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Emerging Infectious Disease and Emergency Medicine

Introduction

Emerging infectious diseases are defined as those due to pathogens that have appeared recently or reappeared within a population, or those with an incidence or geographic range that is expanding rapidly or has the potential to increase dramatically in the near future. There are many different causes, including factors related to the infectious pathogen itself, as well as environmental/societal effects of the population.[1] Microbial adaption, changing human susceptibility, and multi-drug resistance contribute to genetic modification of diseases, while war, climate/weather, economic development, and travel also contribute to the modification of disease but, perhaps more importantly, permit rapid spread of these infections across the globe.[2] Although many infections may not represent true emergencies, it is important for ED providers to understand the epidemiology, presentation, and treatment of some of today's common and life-threatening infections.

The five reviewed here were chosen as examples of different varieties of emerging infections. Middle East respiratory syndrome is genuinely new, and has the potential to spread to populations not previously exposed. *Neisseria gonorrhea* is not a new organism, although the development of resistance is new, and the difficulty in treatment has become alarming in some locations. *Acinetobacter* represents bacteria that have afflicted very ill hospitalized patients and caused concern among hospital administrators and intensive care staff as another organism that has become nearly impossible to eradicate. Extended-spectrum beta-lactamase (ESBL) producers have been around for some time but increasingly are prevalent, similar to *Acinetobacter*, especially in chronic healthcare utilizers who frequently develop recurrent infections. Measles, which essentially vanished with the development of an effective vaccine, is making a devastating resurgence, particularly as a result of anti-vaccination efforts across the United States.

Middle East Respiratory Syndrome

Epidemiology. Middle East respiratory syndrome coronavirus (MERS-CoV or MERS for short) first was identified in two separate case reports in 2012.[3] The first case identified a man in Saudi Arabia who developed pneumonia and subsequently acute kidney injury, whereas the second case involved a man from Qatar who was hospitalized in England but had traveled recently to Saudi Arabia.[4,5] Since then, approximately 1,936 laboratory confirmed cases of MERS-CoV have been reported in 27 countries, with 690 deaths.[6] Although most cases have been reported in Saudi Arabia, the reach extends from the United States to South Korea.

EXECUTIVE SUMMARY

- The key to suspecting Middle East respiratory syndrome is obtaining a history of travel to the Middle East within 14 days of developing symptoms and signs of a respiratory infection.
- There is only one antibiotic class — cephalosporins — and only two agents — ceftriaxone and cefixime — that are proven reliable in eradicating uncomplicated genitourinary gonococcal infections.
- Combination therapy is recommended for the initial treatment of suspected *Acinetobacter* infections.
- Carbapenems are recommended for the treatment of extended-spectrum beta-lactamase-producing organisms.
- Because measles is highly contagious, high vaccine coverage (90% to 95%) is necessary to achieve herd immunity.

Pathophysiology/Virology. Although the pathogenesis of the MERS-CoV is poorly understood, the virus is known to be a part of the lineage of C betacoronavirus that is similar to human viruses such as severe acute respiratory syndrome coronavirus (SARS), but it actually is related more closely to bat coronaviruses.[7]

Camels likely serve as the host for MERS-CoV. One multivariable analysis of 34 primary cases (i.e., infection was not traceable as person-to-person transmission) compared to 116 matched controls showed that direct contact with camels in the preceding 14 days, diabetes mellitus, smoking, and heart disease all were independently associated with MERS-CoV.[8] This has been corroborated with MERS-CoV strains that have been isolated from camels, including one example of full genome sequencing between a camel and a fatal case of disease in its previously healthy owner.[9] Although camels likely serve as the initial host, analysis of cases in Saudi Arabia suggest that only 12% were due to direct camel exposure, while the remaining cases were from human-to-human contact.[10] In particular, the presumed droplet or contact transmission has been identified as being responsible for large-scale, hospital-associated outbreaks, as well as small-scale outbreaks in various European countries and a large-scale (186 cases) outbreak in South Korea.[11,12,13]

Clinical Presentation and Diagnostic Studies. Most reported cases of MERS-CoV infections present with pneumonia often complicated by acute respiratory distress syndrome and usually acute kidney injury. Nonspecific findings, such as fever, cough, and shortness of breath, also are common, and occur in 70% to 98% of cases. Less common are gastrointestinal symptoms, including vomiting, diarrhea, and abdominal pain, present in between 20-30% of patients with confirmed disease.[14,15]

Children also can be affected; a case series described 31 infections in children, with two reported deaths (from children who had significant comorbidities such as cystic fibrosis and congenital nephrotic syndrome).[16,17,18] Cases also have been reported in pregnant women, with no identified transmission to the fetus when live birth occurred.[19,20]

Laboratory abnormalities on readily available bloodwork generally are nonspecific and can include leukopenia, anemia, thrombocytopenia, elevated aspartate aminotransferase and alanine transaminase, and elevated lactate dehydrogenase. Blood urea nitrogen and creatinine elevations are seen when cases progress to acute kidney injury/renal failure.[15]

A variety of nonspecific imaging findings almost always are seen, ranging from increased bronchovascular markings to patchy consolidations to pleural effusions or total opacification of lung segments.[21]

Different diagnostic tests are available, ranging from reverse-transcriptase polymerase chain reaction assays to immunofluorescence and protein microarray assays.[22] However, more important is recognizing who should be tested. In the United States, the Centers for Disease Control and Prevention (CDC) recommends testing patients who meet the criteria listed in Table 1.[23,24]

Management/Prevention. The mainstay of treatment is supportive care (intravenous fluids, respiratory support, etc.), as there is no antiviral effective for treatment of MERS-CoV in humans.[25] One study suggests efficacy of some antivirals (such as lopinavir/ritonavir) in primate models, but further testing is warranted.[26] Studies to assess the efficacy of ribavirin and interferon alpha-2a as adjuncts to supportive therapy failed to show significant mortality benefit at 30 days.[27] Glucocorticoid treatment also has shown no clear benefit.[28,29]

There is no licensed vaccine for MERS-CoV; however, some experimental candidates are being developed, including with vaccines aimed at camels to help prevent initial transmission.[30,31] Because there is no cure, prevention of transmission is key. The World Health Organization (WHO) recommends droplet precautions for all suspected airborne illness as well as contact and eye precautions for confirmed cases of MERS-CoV. Patients who do not require hospitalization can be cared for in their homes under isolation.

Although there are no specific travel restrictions or screening, the WHO recommends that countries outside of the affected region maintain a high level of vigilance, especially countries with large numbers of travelers or guest workers from the Middle East.[32,33,34] As of February 2017, 677 of 1,905 patients with laboratory confirmed MERS-CoV died. This mortality may be overstated since mild cases may not have been tested.[35] Regardless, clinicians should stay on high alert for potential cases, even in countries where the incidence has been low, especially with travel and exposure risk factors.

Gonorrhea

Epidemiology. Gonorrhea is a major burden to health worldwide, causing not only genitourinary infections, but also disseminated infections like arthritis and meningitis. The CDC reported nearly 400,000 cases in 2015 alone.

Table 1. Diagnostic Criteria for Middle East Respiratory Syndrome

A) Fever **and** pneumonia or acute respiratory distress syndrome **and either:**
   1) A history of travel from countries in or near the Arabian Peninsula within 14 days before symptom onset **or**
   2) Close contact with a symptomatic traveler who developed fever and acute respiratory illness within 14 days after traveling from countries in or near the Arabian Peninsula **or**
   3) A history of being in a healthcare facility (patient, worker, or visitor) in South Korea within 14 days before symptom onset **or**
   4) Is a member of a cluster of patients with severe acute respiratory illness (e.g., fever and pneumonia requiring hospitalization) of unknown etiology in which MERS-CoV is being evaluated in consultation with state and local health departments

   OR

B) Fever and symptoms of respiratory illness (e.g., cough, shortness of breath) and being in a healthcare facility (as a patient, healthcare worker, or visitor) within 14 days before symptom onset in a country in or near the Arabian Peninsula in which recent healthcare-associated cases of MERS-CoV have been identified

   OR

C) Fever **or** symptoms of respiratory illness (e.g., cough, shortness of breath) and close contact with a confirmed MERS-CoV case while the affected person was ill

Overall rates declined after the mid-1970s to a low of 98.1 cases per 100,000 people in 2009; however, these rates have been climbing since.[36] The initial downtrend is thought to be multifactorial from increased public education, cultural changes in sexual behavior due to HIV, and increased antibiotic use. However, the current uptrend now poses a serious threat to the management of the disease.[37,38]

Resistance. The earliest treatment for gonorrhea was with sulfonamide antibiotics introduced in 1936, but this was short-lived because of resistance patterns emerging by 1945. Penicillin subsequently became the next antimicrobial of choice for the next 40 years;[39] however, by 1985 *Neisseria gonorrhoeae* had developed both chromosomal-mediated resistance and plasmid/penicillinase resistance. Similar resistance patterns developed with tetracycline antibiotics, leaving the third-generation cephalosporin ceftriaxone as the mainstay of treatment, with ciprofloxacin as an alternative.[40,41]

The WHO currently reports widespread resistance to ciprofloxacin and azithromycin (97% and 81%, respectively, in countries involved in the data collection between 2009-2014 and that reported resistant strains). Strains resistant to extended-spectrum cephalosporins have been reported in 66% of countries.[42] Interestingly, a higher pattern of resistance is seen among men who have sex with men (MSM) compared to men who have sex exclusively with women. This is thought to be due to MSM networks more likely having circulating resistant strains.[43]

Resistance Mechanisms. Gonorrhea has evolved multiple mechanisms of resistance to the above-mentioned antibiotics. Penicillin resistance, in general, developed from overuse, leading to chromosomal-mediated resistance and penicillinase-mediated resistance. The former involves the genetic coding for penicillin binding proteins (PBPs), which have slowly evolved to producing PBPs now that no longer recognize beta-lactams, rendering the bacteria not susceptible to this class of antibiotics. The other major mechanism is penicillinase production, in which the penicillinase enzyme will bind to the beta-lactam ring of penicillin and hydrolyze it, rendering the medication ineffective.[44,45]

Quinolone resistance also developed mostly through chromosomal-mediated resistance. DNA gyrase and topoisomerase aid in DNA replication by negative supercoiling (unwinding), and are inhibited by fluoroquinolones, leading to failure of replication. Over time, genes mutated to synthesize gyrase and topoisomerase, which are altered and unable to be bound by quinolones.[45]

Efflux pumps are proteins coded by the mtr gene that aid in antibiotic resistance for many organisms. Efflux pumps are proton antiporters that expel antibiotics in exchange for a proton, and also mediate resistance to detergents and dyes. Porins are cell membrane components that decrease permeability of the cell membrane to antibiotics. Upregulation in both efflux pumps and porins is thought to be a contributing factor to resistance for penicillins, aminoglycosides, and, perhaps most importantly, cephalosporins.[45]

Presentation and Treatment. Gonococcal infection can present with both genital and extragenital manifestations. In both men and women, genital infections are more common, with women presenting with cervicitis, urethritis, or pelvic inflammatory disease. The latter of these three is associated with the most significant complications and is caused by *N. gonorrhoeae* in 40% of cases. Pelvic inflammatory disease presents with pelvic/abdominal pain, vaginal bleeding/discharge, dyspareunia, or even right upper quadrant pain in Fitz-Hugh-Curtis syndrome when there is perihepatic inflammation.[46,47] Complications include fallopian tube scarring and an increased likelihood of ectopic pregnancy. Gonoccocal infection in pregnancy has two to five times more likelihood of complication, including chorioamnionitis, premature rupture of membranes, preterm birth, low birth weight or small for gestational age infants, and spontaneous abortions.[48,49]

Gonococcal genital infections in men usually present with urethritis or epididymitis, and are more likely to be asymptomatic than women.[50] As mentioned, gonococcal infections may have a variety of extragenital presentations. Two more common extragenital presentations are proctitis and pharyngitis.

Proctitis is more common in MSM, but also is seen in women (thought to be from both proximity of the vagina to

Table 2. High-risk Groups for Gonorrheal Infections

- HIV-infected men and women
- Sexually active women < 25 years old
- Individuals with new or many sexual partners
- Men who have sex with men
- Sexually active individuals living in areas of high *N. gonorrhoeae* prevalence
- Individuals with a history of other sexually transmitted infection(s)
- Women ≤ 35 years old and men ≤ 30 years old entering correctional facilities, at every initial intake

the anus as well as anal receptive intercourse). Proctitis often presents as anorectal bleeding, mucopurulent discharge, pain with defecation, constipation, or rectal fullness.[51,52,53,54]

Gonoccocal pharyngitis is most commonly obtained via oral sexual exposure and is more likely to be obtained from performing fellatio over cunnilingus. Higher rates are estimated in MSM than in women.[50]

Disseminated gonococcal infection is less common (0.5% to 3% of infected patients) but is very serious and can lead to polyarticular and purulent arthritis, tenosynovitis, dermatitis, osteomyelitis, endocarditis, and meningitis.

The gold standard for diagnosis of gonococcal infection is nucleic acid amplification testing (NAAT). Since these results take one to three days, most clinicians initiate empiric therapy based on symptoms and signs. Because many cases in both men and women can be asymptomatic, NAAT screening should be offered to those in high-risk groups.[54] (*See Table 2.*)

Because of the development of resistance, there is only one antibiotic class that can be relied upon to treat gonococcal infection: cephalosporins. The CDC-recommended regimen for uncomplicated urogenital gonococcal infections is ceftriaxone 250 mg IM once and azithromycin 1 gram PO once (which also covers chlamydia, and is useful because of a high coinfection rate).[54] Doxycycline 100 mg PO twice a day for seven days is an alternate therapy when azithromycin is contraindicated, such as in patients with congenital prolonged QT syndrome.

For patients with severe allergy to cephalosporins, the CDC Sexually Transmitted Diseases Treatment Guidelines do not provide a recommendation, only two suggestions.[54] The first is oral gemifloxacin 320 mg plus oral azithromycin 2 g. The second is intramuscular gentamicin 240 mg plus oral azithromycin 2 g. Both appear to be effective in small studies, but are limited by the occurrence of vomiting, necessitating repeat dosing.

Spectinomycin (2 g intramuscularly) is a safe and effective parenteral alternate for patients with a history of severe penicillin or cephalosporin allergy; however, it is no longer available in the United States and is in limited production elsewhere.[55]

Novel Treatments and Future Implications. As of July 2017, three new antibiotics are in clinical trials for the potential treatment of gonorrhea and other resistant microbes: solithromycin, for which a Phase III trial has been completed recently; zoliflodacin, which has completed a Phase II trial; and gepotidacin, which also has completed a Phase II trial. The research and resource investment for pharmaceutical companies to develop new antimicrobials often is seen as less financially rewarding than for medications that are taken on a chronic basis.[42]

Acinetobacter

Acinetobacter epitomizes the trend toward the emergence of general resistant to all known antibiotic agents. It is a very effective colonizer in the hospital environment, and has been reported not only in developed areas in both hemispheres, but also in areas as remote as Tahiti in the South Pacific. It affects debilitated patients in intensive care units, as well as U.S and U.K. military personnel returning from Iraq and Afghanistan.[56] Thus, it has become a well-known organism in infection control for all critical care hospitals and units caring for the elderly with indwelling devices and catheters, but also in facilities that treat combat-associated wounds.[57]

Treatment of this species is difficult for a number of reasons. It may be unclear as to whether the organism is a benign colonizer or whether it is acting as a pathogen. It appears to be well-suited for genetic exchange, and these organisms have been described as "naturally transformable," allowing the ready uptake of resistance genes. It has acquired resistance to almost all available chemotherapies. This organism leads to prolonged occupancy and increased morbidity rates.

Organisms such as *Acinetobacter* have generated terms such as multidrug resistant, extensively drug resistant, and pandrug resistant. (*See Table 3.*)

Organism. *Acinetobacter baumannii* is a gram-negative oxidase-negative bacillus. The genus *Acinetobacter* was not definitively established until 1971.[58] It is found in many healthcare environments, and is a very effective human colonizer in the hospital. *Acinetobacter* infections may be an indicator of the severity of a patient's underlying illness, as it is widely spread in the environment, but tends to afflict the sickest patients.[59] While there are at least 25 species of *Acinetobacter*, this discussion will focus on *A. baumannii*, which has been associated with ventilator-associated pneumonia (VAP), septicemia, meningitis, urinary tract infection, osteomyelitis, endocarditis, wound infection, and septic shock.[60]

The *Acinetobacter* genus is pervasive in nature, found in soil, water, human skin, the throat, and the respiratory tract. It also has been found on gowns, gloves, curtains, laryngoscope blades, door handles, mops, keyboards, and the hands of healthcare providers.[60,61] *Acinetobacter* species persist in either dry or moist environments, contributing to its transmission.[62]

The bacteria commonly colonizes in irrigating solutions and intravenous fluids. It has been found on mattresses, pillows, bed curtains, door handles, telephone handles, tabletops, and blankets. It is found particularly in patients who are intubated, and who have multiple

Table 3. Extent of Resistance as Applied to *Acinetobacter*

Multidrug-resistant
Resistant to at least three classes of antimicrobial agents: all penicillins and cephalosporins, fluoroquinolones, and aminoglycosides

Extremely drug resistant
Also resistant to carbapenems (e.g., meropenem, imipenem)

Pan-drug resistant
Also resistant to polymyxins and tigecycline

Table 4. Risk Factors for Colonization of Infection With Multidrug-resistant *Acinetobacter baumannii*[62]

- Prolonged length of hospital stay
- Exposure to an intensive care unit
- Mechanical ventilation
- Prolonged antibiotic exposure, as in home antibiotic therapy
- Selective pressure from carbapenems and fluoroquinolones
- Recent surgery
- Invasive procedures
- Underlying severity of illness
- Foley catheterization
- Comorbidities: ischemic heart disease

intravenous lines, monitoring devices, surgical drains, or indwelling urinary catheters. Mechanical ventilation, in particular, appears to be a risk for infection.[58] (*See Table 4.*) The associated crude mortality is high, reportedly from 26% to 68%, although the attributable mortality due to the organism itself is difficult to tease out from the underlying illness. These organisms vary genetically, and different *A. baumannii* have been typed by pulsed-field gel electrophoresis.[60]

Treatment. During the early 1970s, *Acinetobacter* species usually were susceptible to gentamicin, nalidixic acid, ampicillin, and minocycline. Until the 1980s, it was almost uniformly susceptible to imipenem.[58] Treatment of *A. baumannii* infections typically has included aminoglycosides such as amikacin or tobramycin with a beta-lactamase stable beta-lactam such as piperacillin-tazobactam. However, since the 1980s, acquired resistance of *A. baumannii* to antimicrobial drugs has been noted, including to newly developed ones.[62]

Historically, carbapenems, such as imipenem, meropenem, or ertapenem, have been effective against multidrug-resistant *A. baumannii*. However, susceptibility should not be assumed, as some organisms are susceptible to imipenem but resistant to meropenem, and vice versa.[58] For carbapenem-resistant *A. baumannii*, alternative agents have included tigecycline, colistimethate (which is metabolized/hydrolyzed to colistin), and doripenem, as well as the polymyxins such as colistin (polymyxin E) and polymyxin B. With extremely drug-resistant organisms, polymyxins and tigecycline are considered by some as drugs of last resort.[63]

Tigecycline, a minocycline derivative, first received FDA approval in 2005. It is available only in parenteral form, generally with a loading dose of 100 mg, and a maintenance dose of 50 mg every 12 hours. Unfortunately, even this agent is not currently uniformly effective. By 2000, pan-drug-resistant *A. baumannii* was noted in Taiwan in 6.5% of isolates. Selective pressure following carbapenem use or fluoroquinolone use has been cited as contributing directly to pan-resistance.[62]

Doripenem, a newer carbapenem, has shown promise as therapy, although *Acinetobacter* isolates that produce certain enzymes have exhibited resistance to this agent.[59]

Ventilator-associated pneumonia is one of the most dreaded infections due to *Acinetobacter*. While the carbapenems traditionally have been the antimicrobials of choice, antimicrobial resistance dictates that colistin (polymyxin E) has attained more significance as a drug of last resort. For patients with normal renal function, the dose cited is 2.5 to 5 mg/kg/day divided into three doses.[63] Colistin has been administered to children at 5 mg/kg every eight hours.

Mechanisms of Resistance and Clinical Significance. Because of widespread resistance, combination therapy has been advocated to achieve synergy against multidrug-resistant strains. Mechanisms of antimicrobial resistance in *A. baumannii* fall into three categories: antimicrobial-inactivating enzymes, reduced access to bacterial targets, and mutations that change antibiotic targets or cellular functions (i.e., alterations in binding proteins).

In microbiology, natural genetic competence refers to the ability of bacteria to take up extracellular DNA and stably maintain it either on the chromosome or as a plasmid, thus transforming the bacteria's genetic structure. This stable incorporation of DNA into bacteria allows for the horizontal transfer of antibiotic resistance genes. The number of resistance genes is impressive: One study noted one *A. baumannii* ATCC isolate possessed a potential 74 drug resistance genes, such as permease genes, efflux pump genes, and resistance to heavy metals.[64]

As discussed, resistance to beta-lactams may be via hydrolysis by beta-lactamases, changes in penicillin-binding proteins, alterations in structure, and a number of porin or outer membrane proteins. Porin channels enable transport of antimicrobial agents into the cell, so loss of these enables resistance to carbapenems.[60] There are dizzying numbers of

other genes and enzymes conferring resistance to penicillins, extended-spectrum cephalosporins, and carbapenems. Found in Scotland in 1985, OXA-23 was the first of the OXA carbapenemases to be described.[59] Class D (OXA) carbapenemases are the main cause for carbapenem resistance in *A. baumannii*. In addition, there are named metallo-lactamases that may be transferred easily among bacteria so that resistance may be acquired from other bacterial species, such as *Pseudomonas*, *Salmonella*, or *Escherichia coli*. Whereas *Acinetobacter* resistance to carbapenems was nearly 0% in 1980, by 2006 it had approached 40-45%.[58]

In addition to the above, efflux pumps found in *A. baumannii* have conferred resistance to aminoglycosides, cefotaxime, tetracyclines, erythromycin, chloramphenicol, trimethoprim, and fluoroquinolones. Resistance to tigecycline has been reported since 2007.[65] Aminoglycoside-modifying enzymes also play a central role in *Acinetobatcer* resistance to amikacin.

Finally, resistance has been reported to the antibiotics of last resort — the polymyxins. These are polymyxin B and polymyxin E (colistin, or colistimethate sodium). Reports of polymyxin resistance understandably have caused great alarm.[59] Resistance has spawned terms such as CRAB (carbapenem-resistant *A. baumannii*) and PDRAB (pan-drug-resistant *A. baumannii*).[66]

Prevention of Transmission. Standard precautions start with adequate hand washing or alcohol hand decontamination, consistent glove use, and gown and eye protection as indicated. Contact precautions entail dedicated patient care equipment, as well as the aforementioned gown and glove use for healthcare personnel entering an isolation room.

Antibiotic stewardship has been mentioned above. Programs to promote judicious antimicrobial use may prevent the emergence of resistant strains. Proposed control measures include restriction of antibiotic use, particularly carbapenem use in the intensive care unit.[66]

Meticulous environmental decontamination and cleansing of equipment can be critical. Widespread environmental contamination often is present in the epidemic setting. Environmental reservoirs likely are a factor in the endemic setting, making surveillance an important consideration.[60]

Point source control when a point source can be identified has been employed. Surveillance has included swabbing from certain bodily areas, such as nose, forearms, axillae, and perirectal, as well as environmental cultures in an effort to identify a reservoir of organism.[62] Therefore, prevention may include chlorhexidine baths, for example.

Cohorting patients entails grouping colonized and infected patients when single patient rooms are not available. Healthcare personnel can be cohorted as well, so that designated staff care only for patients infected with this organism.[60]

Clinical unit closure has been employed as well to allow for thorough environment disinfection to interrupt transmission. (*See Table 5.*)

Prevention of Antibiotic Resistance. Prevention of antibiotic resistance starts with antibiotic stewardship, especially for those agents with broad-spectrum activity. Patients with *Acinetobacter* colonization often have a history of prolonged hospitalization or antimicrobial therapy. This especially means restricting the use of antibiotics of last resort. This also may include using the narrowest spectrum required to eradicate a bacterial infection and administering for the shortest period of time required for the patient to recover when antibiotics are administered.

It may be advisable to give combination therapy (rifampin with imipenem, or colistin with tigecycline), so that resistance to a specific antimicrobial agent might be avoided.[67] Although no specific regimen is known to be superior, various combinations of antibiotics have been proposed for the initial treatment of *Acinetobacter* infections. (*See Table 6.*)

Table 5. Mechanisms to Prevent Spread of *Acinetobacter*

- Adequate hand washing
- Contact precautions
- Alcohol hand decontamination
- Barrier nursing
- Meticulous environmental decontamination
- Chlorhexidine baths
- Point source control (when a point source can be identified)
- Cohorting patients: grouping colonized and infected patients
- Clinical unit closure: to allow for thorough environment disinfection to interrupt transmission

Table 6. Some Suggested Combinations of Antibiotics for *Acinetobacter* Infections[58]

- Sulbactam with aminoglycosides
- Rifampin, azithromycin, and imipenem
- Imipenem and aminoglycosides/amikacin
- Quinolones and beta-lactams
- Colistin plus rifampin with or without tigecycline
- Colistin plus azithromycin and meropenem
- Polymyxin plus imipenem
- Cefepime plus sulbactam
- Imipenem plus sulbactam/ampicillin
- Meropenem plus rifampin

Future Possibilities for Management. Novel classes of antibacterial agents, such as peptide deformylase inhibitors and LpxC inhibitors, are under trial. Of interest is the possible development of a vaccine against *Acinetobacter*. The first trial for passive immunization appeared in the early 2000s in India, and since 2010, several countries have continued the effort to develop antisera against whole cells, polysaccharide capsule, or surface protein.[61]

Extended-spectrum Beta-lactamase-producing Organisms

Epidemiology. Extended-spectrum beta-lactamase-producing organisms (ESBLs) are similar to, and in some definitions include, *Acinetobacter* as described above. Many of the implications of ESBL-producing organisms are similar to those of *Acinetobacter*. More broadly speaking, ESBL resistance is found exclusively in gram-negative microbes, including *Klebsiella*, *Burkholderia*, *Enterobacter*, *Pseudomonas*, *Salmonella*, *Serratia*, and *Shigella* species.

The start of ESBL resistance was first noticed in *Klebsiella* shortly after the introduction of cefotaxime in Europe during the mid- to late 1980s.[68] Since then, infections particularly due to ESBL-producing *Klebsiella* and *E. coli* have been noted in hospitals around the globe, including community-onset infection of ESBL-producing *E. coli* with no obvious healthcare-associated risk factors.[69]

In a 2012 sample of more than 5,700 isolates from 72 hospitals in the United States, the overall frequency of ESBLs was 16% in *Klebsiella pneumoniae*, 11.9% in *E. coli*, 10% in *Klebsiella oxytoca*, and 4.8% in *Proteus mirabilis*. Even higher rates of resistance were identified in isolates from Asia, Latin America, and the Middle East, reaching as high as 60% in *K. pneumoniae* and 48% in *E. coli*.[70,71,72]

Pathophysiology and Transmission. There are several categories of ESBL resistance based on whether there are amino acid substitutions or plasmid-mediated beta upregulation in genes that confer the beta-lactamase resistance mechanism. Subtypes include TEM, SHV, CTX-M, and OXA beta-lactamases. Most TEM and SHV subclasses have resistance to penicillins and narrow-spectrum cephalosporins, but not all have extended-spectrum resistance.[73] CTX-M beta-lactamases have greater activity against cefotaxime than other oxyimino-beta-lactam substrates, but there has been increasing resistance to other drugs in the class, including ceftazidime. The OXA subclass, mainly found in *Pseudomonas,* hydrolyzes oxacillin and related anti-staphylococcal penicillins.[74]

ESBL-producing gram-negative bacilli are isolated most often from hospitalized patients but are an increasing cause of community-acquired infections. Risk factors for infection include prior administration of an antibiotic, presence of urinary or vascular catheters, and longer hospital or ICU stays.

Data on actual transmission mechanisms are limited; however, infection has been seen in both nosocomial and community-acquired settings. Multiple observational studies out of Switzerland showed in-hospital transmission rates varying from 1.5% to 4.5% in ESBL-producing organisms for patients in tertiary care centers, while rates as high as 25% were seen for in-home transmission of species (granted, there were small patient populations in these studies).[75,76] Perhaps more concerning is that multiple sources of environmental, animal, and food contamination have been implicated with ESBL-producing gram-negative organisms. Bacteria with ESBL resistance have been isolated from rivers, livestock, seagulls, and even retail meat.[77,78,79]

Management and Implications. The general mainstay of treatment for ESBL-producing organisms is carbapenems, which have shown the best outcomes in survival and bacteria clearance. In particular, one study demonstrated one death at 14 days among 27 patients treated with carbapenem monotherapy, compared to four deaths in nine patients treated with cephalosporin or beta-lactam/beta-lactamase inhibitor combination monotherapy, and seven deaths in 11 patients not receiving any antibiotic active against ESBL-producing organisms.[80,81]

The emergency physician dealing with known ESBL-producing organisms often will have at least some preliminary data on antibiotic sensitivities based on cultures and should tailor treatment based on this and should have a potential discussion with the inpatient hospital team/infectious disease team and/or pharmacy, particularly when an antimicrobial stewardship program is in place at the institution.

With increased carbapenem use, carbapenem resistance has become a growing concern since the early 2000s. As described above, *Enterobacteriaceae* are among the most common pathogens in humans, implicated in cystitis, pneumonia, peritonitis, and meningitis.[82] *Klebsiella*-producing carbapenemase (KPC) was first reported in 2000, with imipenem-specific resistance reaching 4.3% by 2010.[83] Mortality rates of up to 50% have been recorded. In particular, these strains are noted in elderly populations with multiple comorbidities, including patients who were incontinent and were exposed to multiple medical devices.[84,85]

Particularly concerning is the potential to spread carbapenem-resistant *Enterobacteriaceae* (CRE) via fecal-oral route, meaning that even healthy individuals can harbor the bacteria for years. Again, although data on transmission are limited, the hospital potentially could be a dangerous environment for spread even in patients undergoing simple, elective procedures. Known risk factors include immunocompromised status, recent catheterization, mechanical ventilation, dialysis, and previous antibiotic use.[82] Although still being researched, current treatment options include aminoglycosides like polymyxin, amikacin, and tigecycline (with polymyxin-resistant *Klebsiella* also being reported).[86]

Measles

Epidemiology and Presentation. Measles is a highly contagious viral illness, with a worldwide spread, but also with the potential for elimination. The infection is characterized by fever, cough, coryza, and conjunctivitis, followed by exanthem. Measles is highly contagious; approximately 90% of exposed and susceptible individuals will develop measles. The contagious period is estimated to be from five days before the appearance of the rash

to four days afterward, and the incubation period ranges from one three weeks (typically 10-12 days). Koplik spots on the oral mucosa may appear days before the rash.

The diagnosis of measles should be considered in a patient presenting with a fever, rash, and clinically compatible symptoms. It may be confirmed by a serum sample for measles IgM, a throat or nasopharyngeal swab for viral culture, and a urine sample for viral culture or measles RNA by real-time polymerase chain reaction.

Severe complications from measles include secondary infections such as diarrhea, pneumonia, encephalitis, or delayed neurologic degeneration (subacute sclerosing panencephalitis). Before a vaccine against measles was introduced, 500,000 cases occurred each year in the United States, causing approximately 500 deaths, 48,000 hospitalizations, and 1,000 cases of brain damage from encephalitis.[87] Treatment tends to be supportive, although vitamin A may be beneficial.

Strictly speaking, measles is not an emerging disease. The reason for this discussion, and the reason this disease has been in the news, is that when immunizations lag, measles re-emerges as a public risk. Measles is estimated to cause more than 100,000 deaths annually,[88] and the WHO has established a goal of eliminating measles via universal immunization by the year 2020. This discussion will focus on immunization status.

WHO policy recommends giving measles vaccine at 9 months of age in high-risk settings in the developing world, and at 12-15 months if the risk is lower. The CDC recommends a two-dose series of measles, mumps, and rubella (MMR) vaccine, the first at ages 12 through 15 months and second at 4 through 6 years.[89] Earlier vaccination in the presence of maternal antibody interferes with the development of vaccine-induced immunity.[90]

Resurgence. Vaccine hesitancy and resulting decline in childhood vaccination risks a resurgence of many infectious diseases, the most prominent of which is measles.[91] Vaccine hesitancy is defined as a delay or refusal to accept vaccination despite availability based on personal or religious beliefs, or simply because there is a low perceived risk of measles. For example, anti-vaccine advocates reportedly visited the Somali community in Minnesota and advised them to avoid the MMR vaccine because of an increased risk of autism. In April 2017, 50 people, mostly unimmunized children, were diagnosed with measles in Minnesota.[92] It is estimated that a small decline of 5% in MMR vaccine could result in a three-fold increase in annual measles cases.[90]

There also is a marked difference in risks by country. One analysis listed susceptibility to measles to be more than 10% in Kenya and Ethiopia.[93] In relatively high-income (and low-fertility) countries such as the United States, low levels of transmission allow unvaccinated individuals to be susceptible to measles at older ages.[94]

Although endemic measles was eliminated in the United States in 2000, sporadic outbreaks have occurred because of importation of the virus from other countries. In 2014, the United States had the largest outbreak of measles in more than 20 years, with 667 cases, because of infected travelers returning from abroad. The following year, 188 cases were reported, including a noted outbreak associated with Disneyland, considered to be the result of a park visitor who had traveled overseas.[87]

It is routine to evaluate the MMR vaccination status of refugees upon arrival into the United States.[95] However, among American citizens, it was noted that fewer than half of adults who were eligible for MMR vaccine at a pretravel clinic were vaccinated.[96]

Management/Vaccination. The existence of a safe, inexpensive vaccine for measles, as well as high case fatality rates associated with measles in children, makes measles vaccination a valuable, highly cost-effective public health initiative.[97] Vaccination has been estimated to have averted 13.8 million deaths between 2000 and 2012.[98] However, to reduce global prevalence to zero, endemic areas must be eliminated, and elimination must be maintained in areas where measles currently is absent.

Vaccine failure after the initial dose of MMR is approximately 14% at 9 months, likely as a result of interactions with maternal immunity. Countries in the Americas, which have effectively eliminated measles, have achieved success through the introduction of a second vaccine.[97]

High vaccine coverage (90% to 95%) is required to achieve herd immunity, based on an assumption of 95% efficacy. Large reductions in MMR vaccine could allow measles to become endemic again.[99] Unfortunately, the general public does not understand the severity of the disease because of the low incidence of measles in the United States.

Conclusions

There are many emerging infections for which the emergency physician must remain clinically vigilant. Particularly when the disease state manifests as a variety of nonspecific complaints, such as MERS-CoV or measles, an adequate and thorough history, such as travel or immunization, respectively, coupled with high clinical suspicion is crucial. As discussed, early recognition, testing, and management can lead to improved patient outcomes and mortality.

Acinetobacter and ESBL-producing infections have spread rapidly in recent years, with emergence of resistance to even the newer antimicrobials. These organisms have the ability to acquire resistance quickly, and easily survive and spread in a hospital environment. Many *Enterobacteriaceae*, including the superbug multidrug-resistant *Acinetobacter,* have become established as one of the most difficult pathogens to treat. Its victims are critically ill, and frequently are subject to invasive life-support measures, including mechanical ventilation, intravascular catheters, and surgical drainage systems. Effective control will require close collaboration with infection-control, housekeeping, microbiology, pharmacy, intensive care, and all other providers.

In terms of *Acinetobacter*, other ESBL-producing organisms, and gonorrhea, we may be facing in some way the end of the antibiotic era when organisms increasingly develop resistance to all antibiotics. Whether newer agents, alternative preventive strategies, or innovative immunization techniques are the answer remains to be seen.

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CME/CE Questions

1. What is the proposed major mechanism of resistance of gonorrhea to cephalosporins?
   a. Efflux pump and porin upregulation
   b. DNA gyrase and topimarase modification
   c. Cell wall glycoprotein modification
   d. Penicillinase production
2. What is the hallmark of treatment for suspected Middle East respiratory syndrome?
   a. Ribavirin and fluids
   b. Interferon and ribavirin
   c. Glucocorticoids and fluids
   d. Intravenous immunoglobulin
   e. Fluids and supportive care
3. What is a risk factor for acquiring *Acinetobacter* in the hospital setting?
   a. Overnight stay in an observation unit
   b. Mechanical ventilation
   c. Healthy traveler returning from West Africa
   d. Patient has not taken antibiotics for the past 12 months
   e. Patient has had four dental implants within the past 90 days
4. How should a 23-year-old male with congenital prolonged QT syndrome be treated for gonorrhea and chlamydia?
   a. Penicillin
   b. Ciprofloxacin
   c. Ceftriaxone and azithromycin
   d. Ceftriaxone and doxycycline
   e. Tetracycline
5. Gram-negative bacilli have demonstrated beta-lactamase resistance since the 1980s. To which class of antibiotics have newer (i.e., 2000s) strains been resistant?
   a. Tetracyclines
   b. Carbapenems
   c. Aminoglycosides
   d. Macrolides
6. Which of the following is *not* a mitigating factor in prevention of *Acinetobacter* infection?
   a. Disinfection of equipment and the environment
   b. Isolation precautions
   c. Cohorting of staff
   d. Recent treatment with metronidazole
7. What is the major cause for measles recurrence?
   a. Superinfection with co-existing bacteria that can reactivate the virus
   b. Viral mutations that render the vaccine ineffective
   c. Vaccine hesitancy
   d. Measles rates are similar now to the early 1900s.

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EMERGENCY MEDICINE **REPORTS**

Emerging Infectious Disease and Emergency Medicine

Diagnostic Criteria for Middle East Respiratory Syndrome

A) Fever **and** pneumonia or acute respiratory distress syndrome **and either:**
   1) A history of travel from countries in or near the Arabian Peninsula within 14 days before symptom onset **or**
   2) Close contact with a symptomatic traveler who developed fever and acute respiratory illness within 14 days after traveling from countries in or near the Arabian Peninsula **or**
   3) A history of being in a healthcare facility (patient, worker, or visitor) in South Korea within 14 days before symptom onset **or**
   4) Is a member of a cluster of patients with severe acute respiratory illness (e.g., fever and pneumonia requiring hospitalization) of unknown etiology in which MERS-CoV is being evaluated in consultation with state and local health departments

   OR

B) Fever and symptoms of respiratory illness (e.g., cough, shortness of breath) and being in a healthcare facility (as a patient, healthcare worker, or visitor) within 14 days before symptom onset in a country in or near the Arabian Peninsula in which recent healthcare-associated cases of MERS-CoV have been identified

   OR

C) Fever **or** symptoms of respiratory illness (e.g., cough, shortness of breath) and close contact with a confirmed MERS-CoV case while the affected person was ill

Extent of Resistance as Applied to *Acinetobacter*

Multidrug-resistant
Resistant to at least three classes of antimicrobial agents: all penicillins and cephalosporins, fluoroquinolones, and aminoglycosides

Extremely drug resistant
Also resistant to carbapenems (e.g., meropenem, imipenem)

Pan-drug resistant
Also resistant to polymyxins and tigecycline

High-risk Groups for Gonorrheal Infections

- HIV-infected men and women
- Sexually active women < 25 years old
- Individuals with new or many sexual partners
- Men who have sex with men
- Sexually active individuals living in areas of high *N. gonorrhoeae* prevalence
- Individuals with a history of other sexually transmitted infection(s)
- Women ≤ 35 years old and men ≤ 30 years old entering correctional facilities, at every initial intake

Risk Factors for Colonization of Infection With Multidrug-resistant *Acinetobacter baumannii*

- Prolonged length of hospital stay
- Exposure to an intensive care unit
- Mechanical ventilation
- Prolonged antibiotic exposure, as in home antibiotic therapy
- Selective pressure from carbapenems and fluoroquinolones
- Recent surgery
- Invasive procedures
- Underlying severity of illness
- Foley catheterization
- Comorbidities: ischemic heart disease

Mechanisms to Prevent Spread of *Acinetobacter*

- Adequate hand washing
- Contact precautions
- Alcohol hand decontamination
- Barrier nursing
- Meticulous environmental decontamination
- Chlorhexidine baths
- Point source control (when a point source can be identified)
- Cohorting patients: grouping colonized and infected patients
- Clinical unit closure: to allow for thorough environment disinfection to interrupt transmission

Some Suggested Combinations of Antibiotics for *Acinetobacter* Infections

- Sulbactam with aminoglycosides
- Rifampin, azithromycin, and imipenem
- Imipenem and aminoglycosides/amikacin
- Quinolones and beta-lactams
- Colistin plus rifampin with or without tigecycline
- Colistin plus azithromycin and meropenem
- Polymyxin plus imipenem
- Cefepime plus sulbactam
- Imipenem plus sulbactam/ampicillin
- Meropenem plus rifampin

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