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Rapidly Fatal Infections

Introduction

The medical literature is rife with information on the trends of various infectious diseases. Much of this begins with the diagnosis made and helps us connect the diagnosis to a preferred regimen of antimicrobials or antivirals. The real detective work starts before this. Our tools are constant vigilance for subtle clues in the history and physical examination, some nonspecific laboratory tests (for example white blood cell [WBC] count or lactate), and a high level of suspicion for infection.

Most of the diseases covered here share a common endpoint in the sepsis cascade. What separates them from some others is the importance of early detection and therapy.

Neutropenic Fever

Case 1. *A woman presents with fever. She has a history of breast cancer and is on chemotherapy. Her vital signs are normal, except for a temperature of 39 °C. She is asymptomatic with no evidence of infection on physical exam or with ancillary tests. She has good support at home, has good follow-up, and is reliable.*

Case 2. *A man with known hematologic malignancy presents with fever and mild cough, which began today. He has normal vital signs, except for a temperature of 38.7 °C. He has a mild non-productive cough with no dyspnea. On exam, he appears well, and his lungs are clear. The chest X-ray shows a small infiltrate.*

Case 3. *A woman with AML presents with fatigue for 2 days. She is hypotensive, tachycardic, with mild fever. Her physical exam is normal, as are ancillary tests.*

Neutropenia most commonly affects patients who are undergoing chemotherapy, radiation therapy, or who have hematologic malignancies. While neutropenia is a significant risk factor for developing a life-threatening infection, only 20-30% of patients presenting with fever will have a specific pathogen identified.[1] Thus, the majority of neutropenic patients who present with fever will have no focus of infection and negative blood cultures.

Some immunocompromised patients with infection may present without fever. Instead, a septic neutropenic patient may manifest with isolated tachycardia or tachypnea, change in mental status, metabolic acidosis, hypotension, rapid changes in glucose or sodium, or localized pain, such as acute abdominal pain.[2]

The most common sites of focal infection are the oral mucosa, lungs, gastrointestinal tract, and skin/soft tissue. A thorough physical exam is warranted, especially because the inflammatory response to infection is blunted. Thus, cellulitis may present as mild erythema, or pneumonia may present with minimal cough or only vague symptoms. Examining the oral mucosa is extremely important, as mucositis is a poor prognostic indicator. Mucositis is typically very painful and is often associated with *Streptococcus viridans* bacteremia, which can be rapidly debilitating.

Patients at high risk include those with profound neutropenia (ANC < 100) and with anticipated neutropenia of greater than 7 days. Most commonly, the

Executive Summary

- Infections in patients with neutropenia are often rapidly fatal, but may present with few signs of the source of infection. Broad-spectrum antibiotics are recommended.
- Rabies infection, once established, is nearly 100% fatal. Individuals bitten by stray or wild animals, particularly raccoons, or who find a bat in their bedroom should be considered for prophylaxis. Local health departments can help determine the need for prophylaxis.
- Necrotizing fasciitis and Fournier's gangrene are best treated with surgery. Antibiotics slow the progression of the infection, but do not cure it.
- Steroids have been shown to be useful for patients with pneumococcal meningitis, but only if given prior to or concurrent with antibiotics.

patients at risk for prolonged neutropenia are undergoing induction chemotherapy for AML or hematopoietic stem cell transplantation (HSCT) preparation. Additional high-risk features include hypotension or hemodynamic instability, pneumonia, acute abdominal pain, neurologic changes, and those with poor physiologic reserve (elderly, heavy tumor burden, chronic obstructive pulmonary disease).[1] Many febrile neutropenic patients at high risk of developing significant infections do quite well. In the ED, it can be difficult to predict which patients may go on to develop complications, especially if they appear healthy upon initial clinical evaluation. In a retrospective study of 168 patients with 192 episodes of febrile neutropenia, there were three factors that helped to predict which patients subsequently developed hypotension, respiratory failure, disseminated intravascular coagulation (DIC), renal failure, and death. The three factors included platelet count < 50,000 cells/mm^3, C-reactive protein (CRP) greater than 10 mg/dL, and pulmonary infiltrate on chest X-ray.[3] Thus, the patient in case 2 should be watched very closely and treated aggressively, even if well-appearing because of the pulmonary infiltrate.

The emergency physician should perform a thorough history and physical exam to assess for localizing signs or symptoms of infection. The initial work-up should include CBC with differential, blood urea nitrogen, creatinine, electrolytes, hepatic transaminase enzymes, total bilirubin, and urinalysis.[2] Obtain a chest X-ray if there are respiratory signs or symptoms. Consider ordering a serum lactate, stool/urine/skin/sputum cultures, computerized tomography (CT) imaging, or cerebrospinal fluid (CSF) studies, depending upon presenting signs and symptoms. While CRP > 10 mg/dL predicts a complicated course, there are no specific guidelines calling for its routine use. A minimum of two blood cultures should be obtained and should include samples from all in-dwelling intravascular catheters. While blood cultures are the standard of care, it has been shown that specific pathogens are identified in only about 20-30% of febrile neutropenic cases.[1] Most patients are managed successfully with empiric antibiotics. PCR analysis of bacteria from blood is more sensitive than blood culture; however, it is only helpful in the diagnosis and treatment of patients with empiric-therapy-resistant febrile neutropenia. While PCR analysis may not be helpful in the ED, it may be helpful for subsequent inpatient care.[1]

Empiric antibiotics should be given early, preferably within the two hours of presentation, to prevent the possible rapid progression of infection. The choice of empiric antibiotics may be guided by allergies, suspected focus of infection, history of antimicrobial prophylaxis, local antimicrobial resistance, and hepatic and renal function.[2] Monotherapy is preferred over polytherapy because it is effective and reduces the number of side effects. For high-risk patients, empiric intravenous antimicrobial options include piperacillin/tazobactam, cefepime, ceftazidime, or carbapenems. Most penicillin-allergic patients tolerate cephalosporins, but if reaction is an immediate-type hypersensitivity, consider ciprofloxacin plus clindamycin, or aztreonam plus vancomycin. Note that vancomycin is otherwise not recommended for routine empiric therapy out of concern for the development of vancomycin-resistant microbes. It is recommended to add vancomycin in suspected catheter-related infections, cellulitis, pneumonia, and gram-positive blood cultures. It is recommended to add an aminoglycoside and switch to a carbapenem for pneumonia and gram-negative blood cultures. For patients with abdominal symptoms or suspected *Clostridium difficile* infection, add metronidazole. Consultation with an infectious disease specialist may be helpful to provide the most appropriate broad-spectrum coverage.

The diagnosis of a systemic fungal infection can be quite difficult, especially in the ED. Thus, the initiation of antifungals is typically added to the inpatient antimicrobial regimen of patients with persistent fevers.[4] Similarly, empiric antiviral therapy is also not recommended in the ED.[2]

A formal risk classification has been introduced to assist with risk stratification. The MASCC (Multinational Association for Supportive Care in Cancer) scoring system includes eight weighted characteristics that may be summed up to a maximum

score of 26. (*See Table 2.*) Two of the characteristics include "burden of febrile neutropenia," including the degree of associated symptoms. This is a subjective measure that relies on a physician's clinical gestalt of how sick the patient appears. Thus, the application has limitations, but may be helpful. Low-risk patients have a MASCC score of greater than or equal to 21. The low-risk population typically has very good outcomes. Low-risk patients include those with anticipated brief duration of neutropenia of less than 7 days, and no or few co-morbidities.[2] If the patient has any high-risk features, as described above, then he or she must be treated as high risk.

High-risk patients with neutropenic fever generally require admission to the floor or intensive care unit (ICU) for IV antibiotics. The disposition of low-risk patients is less clear and is an area of ongoing research. In some centers, carefully selected low-risk patients who present with neutropenic fever have been managed as outpatients with oral antibiotics.[5] The potential benefits of outpatient management include the prevention of nosocomial co-infection with resistant microbes and reduced cost. The most studied oral antibiotic regimen is ciprofloxacin plus amoxicillin-clavulanate. Successful outpatient management of this population is dependent on good patient compliance, patient reliability, home support, availability of frequent follow-up, and reasonable distance to a hospital in case of emergency. The decision to treat as an outpatient should be made in consultation with the patient's oncologist. An alternative is to treat with oral antibiotics and admit briefly or remain in the ED for observation.

Table 1: Neutropenic Fever

Neutropenia	Absolute neutrophil count (ANC) < 500 OR ANC expected to decrease to < 500 in 48 hrs
Absolute neutrophil count (ANC)	Total WBC x % neutrophils + bands
Fever in neutropenic patient	Single oral temperature of 38.8◦C or higher OR Oral temperature of 38◦ C or higher over 1 hr Note: Axillary (not accurate) and rectal (prevent bacteremia) temperatures are not recommended.
Most common sites of infection — Top 5[6]	Mouth/pharynx (25%) Lung (25%) GI tract (15%) Skin/soft tissue/intravascular catheters (15%) Perineum/anorectal area (10%)
Most common gram-negative bacilli	*Escherichia coli* *Klebsiella pneumoniae* *Pseudomonas aeruginosa*
Most common gram-positive cocci	*Staphylococcus epidermidis* *Viridans* group streptococci
Leading cause of bacterial infections in U.S.	*Enterococcus* species *Staphylococcus aureus*
Resistant bacteria	MRSA — Methicillin-resistant *Staphylococcus aureus* VREs — Vancomycin-resistant *Enterococcus* species ESBLs — Beta-lactam-resistant *Klebsiella* species and *Escherichia coli* KPCs — Carbapenem-resistant *Klebsiella* species and *Pseudomonas aeruginosa*
Most common fungal infections	*Candida* *Aspergillus*

Antibiotic Resistance and Failure in Community-acquired Pneumonia

Case. *A 58-year-old female presents with a five-day history of fevers, cough, and dyspnea on exertion. She was seen two days ago, diagnosed with bronchitis, and prescribed a five-day course of azithromycin. Since that time, she has had worsening of her general malaise and dyspnea. Her vital signs are significant for a fever, tachypnea, tachycardia, and an O_2 saturation of 87% on room air. The physical exam reveals rales present in the bilateral lung bases. The patient rapidly deteriorates and is admitted to the ICU.*

Pneumonia continues to be a major cause of morbidity and mortality in the United States. It is the eighth most common cause of death overall, and the leading cause of death due to primary infectious disease.[7] The mortality of pneumonia has not appreciably decreased since the discovery of penicillin.[8] Mortality may be affected by increasing antibiotic resistance in

Table 2: MASCC Score

Characteristic	Weight
Burden of febrile neutropenia	
with no or mild symptoms	5
with moderate symptoms	3
with severe symptoms	0
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor of hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient status	3
Age < 60 years	2

community-acquired pneumonia (CAP).

Streptococcus pneumoniae is the leading cause of CAP that leads to hospitalization.[9] Outpatient treatment based on the Infectious Diseases Society of America and the American Thoracic Society guidelines list macrolide antibiotics or doxycycline as first-line treatment for uncomplicated CAP, followed by high-dose penicillins or a respiratory fluoroquinolone in patients with comorbidities or risk factors for drug-resistant disease.[10] Listed comorbidities include chronic heart, lung, or liver disease, diabetes mellitus, alcoholism, malignancies, asplenia, immunosuppressing disease or drugs, or antibiotic use in the past three months.[10] However, this list is not exhaustive, and clinical judgment must be used in all cases. Unfortunately, macrolide resistance is increasing, and treatment failures can lead to significant morbidity. In the United States, macrolide resistance is seen in nearly 30% of isolated cases of *S. pneumoniae*, and can be seen in greater than 75% of cases in certain Asian countries.[9] There is increasing evidence for worsening morbidity and mortality outcomes in patients treated with macrolides that have resistant isolates, with some studies quoting a 52% progression to pneumococcal bacteremia.[11] Although macrolides are considered a standard for initial empiric therapy in CAP, their primary advantage is coverage of atypical pathogens. Therefore, if *S. pneumoniae* is a proven pathogen by laboratory testing or likely by history, then initial therapy should be either high-dose beta-lactam or a respiratory fluoroquinolone.[11]

Although penicillin antibiotics have been implicated in increasing resistance, recent literature has suggested that in vitro resistance may not correlate well with clinical outcome. New antibiotic concentration break points instituted in 2008 for nonmeningitis pneumococcal infections have reclassified resistance in an attempt to more accurately reflect clinical outcomes. Prior to the change in laboratory concentration levels, intermediate resistance was listed as high as 15%, but is now only 5.6% of isolated strains, and complete resistance rates, which were previously 10.3%, are now cited at 1.2%.[11]

Community-acquired methicillin-resistant *Staphylococcal aureus* (CA-MRSA), fortunately, remains a relatively uncommon cause of CAP, accounting for only 1-5% of cases. However, there is some concern that the incidence may be increasing, and it is subject to underreporting, as rigorous population based studies are lacking.[11] Some reports have suggested that CA-MRSA infections are more common in winter, and often include co-infection with viral pneumonias.[11,12] However, this may be due to selection bias, since many studies are limited to the ICU setting, and viral coinfection worsens the disease course.[12] Regardless, viral coinfection or preinfection should not be considered a requisite to development of MRSA pneumonia.[12] Patients with CA-MRSA pneumonia are generally younger than those with other forms of pneumonia, and the disease can be particularly aggressive, leading to pulmonary necrosis and fatal outcomes reported in 20-60% of patients.[9] Broadening antibiotic coverage is suggested for young persons with rapidly worsening disease, co-infection with a viral source, cavitary pneumonia, or previous infection with MRSA.[11] Current recommendations for patients at higher risk of CA-MRSA include the addition of vancomycin or linezolid.[10] Linezolid does have a theoretical advantage of decreased toxin production and higher concentration in the lung parenchyma when compared to vancomycin, but this has not been shown to be clinically significant in prospective studies.[11]

Acinetobacter baumannii is an uncommon but devastating cause of antibiotic-resistant pneumonia. Additionally, community-acquired *A. baumannii* appears to be more aggressive than hospital-acquired strains. As it is an uncommon cause of CAP, empiric therapy rarely provides appropriate coverage. Risk factors for *A. baumannii* are similar to those for other uncommon causes of pneumonia, and include smoking, alcoholism, diabetes, organ failure, and malignancy. Most patients require hospital admission. Appropriate antibiotic treatment includes anti-pseudomonal penicillins, aminoglycosides, and a carbapenem.[11] Of note, standard protocols for hospital antibiotics may not treat *A. baumannii* well, as respiratory quinolones will not give reliable

coverage. Although increasing in incidence, it still remains rare enough that empiric treatment for coverage is not justified, and there are few reliable criteria that can help guide the emergency physician in choosing to broaden coverage for this devastating pathogen.[11]

The decision for admission of patients with CAP can be guided by clinical decision-making tools such as the CURB-65 score or the PORT score, but, ultimately, is at the discretion of the physician. Since emergency physicians rarely have the benefit of knowing the infecting microbe in a patient with pneumonia, adherence to antibiotic coverage guidelines remains the best defense against unnecessary treatment failure. Guidelines for hospitalized patients with CAP are summarized in Table 3.[10]

Table 3: Guidelines for Hospitalized Patients with CAP

Inpatient Non-ICU	Inpatient ICU	ICU with Possible *Pseudomonas* Infection	Possible *S. aureus* Infection
1. A respiratory fluoroquinolone *or* 2. An extended-spectrum beta-lactam *plus* macrolide	An extended-spectrum beta-lactam *plus* a respiratory fluoroquinolone *or* a macrolide	1. Antipneumococcal, antipseudomonal beta-lactam *plus* ciprofloxacin or levofloxacin 2. Above beta-lactam *plus* an aminoglycoside *and* azithromycin 3. Above beta-lactam *plus* an aminoglycoside and an antipneumococcal fluoroquinolone	Add vancomycin *or* linezolid
Adapted from Mandell et al. 2007.			

Extensive laboratory testing in the emergency department is an area of debate in the literature. The American College of Emergency Physician recommends against blood and sputum cultures in routine cases of CAP, citing that it has low yield and rarely leads to a change in patient treatment, even in the inpatient setting.[8] This point is conceded in the 2007 recommendations by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society. However, the IDSA still loosely recommends searching for an etiologic agent, as it is important from an epidemiologic standpoint and may provide critical information in individual cases.[10] Both sets of guidelines recommend extended testing in all patients being admitted to the ICU, as well patients with the above outlined risk factors for uncommon pathogens.[8,10] Routinely performing urinary antigen testing for *S. pneumoniae* is gaining momentum as a higher yield method for diagnosing pneumococcal pneumonia, with one recent study citing a sensitivity of 78% and a specificity of 96%.[13] This strategy does have theoretic potential in helping to provide appropriate antibiotic coverage of CAP patients, particularly in the face of increasing macrolide resistance for pneumococcus, but is still relatively early in its use, and further research is ongoing.[13]

Novel Influenza

Case. *A healthy 25-year-old female presents with cough and shortness of breath for the past 24-36 hours, and feels as though she is quickly getting worse. Her vital signs are significant for tachypnea, tachycardia, fever, and hypoxemia. The patient is in mild distress, has rhonchi bilaterally, and a chest X-ray shows bilateral infiltrates. She is admitted, and within 24 hours, she deteriorates, requiring mechanical ventilation.*

The H1N1 influenza, or "swine flu," epidemic of 2009 started in Mexico in March. It appeared throughout North America within the first three weeks of April, and by late April, it was confirmed that the respiratory illness was, in fact, a novel influenza of swine origin.[14] By May 1, the disease was confirmed in Hong Kong, and within eight weeks after it was first described, it met the World Health Organization (WHO) definition for a pandemic.[15]

The vast majority of cases were mild and self-limited. It presented as common pathological entities such as pneumonia, asthma, and COPD exacerbations, as well as croup and bronchiolitis in the pediatric population. These mild cases were easily managed with symptomatic treatment.[16] The case fatality rate was relatively low, reported between fractions of a percent and 1.2% of confirmed cases.[14,16] Predictably, many of the serious cases were in patients with underlying chronic disease, such as asthma, COPD, diabetes mellitus, neurologic/neuromuscular disease, and immunosuppressing conditions.[14] Unique conditions during the H1N1 pandemic contributing to clinical deterioration included pregnancy and obesity, as well as having surprising virulence in adolescents and young adults.[14] Regardless, it has been remarked by some authors that one of the biggest surprises of the pandemic was how mild the disease was.[15]

Some aspects of the pandemic were unique. The H1N1 virus spread more rapidly than seasonal influenza, as the majority of the population was immunologically naïve to swine influenza.[15] Patients were generally younger than those having serious consequences from seasonal influenza, with 87% of deaths from H1N1 being between the ages of 5 and 59 in one study.[16] Lastly, the rapid progression of the disease in

many patients was a surprise, with many patients requiring ICU admission between two and six days of illness onset.[16] By the end of the surge, the CDC estimated that in the United States, H1N1 had infected between 41–81 million people, and was responsible for between 8,000 and 18,000 deaths.[17]

While diagnosis and treatment were straightforward, from an administration, public health, and resource allocation perspective, there are many lessons learned.

Attempts to contain the epidemic were relatively ineffective.[15] Even with deployment of entry screening, the disease spread globally within two months. Some estimates suggest that entry screening would prevent local transmission for only 1-2 weeks. This modest gain must be balanced against the manpower required to implement screening.[15]

In the ED, the surge of patients stretched resources, particularly in pediatric centers, where patient census often increased by more than 50%.[18] Rapid screening processes were able to adequately treat this surge of patients by identifying risk factors for serious disease and using dedicated teams for patients with flu-like illness.[18,19] Both Fagbuyi et al and Cruz et al describe successful rapid screening processes that discharged 17% and 18% of presenting patients.[18,19] The fear of the disease drove many to the ED. McDonnell et al showed that despite the disease still being absent from the state of Utah during the last week of April 2009, ED visits increased 19.7% for pediatrics and 7% overall. This week coincided with news of the first death from H1N1 in the United States, and preceded the presence of H1N1 in Utah by a week.[20] The number of ED visits only modestly increased from these numbers after the disease arrived in the study area.[20]

Novel influenza strains will continue to emerge. The virulence of each strain is not entirely a factor of which "N" or "H" strain they acquire. These major antigens and previous vaccination cycles play a role in determining the emergency of a specific virus within humans; however, other features contribute to disease severity and contagion.

Rapid diagnosis using laboratory tests for novel influenza is of questionable utility to the emergency physician. During the 2009 pandemic, sensitivity reports of the rapid influenza tests ranged from 10-70%, and recommendations suggested limiting these tests to patients requiring hospital admission or those at high risk for worsening disease.[14]

Influenza is a difficult virus to treat. Due to its rapid antigenic drift, the seasonal flu has some resistance to older antivirals such as amantadine, even in areas where antiviral use is minimal.[21] It is difficult to predict the effectiveness of current antivirals for any future epidemics.

In the 2009 H1N1 epidemic, antiviral treatment was limited to patients with severe disease or risk for rapid progression. Early treatment (within 48 hours of symptom onset) with the neuraminidase inhibitors oseltamivir or zanamivir improved the outcome of patients with risk factors for disease progression or requiring hospitalization.[16] The adamantines (amantadine, rimantadine), already limited in efficacy for treatment of seasonal influenza, were ineffective for treatment of the H1N1 virus.

Although the efficacy of antiviral therapy on the next wave of novel influenza is impossible to predict, judicious use of antivirals makes sense in the early stages of an epidemic. EDs should have a plan in place to deal with the surge of patients, and hospitals should prepare to move critically ill patients out of the ED even when floor beds or ICUs are at capacity.

Rabies

Case. *A 20-year-old male is bitten by a raccoon on the hand. Two months later, he presents with malaise, fever, and paresthesias to that hand. The patient is admitted and becomes acutely confused and hyperactive, thrashing and biting things, and appears to be hallucinating. Later, he is calm and cooperative, but any stimuli trigger a "furious episode." Over the next few days, he develops multi-organ system failure and dies.*

A bite from a rabid animal is initially like any other animal bite. Meanwhile, the virus enters the peripheral nerves and travels centrally as it replicates. Since the virus is hidden in the CNS, the immune system is unable to mount an immune response. This asymptomatic incubation period lasts for 20-90 days. Then, the patient may have symptoms consistent with a viral syndrome, agitation, insomnia, and/or depression. This prodrome leads to the acute neurologic phase, which typically lasts for 2-7 days. With furious rabies, as in the case above, almost half of patients will have the pathognomonic sign of hydrophobia — attempting to drink or the suggestion of drinking results in severe laryngeal or diaphragmatic spasms and the sensation of choking. Twenty percent of patients may develop paralytic rabies.[22] Even if the patient survives this acute phase, the patient will likely slip into a coma with varied duration. Recovery is very rare. While rabies is classically transmitted by animal bites, there are reports of rabies transmission from organ transplantation, including the cornea.

When a patient presents to the ED with a recent history of an animal bite, important historic information includes when the patient was bitten and the circumstances surrounding the attack; whether it was provoked or unprovoked; the type of animal and if it was captured; and if the patient has had prior rabies vaccination. A provoked attack is defined as attempting to feed an animal, trespassing on an animal's territory, breaking up an animal fight, petting or playing with an animal, handling an animal in a veterinary setting, having contact with an injured animal, and walking, running, or riding past an animal.[23] Examine the wound; clean and irrigate copiously.

The decision regarding post-exposure prophylaxis is not always straightforward. In the United States, the most common mammals

that carry rabies are raccoons, skunks, and foxes. Most human infections with rabies, however, result from exposure to bats. Post-exposure prophylaxis should be strongly considered for any potential exposure or contact with a bat, whether a bite wound is suspected or not, and especially if a bat is discovered in a household area used for sleeping or if the bat may have been around unattended children, mentally disabled people, or intoxicated persons.[24]

Consult the local or state public health department to assist in making an informed decision regarding human risk of rabies exposure. Further questions and consultation should be referred to the rabies section of the CDC. If the offending animal is caught, it can be euthanized for brain biopsy (wild animal) or quarantined for 10 days (domestic) to observe for symptoms of rabies. The strict enforcement of rabies vaccination among cats and dogs has drastically reduced the prevalence in the United States. Each year in the United States, approximately 120,000 animals are tested for rabies, of which 6% are found to be rabid. Of domestic animals tested, less than 1% are rabid, compared to more than 10% of wild animals.[25] In a prospective case series of 2,030 patients with animal exposure, case management was considered inappropriate in 40% of patients receiving rabies post-exposure prophylaxis and in 6% of patients who did not receive rabies post-exposure prophylaxis. The most common reason for inappropriate administration of rabies post-exposure prophylaxis was when the animal was available for observation. Meanwhile, the most common reason for inappropriately not providing rabies post-exposure prophylaxis was exposure from an animal in a highly endemic area for which the animal was not available for observation or testing.[23]

For the majority of patients, rabies post-exposure prophylaxis requires both passive and active immunizations. Passive immunization with human rabies immune globulin (HRIG) provides the immune system with antibodies that are ready to bind rabies virus immediately. HRIG should be given at a dosage of 20 IU/kg into and around the wound, if known, and any remaining volume should be given IM, typically in the deltoid or thigh muscle. Active immunization with the rabies vaccine activates the immune system to create its own antibodies. Thus, for patients who have been immunized with rabies vaccine within the past 5 years, only passive immunization is necessary. The rabies vaccine should be injected in a separate location from the HRIG, such as the gluteal muscle, and in a separate syringe from the HRIG to prevent antigen-antibody antagonism.[25] See Table 4 for how to administer post-exposure prophylaxis.[24]

Table 4: Rabies Vaccine Regimens

Vaccine Regimen	Route, Total Doses	Days of Injection
Post-exposure	IM x 4 (HRIG x 1)	0, 3, 7, 14
If previous vaccine course	IM x 2	0, 3

Regarding disposition, if the patient presents in the acute prodromal or acute neurologic phase, MICU admission is warranted for aggressive supportive care. When patients present shortly after an animal bite, obtain a thorough history and physical exam. It is recommended to make the decision to initiate rabies post-exposure prophylaxis in the ED in conjunction with the local or state public health department. With the knowledge of the type of animal, animal behavior, and vaccination status, and if the animal is available for observation, treatment may be initiated immediately or the decision may be delayed after autopsy or 10 days of observation of the offending animal. Either way, the patient may be discharged home safely with proper instructions and very close follow-up care for possible subsequent administration of rabies vaccine.

Necrotizing Fasciitis

Case 1. *A 30-year-old alcoholic male presents with right lower extremity swelling and pain. His vital signs are significant for tachypnea, tachycardia, and fever. He has gross swelling and erythema of the right lower extremity, with tenderness to palpation. Ultrasound shows no findings of thrombotic disease, but a CT scan of the abdomen and pelvis shows signs of necrotizing fasciitis.*

Case 2. *A 45-year-old diabetic male presents for a rash in his perineal region. He recently had surgery for osteomyelitis on his right tibia. Since surgery, he has had increasing pain and redness around his scrotum. The physical exam is significant for an erythematous, tender scrotum with several small draining abscesses across the perineum. A CT scan of the pelvis shows fascial thickening of the perineal planes, small amounts of subcutaneous air, and several abscesses without extension into the rectum.*

Referred to in the lay press as "flesh-eating bacteria," necrotizing fasciitis is a rapidly progressing microbial infection of the skin and soft tissues. Bacteria often gain entry to the deep soft tissue through seemingly benign wounds in susceptible patients. The majority of cases of necrotizing fasciitis are polymicrobial; however, aggressive group A beta-hemolytic streptococcus remains a significant cause of monomicrobial soft-tissue infections.[26]

Fournier's gangrene is a subset of the disease that involves the scrotum and perineal region. It differs from typical necrotizing fasciitis in that it is often from contiguous spread of other pelvic and perineal infections, such as perirectal abscess, colonic perforation, urinary tract infections, epididymitis, or recent instrumentation.[27]

Although ultimate diagnosis is made in the operating room and pathology laboratory, it is crucial

Table 5: Low-risk Characteristics for Meningitis

Age < 60	Normal level of consciousness	No arm or leg drift
Immunocompetent	Able to answer two consecutive questions	No abnormal language
No history of CNS disease	Able to follow two consecutive commands	No abnormal visual fields
No seizure in week prior	No facial palsy	No gaze palsy

that the emergency physician be able to recognize the potential disease on clinical grounds. Delay in surgical intervention is a major clinical predictor in the outcome of patients with necrotizing fasciitis, with some studies noting a mortality difference when surgical debridement is delayed just 12 hours from presentation.[26] McHenry et al reported in their case series of patients with necrotizing fasciitis that the average time to operation in survivors was 20 hours, while time to operation in those who did not survive was 90 hours.[28] For a disease with a mortality rate between 25-35%,[29] this association highlights the important role emergency physicians play in rapidly identifying and initiating treatment.

The diagnosis can be difficult to make in its early stages, as many cases start as seemingly superficial wounds, some of which are never identified. Likewise, simple cellulitis and early necrotizing fasciitis are essentially indistinguishable. A rapidly advancing line of erythema and edema, as well as pain out of proportion to the physical appearance, should alert the emergency physician to the possibility of a more sinister diagnosis. Crepitus of the skin is a specific, although insensitive, physical exam finding.[30] Various laboratory findings can be altered in necrotizing fasciitis, which have led researchers to develop scoring algorithms to differentiate necrotizing fasciitis from less serious soft-tissue infections. WBC count greater than 15,400 cells/mm^3 or a sodium less than 135 mmol/L has been shown retrospectively to have a positive and negative predictive value of approximately 80%.[29] Additionally, Wong et al developed the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC Score), which includes WBC, hemoglobin, CRP, glucose, and creatinine to determine the likelihood of necrotizing fasciitis.[31] They reported a positive predictive value of 92% and a negative predictive value of 96%.[31] However, since publication, the clinical usefulness of this laboratory tool continues to be debated. Regardless, basic laboratory and blood cultures are recommended prior to antibiotics and admission in suspected cases.[30]

Imaging can be helpful when the diagnosis is uncertain clinically. Plain radiographs are of little value, although they are sometimes ordered looking for subcutaneous air, and have been suggested to delay, as opposed to aid, in diagnosis.[26] Although ultrasound is not a recommended imaging study specifically looking for necrotizing fasciitis, ultrasound ordered to rule out testicular torsion or DVT will sometimes show tissue edema, pockets of fluid, and unexpectedly poor image quality if gas is present in the tissue. The emergency physician should be prepared to pursue necrotizing fasciitis as the diagnosis if these findings are present.[27] MRI can show dramatic images of soft-tissue inflammation and destruction, and can differentiate soft-tissue infections that should respond to antibiotics from those requiring surgical debridement.[26] Sensitivity has been reported between 90-100%.[26,29] However, its utility is limited by availability in the ED, as well as the extended time this imaging modality takes to acquire. CT scan is readily available in most EDs and it has similar sensitivity to MRI in diagnosing soft-tissue infections, particularly Fournier's gangrene.[27,30] Although imaging studies can help fill out the clinical picture, it is recommended no imaging should be ordered without consultation with a surgeon if necrotizing fasciitis is the most likely diagnosis. Because the sensitivity of CT and MRI are low, the value of these studies are to demonstrate alternate diagnoses.

Rapid surgical intervention is the cornerstone of treatment of necrotizing fasciitis. Early antibiotic treatment and resuscitation using a sepsis protocol remain critical in the appropriate care of these dangerously ill patients; however, at best, they will slow the progression. Surgical excision is the only way to halt progression. Broad-spectrum antibiotics are always necessary, as the majority of these infections are polymicrobial, with special attention paid to GABS, Clostridium species, and MRSA. Regimens of a beta-lactam, aminoglycoside, and clindamycin have been suggested, and should be considered a reasonable empiric regimen.[26] As MRSA is increasingly a consideration, vancomycin may be added to the regimen or substituted for the beta-lactam.[30] Clindamycin is thought to be particularly important in the treatment, as it has multiple effects, including reduction of toxin production, synergistic effects with other antibiotics, and prevention of further spread of the disease.[26,30]

Meningitis

Case 1. *A 20-year-old college student presents to the ED with the chief complaints of fever, headache, and stiff neck. Her vital signs are significant for fever and tachycardia. On exam, you notice a petechial rash. The patient has altered mentation and a stiff neck. You immediately suspect meningococcal meningitis and treat empirically.*

Case 2. *A 78-year-old woman presents with altered mental status. She has no complaints and is demented. Her vital signs show a temperature of 38.1 °C and mild tachycardia. The*

patient loses consciousness and has a seizure. She is intubated and admitted to the medical intensive care unit. Later CSF shows meningitis.

The most common symptoms of bacterial meningitis are fever, neck stiffness, altered mental status, and headache. According to the Dutch Meningitis Cohort Study, 95% of meningitis patients have 2 of the 4 symptoms.[32] However, the elderly have higher rates of altered mental status, and may be less likely to complain of headache. Patients who are immunocompromised are more likely to have a blunted response and atypical presentation.[33] On physical exam, Kernig and Brudzinski signs are often discussed as evidence of meningeal inflammation. The general consensus is that these meningeal signs have poor sensitivity, but they have a specificity that is clinically relevant.[34] The distinction between meningitis and encephalitis is not often clear at presentation.

The standard work-up for suspected bacterial meningitis includes basic labs, blood cultures, CSF studies, and consideration of neuroimaging. The question arises in regard to which to perform first, the lumbar puncture (LP) or the head CT. There is the perceived risk of uncal and cerebellar tonsillar herniation if the LP is performed without the knowledge of a space occupying lesion, cerebral edema, or increased intracranial pressure (ICP). However, obtaining a head CT first may delay diagnosis and treatment. The more obvious indications to perform a head CT first are focal neurologic deficits, coma, and papilledema. Another approach may be to assess for low-risk patients in whom neuroimaging is not likely to be abnormal. According to a prospective trial of patients with suspected meningitis, low risk may be defined according to Table 5.[35]

The most specific diagnostic test for bacterial meningitis is lumbar puncture. The CSF analysis will likely demonstrate a WBC of 100-10,000 with PMN predominance, protein > 50, and CSF:plasma glucose ratio below 0.6. There may be an elevated opening pressure. Definitive diagnosis is a positive gram stain and culture. The gram stain may provide a rapid diagnosis and is often very sensitive. However, the sensitivity is decreased for gram-negative bacilli, *Listeria monocytogenes*, and after the administration of antibiotics.[33] It is critically important to begin antibiotic treatment early, thus antibiotics should never be delayed to avoid this decreased sensitivity, especially if the patient is severely ill. The choice of empiric antibiotics should take into account the patient's age, immune status, whether the source is community-acquired or nosocomial, and known sensitivities. For community-acquired strains, a common combination is vancomycin plus a third-generation cephalosporin. Ampicillin is added if Listeria is suspected.[36] Patients at risk for Listeria infection include the elderly, immunocompromised, alcoholics, pregnant women, and those with chronic liver and renal disease. The mortality rate for Listeria meningitis is very high.

Meningitis and encephalitis may not be easily distinguished. Thus, it is often essential to broaden the differential to include viral encephalitis. Acute encephalitis may be distinguished by the presence of acute cognitive dysfunction or changes in behavior, focal neurologic deficits, and seizures. In a retrospective medical review of patients ultimately diagnosed with viral encephalitis, only 29% of patients received acyclovir while in the ED. If there are signs and symptoms consistent with meningoencephalitis, it is recommended to give acyclovir.[36]

The use of steroids in acute bacterial meningitis is still an area of controversy. The rationale for giving steroids is to reduce the inflammatory response that occurs with bacteriolysis. Thus, if the decision is made to give steroids, they should be given prior to, or concurrently with, the antibiotics to decrease the inflammatory response. Unfortunately, with reduced inflammation, the blood-brain barrier is less leaky, resulting in decreased concentrations of antibiotics in the CSF, especially vancomycin.[37] Steroids have been found to be beneficial in patients with moderate to severe disease. The most recent recommendations advise the use of steroids in cases of suspected or proven pneumococcal meningitis.[38] While there is no proven benefit for other meningeal microbes, the causative organism is quite unlikely to be known in the ED.

Complications that may occur in the ED include septic shock, DIC, ARDS, and coma. CNS-specific complications may include cerebral edema, cerebral herniation, hydrocephalus, cerebral abscess, intracerebral hemorrhage, and cerebrovascular complications such as thrombosis, wall irregularities, and occlusions.

Conclusion

In many cases, rapidly fatal infections are easy to dismiss as routine patient presentations. As emergency physicians, we are tasked with separating those benign processes from the lethal masqueraders. Many of the warning signs are subtle but have disastrous consequences for our patients. The goal for us is to have a high index of suspicion and adept diagnostic approaches in order to best ensure appropriate and rapid treatment of these rapidly fatal infections.

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Physician CME Questions

1. A 56-year-old man on chemotherapy for ALL arrives with a temperature of 38.9°C. The work-up shows neutropenia but no source of infection. He has good support and follow-up. The most appropriate course is:
   A. cultures and discharge with close follow-up
   B. cultures, oral ciprofloxacin and augmentin, and discharge
   C. cultures, third-generation cephalosporin and aminoglycoside IV, and admission
   D. cultures, IV cefepime and vancomycin, and admission

2. A 78-year-old woman who has stage 4 breast cancer is receiving chemotherapy through a subclavian line. She has a temperature of 38.2°C at home and no specific focus of infection. She lives alone. The best management for her is to draw cultures and:
   A. IV ceftazidime and vancomycin, admission
   B. oral ciprofloxacin and augmentin and DC with close follow-up
   C. IV meropenem and discharge with home nurse for IV antibiotics
   D. IV third-generation cephalosporin and aminoglycoside, admission

3. A young, previously healthy man is treated as an outpatient for CAP with azithromycin. He presents to your ED 4 days later with fever, hypotension, and worsening pneumonia on chest X-ray. Which of the following is true?
   A. Outpatient therapy was not indicated.
   B. Single-agent therapy with azithromycin is no longer recommended.
   C. Up to 30% of *S. pneumonia* in the United States and 75% in some Asian countries is resistant to azithromycin.
   D. Early goal-directed therapy has not been shown to improve survival from community-acquired pneumonia.

4. Which of the following is true regarding the use of blood cultures?
   A. Neutropenic patients with CAP do not need blood cultures.
   B. Urinary testing for Legionella and Streptococcus reduces the need for cultures.
   C. Blood cultures often identify the correct organism and lead to a change in treatment for most patients.
   D. All patients being admitted to the ICU should have blood cultures.

5. Which of the following is true regarding novel influenza viruses?
   A. Quarantine measures proved effective in containing H1N1 "swine" flu.
   B. Rapid influenza testing was 10% sensitive for H1N1 influenza.
   C. Different influenza viruses do not necessarily create similar symptoms.
   D. In emerging influenza infections, treatment of all patients with antivirals will be strongly recommended.

6. Which of the following scenarios would indicate an unprovoked animal attack?
   A. A pet owner is bitten while breaking up a fight between two pets.
   B. A mailman is bitten while putting mail in the mail slot of the animal's home.
   C. A veterinary assistant is bitten while restraining a dog for nail trimming.
   D. A hiker is bitten while sleeping on the ground by a wild dog.

7. Rabies treatment is indicated for which of the following:
   A. a pet owner bitten by a vaccinated dog while breaking up a fight
   B. a jogger is bitten by an unvaccinated, but owned dog after surprising it
   C. a bat is found in the bedroom of a sleeping child
   D. a lab worker is bitten while examining an experimental animal's teeth

8. A patient presents with subcutaneous gangrene in the perineal and gluteal areas. Which of the following is true?
   A. Four-drug therapy for antimicrobial treatment has been shown to have a survival benefit.
   B. A subset of patients may be managed without surgery.
   C. While CT may benefit surgical planning, debridement should not be delayed to obtain imaging.
   D. Plain films of the pelvis may reveal free air and speed up diagnosis.

9. Appropriate antibiotics for necrotizing fasciitis include:
   A. single-agent piperacillin/tazobactam
   B. vancomycin, clindamycin, and piperacillin
   C. cefepime, clindamycin, and gentamycin
   D. tobramycin and clindamycin

10. A 60-year-old alcoholic male presents to your ED with fever and confusion. His chest X-ray and UA are negative. You are going to perform an LP. Which of the following is true regarding this patient's ED care?
   A. Treatment with antibiotics and antivirals should only be started after the results of the LP are known.
   B. If steroids are given, hold steroids for at least 24 hours after starting antibiotics.
   C. A negative gram stain from his LP would eliminate the possibility of meningitis.
   D. An appropriate regimen would include all of the following: vancomycin, third-generation cephalosporin, ampicillin, and acyclovir.

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Rapidly Fatal Infections

Neutropenic Fever

Neutropenia	Absolute neutrophil count (ANC) < 500 OR ANC expected to decrease to < 500 in 48 hrs
Absolute neutrophil count (ANC)	Total WBC x % neutrophils + bands
Fever in neutropenic patient	Single oral temperature of 38.8◦C or higher OR Oral temperature of 38◦ C or higher over 1 hr Note: Axillary (not accurate) and rectal (prevent bacteremia) temperatures are not recommended.
Most common sites of infection — Top 5	Mouth/pharynx (25%) Lung (25%) GI tract (15%) Skin/soft tissue/intravascular catheters (15%) Perineum/anorectal area (10%)
Most common gram-negative bacilli	*Escherichia coli* *Klebsiella pneumoniae* *Pseudomonas aeruginosa*
Most common gram-positive cocci	*Staphylococcus epidermidis* *Viridans* group streptococci
Leading cause of bacterial infections in U.S.	*Enterococcus* species *Staphylococcus aureus*
Resistant bacteria	MRSA — Methicillin-resistant *Staphylococcus aureus* VREs — Vancomycin-resistant *Enterococcus* species ESBLs — Beta-lactam-resistant *Klebsiella* species and *Escherichia coli* KPCs — Carbapenem-resistant *Klebsiella* species and *Pseudomonas aeruginosa*
Most common fungal infections	*Candida* *Aspergillus*

MASCC Score

Characteristic	Weight
Burden of febrile neutropenia	
with no or mild symptoms	5
with moderate symptoms	3
with severe symptoms	0
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor of hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient status	3
Age < 60 years	2

Guidelines for Hospitalized Patients with CAP

Inpatient Non-ICU	Inpatient ICU	ICU with Possible *Pseudomonas* Infection	Possible *S. aureus* Infection
1. A respiratory fluoroquinolone *or* 2. An extended-spectrum beta-lactam *plus* macrolide	An extended-spectrum beta-lactam *plus* a respiratory fluoroquinolone *or* a macrolide	1. Antipneumococcal, antipseudomonal beta-lactam *plus* ciprofloxacin or levofloxacin 2. Above beta-lactam *plus* an aminoglycoside *and* azithromycin 3. Above beta-lactam *plus* an aminoglycoside and an antipneumococcal fluoroquinolone	Add vancomycin *or* linezolid

Adapted from Mandell et al. 2007.

Rabies Vaccine Regimens

Vaccine Regimen	Route, Total Doses	Days of Injection
Post-exposure	IM x 4 (HRIG x 1)	0, 3, 7, 14
If previous vaccine course	IM x 2	0, 3

Low-risk Characteristics for Meningitis

Age < 60	Normal level of consciousness	No arm or leg drift
Immunocompetent	Able to answer two consecutive questions	No abnormal language
No history of CNS disease	Able to follow two consecutive commands	No abnormal visual fields
No seizure in week prior	No facial palsy	No gaze palsy

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