFA) and how they are used to screen patients with possible sepsis.
2. Understand the most recent Surviving Sepsis guidelines.
3. List the most common causes of sepsis.
4. Review the workup and diagnosis of sepsis.
5. Discuss the management of a patient with suspected sepsis and common complications.

Case Studies

Case 1: A 65-year-old female presents with dysuria and flank pain and has a temperature (T) of 101.5 °F heart rate (HR) of 125/min, blood pressure (BP) of 85/55mmHg (mean arterial pressure [MAP] = 65), respiratory rate (RR) of 22/min, and oxygen saturation (O₂sat) of 94% on room air. On exam you note dry mucus membranes, suprapubic tenderness, and flank pain. Her creatinine is 1.8mg/dL, blood urea nitrogen (BUN) 76mg/dL, lactate 5.0mEq/L, white blood cell (WBC) count of 20,000/mm³, and hemoglobin of 9.0g/dL. Urinalysis shows >20 WBC/high power field (HPF) and bacteria. She weighs 70 kg.

Question Prompts:

1. Describe your assessment of this patient? What commonly used screening criteria exist for sepsis?
   a. This patient presents with signs and symptoms consistent with sepsis due to urinary tract infection. The markedly elevated lactate and hypotension are concerning for septic shock.
   b. In the emergency department, identifying patients with sepsis can be extremely difficult. Systemic inflammatory response syndrome (SIRS) criteria were developed over twenty years ago and can be present in a variety of conditions that are not sepsis. For example, patients with ankle fractures may be tachycardic and tachypneic due to pain.
   c. Systemic inflammatory response syndrome is diagnosed when a patient has two or more of the following:

|                  |                   |
|------------------|-------------------|
| **Temperature**  | >100.4°F or <96.8°F |
| **Heart Rate**   | >90/min           |
| **Respiratory Rate or PaCO2** | >20/min or <32mmHg |
| **White Blood Cell Count** | >12,000/mcL, <4,000/mcL, or >10% bands |
Sepsis is defined by SIRS PLUS a confirmed or suspected infection. Severe sepsis is defined as sepsis plus any of the following: signs of end-organ damage, hypotension (systolic blood pressure <90mmHg), and lactate >4mmol/L. Septic shock is defined as severe sepsis with persistent hypotension despite adequate fluid resuscitation (usually at least 30cc/kg).

These definitions, however, have very poor specificity in the emergency department and do not reflect the severity of the patient’s disease.

More recently, quick sepsis-related organ failure assessment (qSOFA) has been proposed as a method of identifying patients with sepsis who are likely to have high mortality. Patients are categorized as high risk if they meet two or more of the following: hypotension with systolic BP <100, altered mental status (any GCS <15), and respiratory rate >22. The specificity of qSOFA is much higher than SIRS (78.7% versus 34.7%) but lacks sensitivity (48.8% versus 84.1%).

In short, there is no universal definition of sepsis, and physicians must use their clinical gestalt to determine which patients require workup and treatment of sepsis.

What additional diagnostic studies should be performed?

A urine culture and two sets of blood cultures should be ordered and ideally drawn prior to initiation of antibiotics. However, do not delay administration of antibiotics if there are significant delays in obtaining cultures.

If there is a concern for an infected ureteral stone, a bedside point-of-care ultrasound (POCUS) can be performed to evaluate for hydronephrosis. Alternatively, if there is high index of suspicion for infected stone or perinephric abscess, a computed tomography (CT) of abdomen/pelvis without contrast can be obtained as well. This patient had no hydronephrosis on her ultrasound.

Describe your plan for resuscitation of this patient. Does your plan change if the patient has congestive heart failure (CHF) or end-stage renal disease (ESRD)?

As mentioned above, this patient presents in septic shock likely from urinary tract infection. This patient should be treated with 30mL/kg of crystalloid fluids. If the patient remains hypotensive, bedside POCUS evaluating the collapsibility of the inferior vena cava (IVC) during inspiration can help guide the need for additional fluid administration. Patients with CHF or ESRD may not be able to tolerate a 30mL/kg fluid bolus. In such cases, crystalloid infusions should be done judiciously with frequent reassessments to assess for volume overload.

If persistently hypotensive (MAP <65) after appropriate fluid resuscitation, the patient should be initiated on vasopressors with norepinephrine being first line. The goal is a MAP >65.

In 2018, the Surviving Sepsis Campaign issued an update in sepsis management replacing the 3 and 6-hour “bundles” with a 1-hour bundle. Per these recommendations, all patients with suspected sepsis should have the following actions completed within an hour of presentation:

1. Measure lactate level
   - Re-measure lactate if initial lactate is elevated >2mmol/L
   - Obtain blood cultures before administering antibiotics
3. Administer broad-spectrum antibiotics
4. Begin rapid administration of 30mL/kg crystalloid for hypotension or lactate >4mmol/L
5. Apply vasopressors if hypotensive during or after fluid resuscitation to maintain MAP >65mmHg

4. What is your general approach to antibiotics in sepsis? What antibiotic would you use in this patient?
   a. In general, septic patients require broad intravenous (IV) antibiotic coverage to target both gram-negative and gram-positive bacteria. Vancomycin is usually first-line to cover gram-positive bacteria and has good methicillin-resistant S. aureus coverage. Efforts should be made to cover for severe gram negatives such as Pseudomonas. Therefore, the regimen should also include anti-pseudomonal antibiotic such as cefepime, piperacillin-tazobactam, or meropenem. Patients at risk for multi-drug resistant (MDR) Pseudomonas (such as those with prior MDR infections, multiple hospital admissions, recent antibiotic use, and residence in long-term care facilities) should be double-covered with the addition of a quinolone or aminoglycoside such as gentamycin.
   b. The goal is to have antibiotics administered within one hour of presentation.
   c. After initial broad-spectrum coverage, antibiotics should be tailored to the specific source of infection once it is known. In this case of urinary tract infection, this would likely be ceftriaxone (pending sensitivities).
   d. Here is a table of commonly used empiric antibiotics in adults (note that antibiotic resistance patterns vary between hospital systems):

| Condition               | Empiric Antibiotics                              |
|-------------------------|--------------------------------------------------|
| Tonsillitis             | Benzathine penicillin G Clindamycin              |
| Cellulitis              | Trimethoprim-sulfamethoxazole + cephalexin Clindamycin Doxycycline |
| Meningitis              | Vancomycin, ceftriaxone, +/- ampicillin (age >50 or immunocompromised) and acyclovir for suspected Herpes Simplex Virus (HSV) |
| Pneumonia:              | Doxycycline, ceftriaxone + azithromycin Vancomycin + cefepime +/- gentamicin |
| Community acquired      |                                                  |
| Healthcare associated   |                                                  |
| Diverticulitis          | Ciprofloxacin + metronidazole                    |
| Urinary tract infection | Cephalexin Nitrofurantoin Trimethoprim-sulfamethoxazole |
| Osteomyelitis           | Vancomycin + cefepime                           |
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**Case 2:** A 50-year-old patient who is getting total parental nutrition (TPN) for chronic short gut syndrome following several remote abdominal surgeries for Crohn’s disease presents with complaints of extreme weakness, high fever, and increasing resistance in her peripherally inserted central catheter (PICC) line. Initially, she denies shortness of breath, chest pain, cough, urinary symptoms, and abdominal pain. She is tachycardic to 130/min and hypotensive with a systolic BP of 70. Her physical examination is unremarkable and the PICC site is only minimally erythematous without tenderness nor purulence. Labs are remarkable for a BUN and creatinine of 40mg/dL and 1.7mg/dL, respectively. Her WBC is 16,000/mm³ with a left shift. Her urinalysis and chest X-ray are normal. Blood and urine cultures are sent and pending. She has just completed a 30 mg/kg fluid bolus and her systolic BP is 60.

**Question Prompts:**

1. What are the potential sources of infection in this patient? What is your approach to source control in this patient?
   
   a. The source of infection in any septic patient includes upper respiratory/pulmonary, urinary, skin/musculoskeletal, gastrointestinal, and central nervous system. In this patient, all possible sources must be considered despite her lack of specific symptoms. Her indwelling intravenous catheter is also a highly probable source of infection. A culture must be obtained from this line in addition to a peripheral line.
   
   b. If there is concern that the source of infection is an indwelling catheter (this includes intravenous catheters, Foley catheters, nephrostomy tubes, etc.) one should consider removing the catheter to achieve source control. Although erythema, tenderness, and purulence around the catheter site are very specific for line infection, these do not occur very often and are not very sensitive for sign of infection. In this case it would be prudent to remove the central line catheter and send the tip for culture.

2. This patient is persistently hypotensive after adequate fluid resuscitation. You start norepinephrine but the patient’s MAP remains <65 despite very high doses. What additional interventions should be considered to optimize her hemodynamics?
   
   a. You can consider the addition of a second vasopressor such as epinephrine or vasopressin.
   
   b. Most sources do not recommend the routine use of glucocorticoids in sepsis. However, corticosteroid therapy may be appropriate in patients with septic shock refractory to fluid resuscitation and vasopressor administration as well as those on chronic steroids. Hydrocortisone can be administered at a dose of 100mg IV once, then 200mg per day divided every 6 hours. It is recommended to use intravenous glucocorticoid therapy if the patient remains in severe septic shock with a systolic pressure less than 90 for more than an hour following adequate fluid resuscitation and vasopressor administration.

**Case 3:** Patient is a 70-year-old male with a history of diabetes and recent admission for a urinary tract infection (UTI) who presents fever, cough, and shortness of breath. You make the diagnosis of healthcare-associated pneumonia. The patient has already received 30mL/kg IV bolus, appropriate antibiotics, and is on norepinephrine at high doses. A central venous catheter has been placed and the patient has adequate intravenous access. While boarding in the ED, he develops worsening shortness of breath and hypoxia.

Ostro B, et al. Emergency Medicine Curriculum Utilizing the Flipped Classroom Method: Infectious Disease and Immunology. JETem 2019. 4(3):C1-55. [https://doi.org/10.21980/J8DD1T](https://doi.org/10.21980/J8DD1T)
repeat chest X-ray shows diffuse infiltrates and you notice bruising of the skin, oozing from IV sites, and pink tinged sputum.

**Question Prompts:**

1. What potential complications are occurring in this patient? What would be your diagnostic strategy to verify these?
   a. This patient may be developing disseminated intravascular coagulation (DIC), characterized by microangiopathic hemolytic anemia, thrombocytopenia, and consumptive coagulopathy leading to hemorrhage.
   b. Diagnostic tests for DIC include a complete blood count (CBC) with smear, lactate dehydrogenase (LDH) (elevated), liver function tests (increased bilirubin), coagulation studies (elevated), fibrin degradation products (elevated), d-dimer (elevated), and fibrinogen (decreased).
   c. The patient’s shortness of breath may be a sign of pulmonary edema from excessive fluid administration or acute respiratory distress syndrome (ARDS). Acute respiratory distress syndrome is an acute inflammatory process within the lungs leading to increased pulmonary vascular permeability. The chest X-ray will show diffuse infiltrates.

2. How would you treat these complications in the ED?
   a. Patients with ARDS will be hypoxic and often require mechanical ventilation. Noninvasive ventilation is not as helpful as mechanical ventilation. During mechanical ventilation low tidal volume ventilation is recommended. The use of positive end-expiratory pressure (PEEP) can be employed according to the low tidal volume (6-8mL/kg ideal body weight) ventilation strategy described in the ARDSnet protocol. For patients who fail the low tidal volume ventilation strategy, prolonged ventilation can be considered.
   b. Regarding DIC, the treatment is aimed toward treating the underlying cause. In the case of sepsis, this is the administration of appropriate antibiotics and source control as well as aggressive hydration. Patients with platelet counts less than 50,000 x 10³/mm³ should be given platelet transfusions if there is serious bleeding or the need for urgent/emergent surgery. Patients with platelet counts of less than 10,000 x 10³/mm³ should be given platelets because of the risk of spontaneous bleeding. Consider the use of fresh frozen plasma in the setting of serious bleeding and significantly prolonged prothrombin time (PT) and partial thromboplastin time (PTT) or a fibrinogen level less than 50mg/dL. Cryoprecipitate can also be considered because this provides a good source of fibrinogen with less volume than fresh frozen plasma.

**Suggested Readings:**

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Appendix B:
Sexually Transmitted Infections

Objectives

By the end of this small group session, the learner will be able to:

1. Discuss the most common sexually transmitted infections (STIs) managed in the emergency department (ED).
2. Describe the appropriate workup, treatment, and disposition of patients with cervicitis and pelvic inflammatory disease (PID).
3. Discuss the state specific guidelines for mandatory health department reporting of STIs.
4. Discuss the evaluation and management of meningitis in patients with human immunodeficiency virus (HIV).
5. Review acquired immunodeficiency syndrome (AIDS) defining illnesses.

Case Studies

Case 1: A 19-year-old female presents to the emergency department for lower abdominal pain. She reports pain in the left lower quadrant ongoing for several days associated with vaginal discharge. She is sexually active with males and does not routinely use barrier protection. On exam, the patient has left lower quadrant tenderness. External genitalia exam reveals shallow, tender erythematous ulcerations along the labia. Pelvic exam reveals purulent discharge from the cervical os. She has exquisite cervical motion tenderness and also tenderness of the left adnexa.

Question Prompts:

1. What testing is needed for this patient?
   a. In patients with suspected pelvic inflammatory disease (PID) with unilateral adnexal tenderness, consider a transvaginal ultrasound to evaluate for evidence of tubo-ovarian abscess (TOA).
   b. The ulcers may be swabbed as well and sent for herpes simplex virus (HSV) culture.
   c. Urinalysis and pregnancy test should also be ordered.
   d. In most practice settings, it is also be appropriate to screen for sexually transmitted diseases such gonorrhea, chlamydia and trichomonas. Common testing also includes screening for Gardnerella vaginalis (bacteria thought to be pathogenic in bacterial vaginosis) and candida. Routine testing for bacterial vaginosis can be deferred to an outpatient basis unless the patient is symptomatic on presentation.
   e. Below is a wet mount image of clue cells diagnostic of bacterial vaginosis:
2. How would you treat this condition? How would your treatment change if your patient had a positive pregnancy test? What if she had a penicillin allergy?
   a. This patient’s clinical picture is suspicious for PID. In addition to the vaginal discharge and dyspareunia seen in cervicitis, clinical findings of PID include cervical motion tenderness, uterine tenderness, and adnexal tenderness. Because of the difficulty of diagnosis and the potential for damage to the reproductive health of women, healthcare providers should maintain a low threshold for the diagnosis and treatment of PID. Patients with minimal symptoms who are immunocompetent, with reassuring vital signs, able to tolerate PO, and have adequate follow up may be managed outpatient with ceftriaxone 250 mg intramuscularly (IM) or intravenous (IV) in a single dose PLUS doxycycline 100 mg orally twice daily (BID) for 14 days. Women with gynecologic instrumentation within the last two to three weeks should also be treated with metronidazole 500 mg orally (PO) BID for 14 days for anaerobic coverage. For patients requiring admission, such as those with tubo-ovarian abscess (TOA) or those unable to tolerate oral intake, treat with doxycycline
PO/intravenous (IV) 100mg BID PLUS either cefotetan 2g IV or cefoxitin 2g IV BID. An alternative regimen is clindamycin 900mg IV three times daily (TID) AND gentamycin 5mg/kg IV daily. Consider adding metronidazole for trichomonas coverage.

b. Patients with isolated cervicitis should be treated with drug regimens effective against both gonorrhea and chlamydia. Treat with ceftriaxone 250mg IM once PLUS azithromycin 1g PO once. An alternative regimen is ceftriaxone 250mg IM once plus doxycycline 100mg PO BID x 7 days. Patients should abstain from sexual intercourse for seven days after treatment AND until resolution of symptoms.

c. In the case of severe penicillin/cephalosporin allergy, patients can be treated with azithromycin 2g PO once. These patients should be re-evaluated seven days after treatment to ensure resolution of symptoms. Additionally, a test of cure should be performed three weeks after completion of treatment. Nucleic acid amplification tests remain positive in the presence of dead organisms and should not be used earlier than three weeks due to risk of false positive results.

d. In general, pregnant patients with PID should be admitted to the hospital and started on IV antibiotics. Doxycycline is category D for pregnancy and should be avoided. Consider alternative regimen such as clindamycin and gentamycin in consultation with obstetrics and gynecology (OB/gyn).

e. Of note, men who present with urethritis, epididymitis, or orchitis with suspected sexually transmitted infection should be treated similarly. Epididymitis may be due to enteric bacteria so also consider levofloxacin 500 mg orally once a day for 10 days (often older patients). Trimethoprim-sulfamethoxazole is an alternative for patients allergic to quinolones or with a history of tendon rupture.

3. What are indications for admission?
   a. Tubo-ovarian abscess
   b. Pelvic inflammatory disease in setting of pregnancy
      i. Pelvic inflammatory disease during pregnancy occurs most commonly within the first 12 weeks before a mucus plug develops which acts as a barrier to ascending infection.
      ii. Pregnant women with suspected PID are high risk for maternal morbidity and preterm delivery. These patients should be admitted and given parenteral antibiotics.
   c. Nausea, vomiting, fever, failure of outpatient therapy.

4. While in the ED her Affirm (rapid polymerase chain reaction [PCR] antigen test) is positive for Gardnerella vaginalis. Is this considered a sexually transmitted infection? What are the treatment options? What are the specific risks in pregnant women?
   a. Bacterial vaginosis (BV) is the most common vaginal infection in women ages 15-44. Sexual activity likely contributes to BV. While BV is not considered an STI, having BV can increase your chances of getting an STI. Bacterial vaginosis rarely affects women who have never had sex. Recommended bacterial vaginosis treatment for symptomatic women is metronidazole 500 mg orally twice daily x 7 days, metronidazole gel 0.5% intravaginally once daily x 5 days, or clindamycin cream 2% intravaginally once each night x 7 days.
b. Pregnant women with BV are more likely to deliver prematurely (early) or with low birth weight as compared to women who do not have BV while pregnant.

5. What is the differential for the patient’s painful vaginal lesions? What is the most likely diagnosis? What is the most appropriate treatment?

The most likely diagnosis is genital herpes simplex virus (HSV). Alternative etiologies include syphilis (painless), chancroid (painful), lymphogranuloma venereum (painless), and granuloma inguinale (painless).

a. All patients with first episode of HSV need to be treated with acyclovir or valacyclovir. The most common treatment recommendation is acyclovir 400 mg orally TID x 7-10 days or valacyclovir 1 g orally BID x 7-10 days. Patients with severe disease or complications (eg, disseminated infection, pneumonitis, or hepatitis) or central nervous system (eg, meningoencephalitis) need hospitalization and IV treatment.

6. The patient is discharged with the appropriate antibiotic regimen. Two days later her cervical swab returns positive for gonorrhea. Is this a reportable disease? What sexually transmitted infections must be reported to the health department?

a. Sexually transmitted diseases should be reported in accordance with state and local statutory requirements.

b. In Ohio, HIV/AIDS, hepatitis (A, B, C, D, E), syphilis, gonorrhea and chlamydia are all reportable. Ohio’s reportable disease list is found at: http://www.odh.ohio.gov/reportablediseases. There are other diseases on the list which are not sexually transmitted.

c. Instructors should review their own states requirements to discuss during the session.

Case 2: A 28-year-old incarcerated male presents to the ED for evaluation of “flu-like symptoms.” He reports having a nonproductive cough for about one week, fever, headache, neck pain, nausea, and vomiting. The prison guards report he has seemed confused over the last 24 hours. Past medical history is significant for HIV with an unknown recent CD4 count. The patient admits he has not seen his infectious disease specialist for more than a year. On exam, your patient is ill appearing. He opens eyes to talk to you, but complains of photophobia. He will not turn his head because it increases pain in his neck and back.

Question Prompts:

1. What is your primary concern in terms of diagnosis?
   a. This patient presents with signs and symptoms concerning for meningoencephalitis. Common pathogens in adults include S. pneumonia, S. aureus, N. meningitidis, and H. influenza.
   b. In immunocompromised patients such as the one described in this case one must also consider opportunistic infections such as Cryptococcus and toxoplasmosis.
      i. Cryptococcal meningitis (due to C. neoforms) – a type of fungal meningitis that usually affects immunosuppressed patients.

2. What type of isolation does this patient require?
3. How is the diagnosis of cryptococcal meningitis made?
   a. Cryptococcal meningitis is diagnosed off cerebral spinal fluid (CSF) analysis.
   b. Cryptococcal antigen testing (latex agglutination testing), PCR, (traditionally seen with India ink staining and microscopic evaluation), cryptococcal culture.
   c. Cerebral spinal fluid (CSF) classically shows low white blood cell count (WBC), slightly elevated protein, and low glucose. Patients will commonly exhibit elevated opening pressures (must be measured in lateral decubitus position).
   d. In the setting of severe altered mental status or focal neurologic deficits, consider computed tomography of the head to evaluate for alternative pathologies such as toxoplasmosis, cerebral abscess, and central nervous system (CNS) lymphoma.

4. What is the treatment?
   a. Intravenous amphotericin B and oral flucytosine
   b. Elevated intracranial pressures
      i. Therapeutic CSF drainage if opening pressure >27mmHg with a goal of <20mmHg.
         a. While there may be a concern for herniation, in the absence of mass this should not occur. This practice is supported by the Infectious Disease Association of America’s guidelines for management of cryptococcal meningitis.
         ii. Patients may require daily lumbar punctures (LP) until asymptomatic & CSF pressure is normal or stable
         iii. May require ventriculoperitoneal shunt

5. What are examples of AIDS defining illnesses?
   a. The list of AIDS defining illnesses include opportunistic infections and malignancies that in the setting of HIV confirm the diagnosis of AIDS.
   b. Below are a list of AIDS defining illnesses published by the Centers for Disease Control and Prevention (CDC):
      i. Bacterial infections, multiple or recurrent candidiasis of bronchi, trachea, or lungs
      ii. Candidiasis of esophagus
      iii. Cervical cancer, invasive
      iv. Coccidioidomycosis, disseminated or extrapulmonary Cryptococcosis, extrapulmonary
      v. Cryptosporidiosis, chronic intestinal (>1 month’s duration)
      vi. Cytomegalovirus disease (other than liver, spleen, or nodes); onset at age >1 month, Cytomegalovirus retinitis (with loss of vision)
      vii. Encephalopathy attributed to HIV
      viii. Herpes simplex: chronic ulcers (>1 month’s duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
      ix. Histoplasmosis, disseminated or extrapulmonary
      x. Isosporiasis, chronic intestinal (>1 month’s duration)
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xi. Kaposi sarcoma
xii. Lymphoma, Burkitt (or equivalent term)
xiii. Lymphoma, immunoblastic (or equivalent term)
xiv. Lymphoma, primary, of brain
xv. Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary; Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary; Mycobacterium, other species or unidentified species, disseminated or extrapulmonary; Pneumocystis jirovecii (previously known as “Pneumocystis carinii”) pneumonia
xvi. Pneumonia, recurrent
xvii. Progressive multifocal leukoencephalopathy
xviii. Salmonella septicemia, recurrent
xix. Toxoplasmosis of brain, onset at age >1 month
xx. Wasting syndrome attributed to HIV

6. If you did not know the patients CD4 count, what routine lab value may be used as a surrogate marker?
   a. A CD4 count less than 200/mm$^3$ is likely if the absolute lymphocyte count (ALC) on the CBC is less than 950/mm$^3$. The CD4 count is unlikely to be less than 200/mm$^3$ if the ALC is greater than 1,700/mm$^3$.
   b. This information can help predict the likelihood of opportunistic infections and which patients should undergo CD4 testing.

Suggested Readings:

Bacterial vaginosis – CDC fact sheet. Centers for Disease Control and Prevention. https://www.cdc.gov/std/bv/stdfact-bacterial-vaginosis.htm. Updated February 16, 2017. Accessed April 6, 2018.

Bacterial meningitis. Centers for Disease Control and Prevention. https://www.cdc.gov/meningitis/bacterial.html. Updated January 25, 2017. Accessed April 6, 2018.

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Appendix C: Tropical Diseases

Objectives

By the end of this small group session, learners will be able to:
1. List some common pathogens and diseases affecting travelers returning from foreign destinations.
2. Describe the typical presentation to the emergency department (ED) for malarial disease.
3. Discuss the risk factors for contracting malaria.
4. Review the treatment of malaria.
5. Describe the clinical presentations of dengue fever and discuss the appropriate workup.
6. Discuss the clinical manifestation of enteric fever and explore treatment objectives.

Case Studies

Case 1: A 16-year-old previously healthy female is brought to the ED by her parents with complaint of fever and fatigue. She has had paroxysmal fever for the past week to 103°F. Review of systems is notable for headache, myalgias, and dry cough. She denies any gastrointestinal symptoms, rashes, and skin lesions. Travel history includes a safari trip to Kenya four weeks ago with her family. She thinks she took her malaria prophylaxis but can’t remember. She does recall some mosquito bites one evening during the safari. Her vitals are temperature (T) 101.0°F, blood pressure (BP) of 110/70mmHg, heart rate (HR) 100/min, respiratory rate (RR) 18/min, and oxygen saturation (O2sat) 100% on room air.

Question Prompts:
1. What factors in the patient’s history raise your concern for possible travel-related illness? What other questions or historical features are useful when assessing fever in the returning traveler?
   a. The features of this presentation that are concerning are the travel to a malaria-endemic area (sub-Saharan Africa), the questionable compliance with malaria prophylaxis, and the mosquito bites. Other considerations for this patient (or any returning traveler with fever) should include: immunization status, immunocompetence, diet history while traveling, sick contacts including any treatment in local healthcare facilities, fresh water exposure, sexual encounters, animal bites or animal exposure, and potential bodily fluid exposures (eg, tattoos).
   b. Keep in mind that illness in a returning traveler does not necessarily represent tropical disease. Clinicians should consider typical domestic causes of fever and other constitutional symptoms such as pneumonia, urinary tract infection (UTI), and soft tissue infections. Also stay mindful of the global disease patterns for worldwide pathogens such as influenza. The peak incidence rates vary from region to region resulting in the ability for a patient to present with a common disease at an uncommon time for that region.
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c. While returning travelers may present with a spectrum of symptoms, fever is by far the most common symptom and also the symptom most consistently seen with acute life-threatening illnesses.

d. The differential for travel-related illness includes the following: malaria, dengue fever, enteric fever, Zika, Ebola, chikungunya, and Middle East respiratory syndrome coronavirus (MERS-CoV)—just to mention a few.

2. What travel-related illness is this patient’s presentation most concerning for and what is the mechanism of transmission for this disease? What are the diagnostic and therapeutic considerations for this disease?

a. While the presentation is somewhat nonspecific (as travel-related diseases often are), the main concern based on the locale traveled to is malaria. Specifically, the provider should be concerned for Falciparum malaria given the presence of *Plasmodium Falciparum* in this area. Malaria is a protozoan infection that is transmitted by the *Anopheles* mosquito. This mosquito tends to be most active at dusk. Typically, the incubation period for *P. Falciparum* is 7-14 days although it can extend up to 6 weeks.

b. The diagnostic test of choice for malaria is a peripheral blood smear with presence of parasites. This test should be performed three times to improve sensitivity. Other screening labs include: complete blood count (CBC), basic metabolic panel, liver function tests (LFTs), coagulation studies, blood culture, and lactate. More specific testing should be guided based on the other symptoms and concern for specific end-organ dysfunction. World Health Organization (WHO) criteria for severe malaria include one or more of the following: prostration, impaired consciousness, respiratory distress, multiple convulsions, circulatory collapse, pulmonary edema, abnormal bleeding, jaundice, hemoglobinuria, severe anemia (hemoglobin less than 7g/dL or hematocrit less than 20% in adults, less than 5g/dL or less than 15% in children less than 12 years), hypoglycemia, acidosis, or elevated lactate.

c. Management is comprised by initial resuscitation, appropriate anti-malarial medication, and screening/treatment of end-organ dysfunction. Most patients, like this one, do not require intervention for airway, breathing and circulation (ABCs), though some patients will have a severe presentation with their malaria. The adequate chemotherapy depends on the suspected strain of *Plasmodium* and the local resistance pattern. For this patient’s travel pattern, artesunate is the preferred parenteral antimalarial drug over quinidine for first-line therapy. For oral therapy, atovaquone-proguanil is preferred over chloroquine for *Falciparum* due to resistance patterns. Chloroquine is still appropriate for non-*Falciparum* malaria. Chemoprophylaxis with anti-malarial medication and reduction of mosquito exposure are cornerstones of disease prevention for malaria.

d. Complications of severe malaria are varied and can include the following: cerebral malaria, acute respiratory distress syndrome (ARDS), anemia, renal dysfunction, jaundice, blackwater fever (massive hemoglobinuria causing dark urine), hypoglycemia, shock, lactic acidosis, gastrointestinal (GI) symptoms, and disseminated intravascular coagulation. The specific complications should be treated aggressively in addition to initiation of the anti-malarial medication.
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e. Chikungunya, a mosquito-borne infection caused by the Chikungunya virus (CHIKV), may present similarly with fever, joint pain, headache, and rash. The infection is typically self-limited with symptoms resolving within a week. However, occasionally patients experience joint pain for months. Treatment is supportive.

f. Over the last five years there have been several outbreaks of Ebola first in West Africa and more recently in the Democratic Republic of Congo. While the World Health Organization declared the most recent outbreak over in July 2018, Ebola should still be considered for any traveler from these areas presenting with hemorrhagic fever.

Case 2: A 28-year-old male with past medical history of gastroesophageal reflux disease presents to the ED with complaint of fever and diarrhea. He has noticed fever over the past two weeks to 102°F. He has two days of loose stool, which is described as “pea soup.” Review of systems is additionally positive for mild abdominal pain, malaise, headache, and arthralgias. His travel history includes returning from a two-week trip to India one month ago. His vitals are temp 101°F, blood pressure (BP) 100/60mmHg, heart rate (HR) 70/min, respiratory rate (RR) 16/min, and oxygen saturation (O₂sat) 98% on room air. His abdomen is slightly distended but soft and without signs of peritonitis.

Question Prompts:

1. What type of travel-related illness is of highest concern? Describe the natural course of this disease process.

   a. The primary etiology for this presentation is enteric fever, which is caused by infection with *Salmonella* species *S. typhi* or *S. paratyphi*. This disease accounts for approximately 20% of travel-related acute life-threatening fever. The distribution is widespread across Central and South Americas, Africa, and Asia—though it is highest on the Indian subcontinent. This is also a disease that can affect pediatric patients more severely. The incubation period is 10-20 days with an illness pattern that follows four one-week phases. The first week includes fever with nonspecific symptoms of headache, congestion, cough, and malaise. The second week shows progression to apathy, higher fevers with relative bradycardia, abdominal distention, and “rose spot” rash. In severe cases the toxicity continues to rise into the third week with tachypnea, diffuse ‘pea soup’ diarrhea, weakness, and mental status changes. The fourth week shows resolution and improvement in these symptoms.

   b. The other travel-related illness that presents with diarrhea is traveler’s diarrhea. This entity typically does not include fever though, and it is much more self-limited and benign. Transmission is via fecal-oral route, but the most common pathogen involved in this disease is Enterotoxigenic *E. coli*. Some other pathogens include *Campylobacter, Shigella*, and *Giardia*. This disease process has a much shorter incubation period than enteric fever and overall illness timeframe. Most cases are self-limiting and management is largely symptomatic with loperamide and oral hydration. Antibiotic therapy with three to five days of ciprofloxacin can be considered for more prolonged cases (greater than 10-14 days), or in severe cases in patients with fever, abnormal vital signs, evidence of dehydration, or electrolyte derangements.
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2. List the treatment objectives and management for this patient.
   a. Enteric fever treatment consists of supportive care for fever and dehydration with use of appropriate antibiotics. The first-line antibiotic may vary by region, but typically includes one of the following: chloramphenicol, amoxicillin, or co-trimoxazole. Second line agents in areas of resistance include ciprofloxacin, ceftriaxone, or azithromycin. Use of dexamethasone is advised for patients with evidence of shock secondary to enteric fever. It is important to note that up to 20% of these patients will relapse and require re-treatment.

Case 3: A 46-year-old female presents to the ED with complaint of fever and diffuse bone and joint pain for 3 days. The fever was abrupt at onset to 103°F. Review of systems is additionally positive for severe headache with retro-orbital pain and myalgias. She denies any gastrointestinal symptoms at this point. She recently returned from a business trip to Colombia. Although she denies any rural exposure, she does admit to several mosquito bites while there. On exam, she is febrile but vital signs are otherwise within normal limits. Neurologic exam is grossly normal and she does not have any evidence of meningismus.

Question Prompts:

1. Peripheral blood smear is quickly done in the ED and negative for malaria. What is the most likely etiology for this patient’s fever and symptoms? Compare and contrast the transmission pattern for this disease with that of malaria.
   a. This patient is suffering from dengue. Dengue comes in two disease patterns: Dengue fever (DF) and dengue hemorrhagic fever (DHF). Dengue viremia inherently and specifically involves endothelial dysfunction. The degree of this dysfunction is what defines DF from DHF. Dengue is the most common arboviral infection with other arboviral infections including yellow fever and Japanese encephalitis virus. This infection is similar to malaria in its mosquito-borne transmission pattern except the vector is a different species of mosquito: the *Aedes aegypti*. This species is different than the *Anopheles* because it is found in urban areas and is more active during daytime hours.
   b. Dengue fever and DHF clinically start in the same pattern with abrupt onset of fever accompanied by headache, vomiting, myalgias, severe arthralgias (hence the colloquial term “break-bone fever”), and sometime rash. This initial phase lasts 3-7 days and is often followed by resolution of symptoms. A smaller proportion of patients will progress to a second critical phase that is defined by a systemic vascular leak syndrome. Evidence of bleeding and increased vascular permeability is what defines DHF from DF.
   c. The WHO criteria for DHF includes:
      1. Fever
      2. Hemorrhagic tendencies
      3. Thrombocytopenia
      4. Evidence of plasma leakage.
   d. This phase is short (48-72 hours) but mortality is high if untreated. The disease terminates in a third recovery phase that includes rapid symptom improvement with lingering rash and fatigue.
2. Describe the medical management of DF and DHF.
   a. Medical management is largely supportive since there is currently no effective antiviral agent for DF/DHF. Pain symptoms are treated with analgesics although aspirin should be avoided due to the bleeding risk. If patients are failing oral hydration, resuscitation with isotonic fluids is indicated. Severe shock can be treated additionally with colloid fluids and possibly blood transfusion if severe DHF with anemia develops.
   b. Prevention is an important concept for dengue, similar to malaria. This consists primarily of measures to reduce mosquito bites (long-clothing, use of DEET, and avoidance of outdoor activity during most active biting periods). Unlike malaria, there is no chemoprophylaxis available for DF/DHF. There is currently one licensed vaccine called Dengvaxia, with more in development. These promise for significant reduction in the disease state of DF/DHF.

Suggested Readings:

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Appendix D: 
Angioedema and Anaphylaxis

Objectives

By the end of this small group session, learners will be able to:

1. Review types of angioedema and hypersensitivity reactions.
2. Differentiate angioedema from histaminergic edema and anaphylaxis.
3. Discuss criteria regarding management of the airway in patients with angioedema or anaphylaxis.
4. Review pharmacotherapy of angioedema and anaphylaxis.
5. Discuss appropriate disposition of angioedema and anaphylaxis.

Case Studies

Case 1: Mr. Jones is a 45-year-old male with a history of hypertension who presents to the emergency department with a chief complaint of lip swelling. He first noticed the swelling when he awoke. The swelling progressed over the first few hours but over the last 6 hours has stabilized. It is not painful nor pruritic. He denies any other symptoms and specifically does not endorse issues breathing, swallowing, rash, or abdominal pain. He denies any known drug or seasonal allergies. He denies recent changes to his antihypertensive medications but cannot remember their names. This has never happened to him, and there is no family history of similar episodes. On exam he is well appearing and in no distress. His vitals are temperature (T) 98.6°F, heart rate (HR) 80/min, blood pressure (BP) 150/80mmHg, respiratory rate (RR) 12/min, oxygen saturation (O$_2$Sat) 100% on room air (RA). Physical exam reveals marked non-pitting, non-tender swelling of the upper lip. Oropharyngeal, pulmonary, and abdominal exams are normal.

Question Prompts:

1. What is the most likely cause of his lip swelling? What is the pathophysiology of this disease process?
   a. There are several subtypes of angioedema. The two most common are angiotensin-converting enzyme (ACE) inhibitor-induced angioedema and hereditary angioedema (HAE). Less common forms of angioedema include physically induced angioedema (brought on by intense heat exposure or physical activity) and acquired angioedema. This patient is most likely suffering from ACE inhibitor-induced angioedema from use of lisinopril. He denies a family history of spontaneous soft tissue swelling so HAE is less likely. He has no urticarial or histaminergic type signs or symptoms so anaphylaxis is also less likely.
   b. The pathophysiology of angioedema, irrespective of the cause, is mediated by bradykinin. Bradykinin is a vasoactive nonapeptide that is formed as an end product of the kinin-kallikrein- system. Bradykinin acts on receptors of the endothelium leading to increased vascular permeability and subsequent formation of edema.
Patients with HAE have deficiency in either the functionality or quantity of C1 esterase inhibitor (C1-INH) which is responsible for inhibiting conversion of kallikrein to bradykinin. Lack of C1-INH leads to increased bradykinin levels and, in turn, angioedema.

Angiotensin I converting enzyme (ACE) is responsible for breakdown of bradykinin. Patients taking ACE inhibitors are thus prone to developing high levels of bradykinin which can cause angioedema.

2. What is the appropriate initial management and diagnostic workup in this patient?
   a. The initial management of patients with angioedema is focused on the need for airway intervention. Patients who demonstrate evidence of laryngeal edema should be intubated early for airway protection. Airway involvement may be ascertained on a clinical basis by evaluating for dysphonia, difficulty tolerating oral secretions, and stridor. These patients should be intubated emergently. Alternatively, in equivocal cases, the airway should be visualized either by laryngoscopy or nasopharyngoscopy with all equipment available for intubation.
   b. In this case, the patient’s airway is patent and he does not have any signs of laryngeal involvement and does not require any immediate interventions. In more equivocal cases, nasopharyngoscopy can be used to evaluate for edema of the glottis structures.
   c. Diagnosis of angioedema in the emergency department is based on clinical presentation, history, and physical examination. Diagnostic testing aimed at determining the exact cause of the angioedema is beyond the means of the emergency department and laboratory testing may take several days to result. Furthermore, there is no definitive diagnostic test for ACE inhibitor-induced angioedema. If there is a suspicion for HAE, serum C4 and C1-INH levels are often ordered as a screening test followed by C1-INH levels for confirmation. (See Case 2)

3. What is the appropriate treatment for this patient? Should he be intubated for airway protection?
   a. The Ishoo staging of angioedema helps predict which patients will require airway intervention based on the location and extent of the edema.

   | Stage | Site       | Episodes (%) | Outpatient Treatment (%) | Floor Treatment (%) | ICU Treatment (%) | Intervention (%) |
   |-------|------------|--------------|--------------------------|---------------------|------------------|------------------|
   | I     | Face, lip  | 31           | 48                       | 52                  | 0                | 0                |
   | II    | Soft palate| 5            | 60                       | 40                  | 0                | 0                |
   | III   | Tongue     | 32           | 26                       | 7                   | 67               | 7                |
   | IV    | Larynx     | 31           | 0                        | 0                   | 100              | 24               |

   b. This patient’s edema is isolated to his lip, making him Ishoo stage I. Patients with stage I angioedema rarely require airway intervention. Thus, it is reasonable to observe this patient. In contrast, edema involving the tongue and larynx commonly requires airway intervention.
Pharmacologic treatment of ACE inhibitor-induced angioedema in the ED has two phases: management of acute episodes and short-term prophylaxis.

i. The first step is discontinuation of the offending agent which in this case is lisinopril.

ii. Unlike histaminergic angioedema such as anaphylaxis, when treating bradykinin-mediated angioedema, antihistamines, steroids and epinephrine have limited, if any, utility. However, due to their low cost and minimal side effects, it is often protocol to administer H1 blockers, H2 blockers, and steroids.

iii. Fresh frozen plasma (FFP) (class II recommendation): Although the data is limited and of poor quality, FFP is often given to patients with angioedema. In theory, administration of FFP will replete the patient’s stores of C1-INH which in turn prevents further production of bradykinin. The dose of 10-15mL/kg.

iv. Icatibant (Class II recommendation): Icatibant is a bradykinin receptor antagonist that is FDA approved for treatment of HAE. In patients with HAE, icatibant was shown to decrease the time to symptom relief from 18.5 to 1.5 hours and complete symptom resolution from 36.0 to 8.0 hours when compared to placebo. The evidence for use of icatibant in ACE inhibitor-induced angioedema has been limited to case reports and case series. It is currently used off-label. Use of icatibant [30mg subcutaneous (SC) every 6 hours with max 90mg per 24-hour period] should be reserved for severe cases and only after discussion with the patient and in consultation with pharmacy since it is expensive (~$7000 per dose). Another option is ecallantide [30 mg (3 mL) SC administered in 3 separate 10 mg (1 mL) injections], which acts by selectively and reversibly inhibiting plasma kallikrein, preventing bradykinin generation. It is used in the same manner as icatibant.

4. What is the most appropriate disposition for this patient?
   a. Disposition should be made on the basis of the clinical presentation and likelihood for needing airway intervention. This can best be predicted with the Ishoo staging system (see above). Patients with isolated lip/face swelling or soft palatal swelling may be placed in observation. Conversely, those with lingual edema should all be admitted to the ICU for close airway monitoring.
   b. Patients admitted placed in observation will be routinely watched for at least 4-6 hours after peak clinical edema before discharge.
   c. For this patient, his swelling is limited to his lip and thus he would be an appropriate candidate for observation.

5. You’re ready to discharge the patient. You have counseled the patient on discontinuation of his lisinopril but you ask yourself, is it safe to start him on an angiotensin receptor blocker (ARB)?
   a. The use of ARBs after an episode of ACE inhibitor-induced angioedema is controversial. A meta-analysis in 2008 showed that the risk of angioedema on an ARB after confirmed ACE inhibitor-induced angioedema is 3.5%-9.4%. Because there are many treatment options for hypertension, many would avoid ARBs in patients with a history of ACE inhibitor-induced angioedema.
Case 2: A 22-year-old female with no known past medical history presents with a chief complaint of hoarse voice, tongue swelling, and difficulty breathing. She states that her symptoms started a few hours prior to arrival. She denies any obvious precipitating factors. She was not eating or taking medications prior to the onset of her symptoms and she has no known allergies. She notes she has had similar albeit milder episodes in the past, but they resolved spontaneously and she never sought medical attention. When asked about family history she says that her mother has had throat swelling several times requiring intubation. Review of systems is remarkable for colicky abdominal pain. She denies pain, rash, pruritus, chest pain, fever, and chills. On physical exam she is in moderate respiratory distress with tachypnea, dysphonia, and mild stridor. Oropharyngeal exam reveals significant lingual edema and swelling of the posterior structures. Her vitals are T 98.6°F, HR 110/min, RR 25/min, BP 110/60mmHg, O₂sat 95% on RA.

Question Prompts:

1. What is the most likely diagnosis? What is a likely explanation of her abdominal pain?
   a. This patient is most likely suffering from HAE. The key to this case is eliciting a family history.
   b. Hereditary angioedema is most often inherited in autosomal dominant fashion.
   c. There are three types of HAE. The differences are beyond the scope of emergency medicine practice.
   d. Just as in anaphylaxis, angioedema can affect the gastrointestinal mucosa and can produce abdominal pain and rarely bowel obstruction when severe.

2. What is the most appropriate management of this patient? What diagnostic tests should be ordered?
   a. In any case of angioedema there should be a low threshold to establish a definitive airway. This patient demonstrates dysphonia, stridor, and tachypnea suggesting that she is suffering from angioedema involving the larynx. The most appropriate next step in management is emergent intubation for airway protection.
   b. When preparing to intubate this patient it is crucial that you identify predictors of difficulty with both bag valve mask ventilation (BVM) and direct laryngoscopy. This patient will be predicted to be difficult to bag due to obstruction from lingual edema. Because this patient cannot be safely rescued with BVM, paralysis and rapid sequence intubation are contraindicated. This patient’s lingual edema will make direct laryngoscopy very difficult. Although video laryngoscopy is an option, it may be difficult to physically fit the blade into the mouth. The most appropriate method of intubation in this case is fiberoptic nasotracheal intubation. The patient should be sat upright and sedated with an agent such as ketamine. A paralytic should be available for use if the cords are adducted. It is vital that a double set up be available at the bedside in case emergent surgical airway is necessary. Of note, laryngeal mask airways (LMAs) or other extraglottic devices may not be effective in cases of severe lingual edema. It should be cautioned that any physical irritation of the airway during evaluation or intubation may increase the edema present and result in further airway compromise.
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c. In patients with suspected but not confirmed HAE, order a C4 and C1-INH functional and quantitative levels. While these will not affect management in the ED, the results will help facilitate inpatient evaluation and future treatment.

3. What options are there for pharmacotherapy?
   a. In addition to antihistamines, steroids, FFP, and icatibant/ecallantide detailed in Case 1, patients with HAE are candidates for C1-INH replacement therapy with C1 esterase inhibitor sold under the brand name Berinert.

4. What is the most appropriate disposition for this patient?
   a. Any patient with concern for airway involvement should be admitted to the ICU for close airway monitoring. Consider using the Ishoo staging when determining the best disposition.

| Stage | Clinical Findings                     | Disposition          |
|-------|---------------------------------------|----------------------|
| I     | Facial rash, facial edema, lip edema  | Home vs Admission    |
| II    | Soft palate edema                     | Home vs Admission    |
| III   | Lingual edema                         | ICU                  |
| IV    | Laryngeal edema                       | ICU                  |

Case 3: A 22-year-old male presents to the emergency department in respiratory distress. The patient was at a church pot-luck when he was found unresponsive. When EMS arrived, they found the patient confused, wheezing, and diaphoretic. The patient’s vital signs were HR 115/min, BP 84/40mmHg, RR 26/min, O₂ sat 92% on RA, afebrile. The medics gave the patient albuterol and started a fluid bolus with minimal improvement. On your evaluation you see a patient in acute distress, with tight breath sounds. You appreciate a rash on the chest and extremities. The rash is erythematous, with smooth, slightly elevated papules or plaques. The patient is unable to provide any history, and no family is present on the patient’s arrival. The registration staff member finds a life-alert card in the patient’s wallet that says the patient is allergic to peanuts.

Question Prompts:

1. What are your first steps in managing this patient? What medication could potentially rapidly improve the patient’s condition?
   a. After making the diagnosis of presumed anaphylaxis, immediately have a nurse obtain epinephrine 0.3–0.5 mg (1mg/ml solution, 1:1000. When managing anaphylaxis, the A in ABC is adrenaline, not airway! Of note, code epinephrine is more dilute 0.1mg/ml or 1:10,000). Have nurse pull it from the pyxis. It comes in a small glass vial. The epinephrine should be administered intramuscular (IM) in the anterolateral thigh. Subcutaneous administration should be avoided because it has a slower onset of action. Intravenous (IV) administration is possible; however, recommendations recommend IM route since may have less chance of cardiac adverse reactions. Never delay administration for placement of an IV.
   b. After ordering epinephrine, evaluate and stabilize airway, breathing, and circulation (ABCs), place an IV line, cardiac and O₂ monitor. Intubate the patient early if there is concern for angioedema causing airway obstruction. Give albuterol. You can also give adjuncts (steroids,
H1 blockers, H2 blockers); however, these adjuncts have not been shown to affect outcomes.

2. Discuss the diagnostic criteria for anaphylaxis
   a. In short, if TWO organ systems are involved (skin, GI, respiratory, cardiovascular), they meet criteria for anaphylaxis. So, patients with nausea and rash should get epinephrine. Also, sick patients who you are thinking about anaphylaxis should get epinephrine.

   ▪ **Criterion 1** — Acute onset of an illness (minutes to several hours) involving the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
     - Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).
     - Reduced blood pressure (BP) or associated symptoms and signs of end-organ malperfusion (eg, hypotonia [collapse] syncope, incontinence).
     - Note: Skin symptoms and signs are present in up to 90 percent of anaphylactic episodes. This criterion will therefore frequently be helpful in making the diagnosis.

   ▪ **Criterion 2** — Two or more of the following that occur rapidly after exposure to a LIKELY allergen for that patient (seconds to several hours):
     - Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).
     - Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).
     - Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).
     - Persistent gastrointestinal symptoms and signs (eg, crampy abdominal pain, vomiting).
     - Note: Skin symptoms or signs are absent or unrecognized in up to 20 percent of anaphylactic episodes. Criterion 2 incorporates gastrointestinal symptoms in addition to skin symptoms, respiratory symptoms, and reduced BP. It is applied to patients with exposure to a substance that is a likely allergen for them.

   ▪ **Criterion 3** — Reduced BP after exposure to a KNOWN allergen for that patient (minutes to several hours):
     - Reduced BP in adults is defined as a systolic BP of less than 90 mmHg or greater than 30 percent decrease from that person’s baseline.
     - In infants and children, reduced BP is defined as low systolic BP (age-specific) or greater than 30 percent decrease in systolic BP.
       - * Low systolic BP for children is defined as:
         - Less than 70 mmHg from 1 month up to 1 year.
         - Less than (70 mmHg + [2 x age]) from 1 to 10 years.
         - Less than 90 mmHg from 11 to 17 years.
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- Note: Criterion 3 is intended to detect anaphylactic episodes in which only one organ system is involved and is applied to patients who have been exposed to a substance to which they are known to be allergic (for example, hypotension or shock after an insect sting).

- There will be patients who do not fulfill any of these criteria, but for whom the administration of epinephrine is appropriate. As an example, it would be appropriate to administer epinephrine to a patient with a history of near-fatal anaphylaxis to peanuts who presents with urticaria and flushing that developed within minutes of a known or suspected ingestion of peanuts.

3. What type of hypersensitive reaction is the patient experiencing?
   a. Anaphylaxis is a type I hypersensitivity reaction caused by Immunoglobulin E (IgE).

| Type I    | Allergy      | IgE            | Anaphylaxis                  |
|-----------|--------------|----------------|------------------------------|
| Type II   | Cytotoxic    | IgM, IgG bind cells | Hemolytic transfusion reactions |
| Type III  | Immune Complex | IgM, IgG bind soluble antigen | Rheumatoid arthritis |
| Type IV   | Delayed      | T-cells        | Contact dermatitis          |

4. After receiving the appropriate treatment, the patient rapidly improves. After 30 minutes, the patient is completely asymptomatic. What is the disposition plan?
   a. Previously recommendations would say to observe all patients for 4-8 hours after improvement in symptoms.
   b. However, there are no consensus recommendations on period of time to observe patients who resolve completely from anaphylaxis.
   c. In general, patients who have complete resolution of symptoms with a single dose of epinephrine can be discharged from the ED after 4-6-hour periods of observation. Patients that presented in profound shock, or required multiple doses of epinephrine, should be observed for at least 8 hours and may require admission.
   d. All patients should be discharged with an epinephrine pen prescription, including instructions on when on how to use the pen correctly.

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Appendix E:
Transplant Related Emergencies

Objectives

By the end of this small group session, the learners will be able to:

1. Review the presentations of common transplant complications in patients with lung, kidney, and pancreas transplants.
2. Discuss the diagnosis and management of complications in solid organ transplant patients.
3. Distinguish features of infection from rejection in patients with renal transplants.

Case Studies

Case 1: A 40-year-old male with long-standing type 1 diabetes and severe hypertension presents 11 months after having a kidney transplant. His course has been unremarkable to date with a baseline creatinine of 1.3. Today he had a low-grade temp to 99.5°F at home, nausea and vomiting, and pain to the right lower pelvis where his graft is located. His vitals are temperature (T) 100.1°F, blood pressure (BP) of 170/95mmHg, heart rate (HR) 100/min, and respiratory rate (RR) 18/min. He has tenderness over his graft and some epigastric tenderness. His labs show a normal white blood cell count (WBC), urinalysis positive for 6 to 10 WBC per high-power field (HPF), positive bacteria and large protein. His creatinine is now 3.4.

Question Prompts:

1. Describe the differential diagnosis and a strategy to work up and treat this patient.
   a. The differential for this patient includes infection (UTI), organ rejection, or toxicity of transplant medications.
      i. Infection:
         1. Infectious etiologies should be considered based on the presence of urine leukocytes, fever, graft tenderness and bacteria in the urine. Urinary tract infections can involve the native kidneys, transplanted kidney, or the lower urinary tract. Because of their immunocompromised status, transplant patients with serious bacterial infections may not present with leukocytosis or a true fever.
         2. Workup: The patient needs to have cultures of blood and urine. Imaging with ultrasound or computed tomography (CT) is indicated to determine if there is hydronephrosis or post-operative complications such as vascular occlusions, hematoma, bleeding, urine leak or lymphocele. The use of intravenous (IV) contrast should be discussed with the patient and transplant specialist and the benefits of using contrast must be weighed against the risks of contrast-induced nephropathy.
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3. Treatment: The patient should receive IV antibiotics. Empiric coverage should be initiated based on hospital antibiogram as well as any of the patient’s previous culture results.

ii. Rejection:
   1. Signs of acute rejection include hypertension, graft tenderness with low grade fever, worsening renal function, oliguria, and proteinuria. Rejection can also be chronic (chronic allograft nephropathy) and if so this is characterized by progressive renal failure and proteinuria
   2. Workup: Complete blood count (CBC), basic metabolic panel (BMP), urinalysis, and renal graft ultrasound. At times a biopsy may be needed to determine if rejection is occurring.
   3. Treatment: The initial treatment of rejection involves IV steroids for three days.

iii. Toxicity of transplant medications:
   1. Workup: If the patient has nephrotoxicity from either cyclosporin or fk506 (Tacrolimus) a trough level (drawn at the time of the expected dose of the medication) will be elevated. Nephrotoxicity can be precipitated by using meds which inhibit the cytochrome P-450 enzyme system such as amiodarone, diltiazem or verapamil.
   2. Treatment: Medication changes and dosage adjustments made in consultation with a transplant specialist.

b. For this patient the fever, leukocytes and bacteria suggest infection but this will need confirmation by cultures. Fever, graft tenderness and proteinuria suggest rejection too. So infection, rejection, or both could be present. The patient should be worked up and treated for infection and work with the transplant specialists to determine if treatment of rejection should be initiated. A cyclosporin or fk506 trough level should be considered.

2. You suspect that this patient’s graft is infected. When is this patient at highest risk for opportunistic infections and what are the most common infections?
   a. In the first month post-transplant: Consider post-operative infections and infections from the donor
      i. Infections related to transplant procedure
      ii. Specific nosocomial infections: Nosocomial pneumonia or UTI, surgical site, from donor organ (bacteria: methicillin-resistant Staphylococcus aureus [MRSA], vancomycin-resistant enterococcus (VRE), tuberculosis (TB); fungi: Candida; parasites: Toxoplasmosis), or C. difficile.
   b. One to six months post-transplant: Opportunistic infection risk is the greatest
      i. Immunomodulating viral infections and Epstein-Barr virus (EBV)
         1. Cytomegalovirus (CMV) can be treated with ganciclovir and CMV specific immunoglobulin
      ii. Hepatitis B and C
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iii. Opportunistic infections: *Pneumocystis*, Histoplasmosis, Coccidioidomycosis, *Cryptococcus*, Hepatitis, CMV, TB, EBV, surgical site infection, reactivation of dormant host infections (CMV, herpes zoster, herpes simplex virus, EBV)

c. More than six months post-transplant:
   i. Increased susceptible to Influenza, *S. Pneumoniae*, UTIs, *Legionella*, and *Listeria*
   ii. Varicella and HSV but still risk of Influenza and EBV

3. How would you determine if there is a transplant medication toxicity?
   a. One should be suspicious of medication toxicity in the setting of rising creatinine and proteinuria without fever. As mentioned above, medication toxicity is best determined by getting a trough level. An elevated trough level is highly suggestive of medication toxicity.

Case 2: A 30-year-old patient presents ten months after a lung transplant. He has noted a dry cough, shortness of breath, and low-grade fevers. Vitals: T 99.6°F, BP 130/85mmHg, RR 22/min, HR 100/min, and O₂sat 90% on room air. Lung exam revealed bilateral crackles and decreased breath sounds at the bases. Labs are pending but the chest X-ray revealed bilateral small effusions and perihilar opacities and diffuse interstitial infiltrates.

Question Prompts:

1. Explain the work up and treatment of this patient.
   a. There are several possible causes of this presentation, but infection and rejection are highest on the differential.
      i. Infection:
         1. Workup: Labs, blood cultures, chest X ray, and early pulmonary consultation for bronchoalveolar lavage (BAL) and transbronchial biopsy (TBB).
         2. Treatment: Empiric antibiotics should be initiated. Acute infections in the first 30 days are usually from colonization of donor lung tissue that can manifest due to immunosuppression. Therefore, coverage at this time includes coverage similar to hospital acquired pneumonia (HAP) (multidrug-resistant *Pseudomonas*, Enterobacteriaceae and MRSA). Antifungals may be considered as well. After the first month post-transplant, atypical infections such as chlamydia, legionella, and mycoplasma are possible and therefore azithromycin should be added to the antipseudomonal beta-lactam and vancomycin.
      ii. Rejection:
         1. Workup: The workup for rejection is the same as for infection because infections should be ruled out and empirically treated while awaiting results of BAL and TBB.
         2. Treatment: Rejection treatment includes high dose IV steroid for at least three days followed by a prednisone taper over several weeks. Anti-rejection medication may need adjusting or changing. But in cases of acute cellular rejection high dose IV glucocorticoids therapy should be initiated for three days followed by a chronic taper of prednisone over weeks.
This patient has a predominant picture of acute rejection. However, infection is still possible. Early consultation for BAL and possible TBB should be done. Initiation of both steroids and antibiotics should be considered.

2. Lung transplant patients have a very high incidence of chronic rejection. Describe how this is diagnosed, evaluated, and treated.
   a. Cellular rejection is the predominant type of acute lung allograft rejection mediated by T lymphocyte recognition of major histocompatibility complexes (termed MHC or HLA). Humoral rejection is less common and due to antibodies directed against donor tissue. Chronic rejection in lung transplantation is mainly due to bronchiolitis obliterans or bronchiolitis obliterans syndrome (BOS). Contributing factors include acute rejection episodes, infections (viral or bacterial or fungal) and gastroesophageal reflux disease. Although dyspnea on exertion and cough are the most common symptoms, decline in pulmonary function tests (PFTs) may be the main sign, and there is usually a decline in FEV₁ (forced expiratory volume-one second) the decline in FEF₂₅₋₇₅ (forced expiratory flow from 25% to 75% of vital capacity) is even more sensitive. Lung transplant patients regularly check home spirometry. Chest X-ray may be normal but later there may be hyperinflation or bronchiectasis on chest X-ray or CT scan. Infectious changes on imaging studies should always be worked up and treated aggressively.
   b. Less commonly, restrictive allograft syndrome causes a restrictive pattern on PFTs. Computed tomography may show reticular opacities more in the upper lung fields and ground glass infiltrates.
   c. Bronchoalveolar lavage is often used to evaluate other causes such as a stricture, chronic infection or malignancy. Transbronchial biopsy is often used to confirm the diagnosis.
   d. Prevention by treating patient with rejection meds, azithromycin, medications for GERD and anti-CMV medications is the best strategy.
   e. Treatment of BOS is initiated by adding azithromycin, changing immunosuppression medications (switching from cyclosporin to tacrolimus, substituting mycophenolate for azithromycin). In refractory BOS, consider photopheresis, total lymphoid irradiation, plasmapheresis, anti-thymocyte globulin, or re-transplantation.

Case 3: A 40-year-old female with a history of pancreatic transplantation two years ago presents with three days of mild abdominal pain, distension, nausea, and low grade fevers. Recent labs including CBC, BMP, liver function tests and lipase done by her transplant specialist were normal two weeks ago. Vitals: T 100.8°F, BP 120/75mmHg, RR 22/min, HR 100/min, and O₂sat 97% on room air. Today her BMP and CBC are normal but lipase is newly elevated.

Question Prompts:

1. How frequently are pancreas-only transplants performed?
   a. Currently 75% of pancreas transplants are done with kidney transplants, and only 9% are performed solely as pancreas transplants.
2. How do most cases of pancreatic rejection present?
   a. Most patients with pancreatic transplant rejection are asymptomatic. Cases are often
diagnosed on outpatient screening labs showing elevated serum lipase and glucose.

3. Explain the work up and treatment for this patient.
   a. In addition to organ rejection, one should also consider other routine sources of abdominal
pain.
   b. Work up of these patients include the usual abdominal pain labs, (CBC, basic metabolic
panel, liver function tests, lipase, urinalysis) but also consider hemoglobin A1C, urine
amylose, C-peptide, serum fk506, or serum cyclosporin.
   c. Regarding rejection, this should be suspected with elevated lipase and/or amylase,
unexplained fever or leukocytosis, tenderness to the graft, and elevated fasting glucoses.
Hemoglobin A1C may also be elevated and there may be hematuria. Lipase is felt to be
more sensitive than amylase. If the pancreas drains in the bladder then urinary amylase can
be measured to see if this is decreasing.
   d. Imaging can be done with ultrasound (US) or CT looking for evidence of pancreatitis or
peripancreatic fluid collection, infection, exocrine leak or small bowel obstruction. If
pancreatitis is present, this may be viral (CMV) or chemical.
   e. Rejection is confirmed by pancreas allograft biopsy which is done with US guidance.
   f. In cases of acute rejection, pulse dose IV steroids are used, and prednisone is tapered over
several weeks. Additional mycophenolate can be used and plasmapheresis with intravenous
immunoglobulin is used in cases of antibody mediated rejection.
   g. This was a case of acute rejection and needed labs, probably US or CT, admission, and
initiation of high dose steroids.

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Appendix F:
Collagen Vascular Diseases

Objectives

By the end of this small group session, learners will be able to:
1. Review common presentations of collagen vascular disease-related problems.
2. Discuss the diagnosis and workup of complications of common collagen vascular diseases including systemic lupus erythematosus, dermatomyositis, and ankylosing spondylitis.
3. Discuss the basic strategies for treatment of collagen vascular diseases.
4. Discuss appropriate dispositions for patients presenting with collagen vascular diseases and associated complications.

Case Studies

Case 1: A 35-year-old female with a long-standing systemic lupus erythematosus (SLE), hypertension, and chronic kidney disease presents with a chief complaint of chest pain. She has noted this pain the past three days and describes it as episodic, both sharp and pressure-like, left-sided, and lasting anywhere from a few minutes to an hour. It has both a pleuritic and exertional component. Associated symptoms include shortness of breath and mild chronic cough. She denies a history of cardiac or pulmonary disease. She takes prednisone and methotrexate for her SLE. Her vital signs are temperature (T) 99.0°F, heart rate (HR) 100/min, respiratory rate (RR) 20/min, oxygen saturation (O2sat) of 94% on room air. On exam her lungs are clear to auscultation. Her electrocardiogram (ECG) show a heart rate of 99 and slightly low voltage. Labs are remarkable for worsening anemia, thrombocytopenia, and renal failure.

Question Prompts:

1. Describe the general approach to the management of SLE. What are the common presenting symptoms? What are the overall goals of treatment?
   a. The goals of treatment are to improve survival, achieve low disease activity, prevent organ damage, minimize drug toxicity, and improve quality of life.
   b. Fatigue is the most common symptom (80% to 100%) but arthritis or arthralgia occur in over 90% and may be migratory and polyarticular and symmetric. Skin involvement with lesions consistent with vasculitis is the next most common. Possible treatments depend on whether the patient has intermittent flares, chronic active disease, or quiescent disease. Flares can be mild (fevers, rash or arthralgia), moderate (chest pain, arthritis) or severe [new or worsening renal disease or central nervous system (CNS) disease]. Medications include glucocorticoids (acute or chronic), hydroxychloroquine, azathioprine, cyclophosphamide and methotrexate. All of these medications are immunosuppressants that inhibit lymphocyte-mediated tissue damage.
c. In general, mild disease can be treated with hydroxychloroquine or low dose prednisone. Those with moderate flares (non-organ threatening) should be treated with short courses of higher doses of prednisone and hydroxychloroquine or chloroquine. Steroids can be tapered once symptoms improve and azathioprine or methotrexate can be used to avoid long term steroid use.

d. Admission is indicated for a new diagnosis and moderate or severe flares characterized by organ- or life-threatening disease. Organs involved with severe or life-threatening disease include renal or CNS as manifested by acute encephalitis or seizures.
   i. These patients require high doses of systemic steroids (0.5 to 1.0 g/day of methylprednisolone) often given in combination with other immunosuppressive agents. A number of other immunosuppressive agents have also been used for refractory disease including rituximab and belimumab. Immunosuppressive agents are also given for frequent flares. These medications should only be initiated by an ED physician after consultation with rheumatology.

2. Discuss the work up and differential for this patient’s chest pain.
   a. Systemic lupus erythematosus patients are at risk for thromboembolic disease especially those with antiphospholipid antibodies. Therefore, pulmonary embolism (PE) and acute coronary syndrome must be in the differential. Serositis including pleuritis and pericarditis should be considered and should be suspected if there is a new pleural effusion. Pericarditis is felt to be the most common cardiac manifestation but myocarditis is also possible and therefore a cardiac echo should be considered. As with any case of pericarditis, a bedside ultrasound should be performed to rule out pericardial effusion which can accumulate rapidly and progress to cardiac tamponade.
   b. The risk of coronary artery disease (CAD) is at least doubled in SLE patients and particularly in young females. Autopsy series in young SLE patients show that up to half had significant atherosclerosis. If initial work up is negative, provocative testing for CAD should be considered.
   c. Systemic lupus erythematosus patients are at high risk of developing infection from the immunosuppression associated with the disease and with the treatment so pneumonia should also be considered.
   d. Emergency department work up for this patient should include ECG (looking for tachycardia, ST-segment changes, right heart strain and conduction system changes), chest X-ray, troponin, complete blood count, acute inflammatory markers, chemistry to assess renal disease. Although D-dimer can be considered, these patients are often high risk for PE rather than moderate or low risk and therefore may need a computed tomography angiography (CTA). In addition, CT can be more sensitive to pick up pulmonary infiltrates.

3. What in this patient’s history can explain her pancytopenia?
   a. Systemic lupus erythematosus can cause pancytopenia, leukopenia or thrombocytopenia. Infections can also cause bone marrow suppression. Since the patient was recently started on methotrexate, if the patient has not been taking folate with this medication, worsening anemia and thrombocytopenia can also be caused by folate deficiency.
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**Case 2:** A 44-year-old female with a history of dermatomyositis (DM) presents with a chief complaint of cough, wheezing, and increased weakness. She explains that the diagnosis of DM was made several months ago after “muscle tests” and lab tests and her presentation of an unusual rash with papules and proximal muscle weakness, creating problems climbing up stairs and standing from sitting positions. She is now taking prednisone 5 mg per day and azathioprine 100 mg per day and has been on this regimen for the last two months. On her exam she is weaker than normal and has wheezes on lung exam. Temperature is 99.0°F with otherwise unremarkable vital signs. Her labs and chest X-ray are negative.

**Question Prompts:**

1. Discuss the usual presentation and treatment of dermatomyositis.
   a. Most patients present during ages 40 to 50 with muscle weakness (90%), and muscle pain (50%) and the skin manifestations may precede the muscle symptoms. Deltoids and hip flexors are the most common muscles involved. Classic skin manifestations include Gottron's papules, which are erythematous to violaceous papules that occur symmetrically over the extensor (dorsal) aspects of the metacarpophalangeal (MCP) and interphalangeal (IP) joints. In addition, these lesions may involve the skin between the MCP and IP joints, particularly when the eruption is prominent. Gottron's papules often have associated scale and may ulcerate. When scaling is present, the lesions may mimic psoriasis or lichen planus. The heliotrope eruption is an erythematous to violaceous eruption on the upper eyelids, sometimes accompanied by eyelid edema. Patients may have midfacial erythema that can mimic the malar erythema seen in SLE. In contrast to those with SLE, patients with DM will often have involvement of the nasolabial fold.
   b. The mainstay of treatment includes glucocorticoid therapy. Ideally, normalization of enzymes and complete recovery of muscle strength should occur before glucocorticoids are tapered. Continuation of high-dose glucocorticoids for more than six weeks may cause steroid myopathy and decline in strength. Steroid sparing medications include azathioprine.
   c. Selected patients with severe life-threatening weakness or patients with severe dysphagia at risk for aspiration may benefit from the addition of intravenous immune globulin (IVIG) to initial treatment with glucocorticoids. Intravenous immune globulin may have a more rapid onset of action than glucocorticoids, but prolonged treatment is limited by difficulty of administration, cost, and potential toxicity. Intravenous immune globulin also has a role in the treatment of resistant and recurrent cases.

2. What is the most likely diagnosis? How might these symptoms be related to her diagnosis of DM?
   a. Patients with DM suffer from weakness of the striated muscle of the upper third of the esophagus. This can result in severe GERD which can lead to severe aspiration and chronic pulmonary disease. These symptoms occurring despite prednisone and azathioprine suggests refractory disease and not recurrent disease. Rituximab and IVIG should be considered if the disease becomes refractory. Gastrointestinal and pulmonary disease along with increased weakness could mean refractory disease requiring admission for IVIG. In addition, rapidly progressive interstitial lung disease in the setting of DM can also be lethal.
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Case 3: A 43-year-old male with ankylosing spondylitis presents with a chief complaint of eye redness, pain, and photophobia. He states that his symptoms were gradual in onset and have been progressive over the last week. He denies trauma to the eye or any precipitating event. He denies fevers, headaches, nausea, vomiting, and eye drainage. He is on infliximab but takes no other medications. His vital signs are all within normal limits.

Question Prompts:

1. Discuss the general approach to ankylosing spondylitis (AS) and the treatment.
   a. Ankylosing spondylitis is a chronic inflammatory disease manifested by back pain and progressive spinal stiffness. Goals of treatment are to eliminate symptoms and prevent complications of spinal disease such as flexion contractures and dorsal kyphosis, and to minimize extraspinal and extraarticular manifestations and comorbidities.
   b. All patients with AS show significant changes in the plain radiographs of the sacroiliac joints in the form of erosions or fusion. In advanced disease, plain radiographs of the spine will reveal "bamboo spine" with virtually complete fusion of the vertebral column. At that stage there is usually fusion of the sacroiliac joints.
   c. Pharmacotherapy includes one or more of the following: nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, and anti-tumor necrosis factor (anti-TNF) agents. Unlike other collagen vascular diseases, systemic glucocorticoids have a limited role, but intraarticular injections may be helpful to some patients.

2. What is the likely diagnosis and treatment for the eye findings in this patient?
   a. The most likely diagnosis here is anterior uveitis. Roughly 30%-40% of patients with AS will develop anterior uveitis in their lifetime.
   b. Although the most likely diagnosis here is anterior uveitis, infectious causes must be ruled out and ophthalmology consultation or at least very close ophthalmology follow-up is indicated.
   c. Anterior uveitis may produce pain, redness, photophobia (and consensual photophobia). The redness is primarily noted at the limbus (the junction between the cornea and the sclera). Such patients can have a constricted pupil, pain, and cells and flare on exam.
   d. Noninfectious causes of anterior uveitis are generally treated with topical glucocorticoids such as prednisolone acetate (1 percent). A mydriatic agent can relieve pain due to spasm of the muscles controlling the pupil and will also help to prevent the formation of posterior synechiae that may interfere with the function of the pupil.

Suggested Readings:

Kaufman R, Reed K, Alex K, Long B. Systemic lupus erythematosus: common complications and emergency medicine pearls. EmDocs. http://www.emdocs.net/systemic-lupus-erythematous-common-complications-emergency-medicine-pearls/. Updated October 2016. Accessed April 3, 2019.
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**Additional References:**

Miner JJ, Kim AH. Cardiac manifestations of systemic lupus erythematosus. *Rheum Dis Clin North Am.* 2014;40(1):51-60. doi: 10.1016/j.rdc.2013.

Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet.* 2003;362(9388):971-982. doi: 10.1016/S0140-6736(03)14368-1.

Amato AA, Barohn RJ. Evaluation and treatment of inflammatory myopathies. *J Neurol Neurosurg Psychiatry.* 2009;80(10):1060-1068. doi: 10.1136/jnnp.2008.169375.

Gladman DD. Overview of the clinical manifestation of SLE in adults. In: Pisetsky DS, ed. https://www.uptodate.com/contents/overview-of-the-clinical-manifestations-of-systemic-lupus-erythematosus-in-adults. Updated January 8, 2018. Accessed October, 2018.

Wallace DJ. Overview of management and prognosis of SLE in adults. In: Pisetsky DS, ed. https://www.uptodate.com/contents/overview-of-the-management-and-prognosis-of-systemic-lupus-erythematosus-in-adults. Updated January 27, 2019. Accessed October, 2018.

Miller ML, Vleugels RA. Clinical manifestations of dermatomyositis. In: Curtis MR, ed. https://www.uptodate.com/contents/clinical-manifestations-of-dermatomyositis-and-polymyositis-in-adults. Updated January 27, 2019. Accessed October, 2018.

Miller ML. Initial treatment of dermatomyositis and polymyositis in adults. In: Curtis MR, ed. https://www.uptodate.com/contents/initial-treatment-of-dermatomyositis-and-polymyositis-in-adults. Updated March 27, 2018. Accessed October, 2018.
Small Group Evaluation

The moderator demonstrated adequate knowledge of subject.

5) Strongly Agree    4) Agree    3) Slightly Agree    2) Disagree    1) Strongly Disagree

The moderator’s facilitation of the conference facilitated my learning.

5) Strongly Agree    4) Agree    3) Slightly Agree    2) Disagree    1) Strongly Disagree

The overall discussion was relevant to the stated topic(s).

5) Strongly Agree    4) Agree    3) Slightly Agree    2) Disagree    1) Strongly Disagree

The faculty/resident’s teaching methods (slides, handouts, videos, etc.) were effective.

5) Strongly Agree    4) Agree    3) Slightly Agree    2) Disagree    1) Strongly Disagree

Faculty Facilitator Evaluation

1. Preparation – was faculty well prepared?

Needs Improvement    Effective    Exemplary

2. Engaged residents - Encouraged discussion and actively participated, demonstrated enthusiasm?

Needs Improvement    Effective    Exemplary

Strengths:

Areas for Improvement:

Reviewer Recommendations:

Resident Facilitator Evaluation

1. Preparation – was the resident facilitator well prepared?

Needs Improvement    Effective    Exemplary

2. Engaged residents – Controlled and led the session and encouraged discussion, active involvement, and demonstrated enthusiasm?

Needs Improvement | Effective | Exemplary

Strengths:

Areas for Improvement:

Reviewer Recommendations:

**Evaluation of the Teaching materials**

1. Were the objectives appropriate for the topic?

Needs Improvement | Effective | Exemplary

2. Was the amount of material appropriate?

Too Short | Appropriate | Too Long

Strengths:

Areas for Improvement:

Reviewer Recommendations:
## Small Group Resident Assessment

| Session:                      | FACILITATOR (S): |
|-------------------------------|------------------|
| DATE:                         |                  |

| Small Group 3                  | Contributes to group discussion |
|-------------------------------|---------------------------------|
| BE/ME/EE                      | Comments                       |
| Resident 1                    |                                 |
| Resident 2                    |                                 |
| Resident 3                    |                                 |
| Resident 4                    |                                 |
| Resident 5                    |                                 |
| Resident 6                    |                                 |
| Resident 7                    |                                 |
| Resident 8                    |                                 |
| Resident 9                    |                                 |
| Resident 10                   |                                 |
| Resident 11                   |                                 |
| Resident 12                   |                                 |

**BE—Below Expectations**
- Minimal discussion during the session
- No discussion on the site discussion board
- Comments not contributory to discussion or distracting to discussion
- Has minimal knowledge of topic as expected of PGY year

**ME—Meets Expectations**
- Contributes to group discussion in a meaningful way
- Incorporate textbook/website/podcast reading into discussion
- Has knowledge of topic appropriate to level of training

**EE—Exceeds Expectations**
- Contributes to group discussion in a meaningful way
- Incorporate literature into discussion
- Has advanced knowledge of topic