INFECTIOUS DISEASES

Potentially Serious Infections in the Aging Person: Diagnosis, Treatment and Prevention

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Infections in the elderly patient are a challenge, since the classical signs of infection are absent or ill defined. The present paper describes the presentation, diagnosis, clinical manifestations and treatment for a selected group of potential serious infections including influenza, bacterial pneumonia, urinary tract infections as well as infections caused by multiresistant bacteria, like vacomycin-resistant enterococcus and methicillin resistant *S. aureus*. We conclude with the need for prevention in the older person with the use of vaccines, specifically the influenza and pneumococcal vaccine as well as the prevention of urinary infections. Influenza is a significant cause of morbidity, whose ill effects can be prevented in many older persons with the use of a vaccine. The use in prophylaxis and treatment of antiviral agents like amantadine, rimatadine, and oseltamivir is presented. Bacterial pneumonia is one of the leading causes of death in the USA among the older persons. The emergence of drug resistant *Streptococcus pneumoniae* leads to the consideration as empiric therapy the newer fluoroquinolones or the use of third or fourth generation cephalosporis. Of importance is the use of pneumococcal vaccine among people age 60 or above. The frequency of urinary tract infections among the elderly is of primary although in many instances important do not require treatment. When infection of the urinary tract is diagnosed, most authors use a fluoroquinolone as empiric theraphy. The emergence of multiresistant bacteria like methicillin resistant *S. aureus* and or vancomycin resistant enterococci leads to the need to consider new agents like quinipristin-dalfopristin, linezolid and deptomycin in the management of such patients.

Key words: Infections, Influenza, Bacterial pneumonia, Anging, Urinary tract infections, Vaccines, Emerging infections, Resistant infections.

Influenza is a common respiratory infection that has an enormous impact worldwide and causes significant morbidity and mortality in older adults. Influenza is responsible for more than $1 billion in annual Medicare expenditures. Of those deaths resulting from influenza, 80 to 90 percent are in adults 65 years and older (5). Older adults are prone to severe and potentially fatal complications from this common illness because of co-existing chronic disease and decreassed immunity. Older adults can benefit most from vaccination, early detection and aggressive therapy.

Diagnosis. Frequently based on clinical and epidemiological findings. Several commercially produced rapid-diagnostic tests intended for use in outpatient settings can detect influenza viruses within 30 minutes (5). In selected patients, obtaining a viral culture may be warranted to acquire specific information on influenza subtypes and strains.

Clinical manifestations. The signs and symptoms of influenza infection in older adults are similar to those occurring in younger patients although, again, a febrile response may be absent. Influenza is typically associated with rapid onset of headache, fever, chills, muscle aches, malaise, cough and sore throat. Most people recover fully within one week, but older adults may develop a persistent weakness that can last for many weeks and are also at higher risk for developing complications, such as pneumonia (6,7).

Treatment. Four antiviral agents—amantadine (Symmetrel), rimantadine (Flumadine), zanamivir (Relenza) and oseltamivir (Tamiflu)—are approved for prevention or treatment of influenza (7,8). These agents must be taken within 48 hours of the onset of illness, which is difficult because most patients treat their illness at home for several

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days before seeking treatment from a physician (9). It is unknown whether therapy with amantadine or rimantandine can prevent complications of Influenza A among persons at high risk, including older adults (10). Rimantadine costs more than amantadine but has fewer adverse effects on the central nervous system like: confusion, nervouness and anxiety. It is also less dependent on renal excretion (8, 9). Zanamivir and oseltamivir are equally effective neuroaminidase inhibitors, but their place in therapy is yet to be determined. Their potential benefit (decrease in duration of symptoms by one to one-and-one- half days) must be considered relative to cost, compliance and adverse effects. In some trials, these agents demonstrated effects in patients 65 years and older that are similar to effects in younger adults. It has not yet been determined whether early initiation of treatment reduces hospital admission and mortality, particularly in elderly and high-risk patients (10,11). The recommended dosage for zanamivir is two inhalations twice daily for five days. Oseltamivir should be taken at a dosage of 75 mg orally twice daily for five days (or once daily in patients with a creatinine clearance less than 30 mL per minute 0.5 mL per second). (See Table 1).

Table 1. Antiviral Agents for Treatment of Influenza

Agent	Types of influenza viruses inhibited	Route of administration	Dosage
Amantadine	A	Oral (tablet capsule, syrup)	200 mg as a single dose or 100 mg twice daily +
Rimantadine-(Flumadine)	A	Oral (tablet, syrup)	100 mg twice daily+
Oseltamivir (Tamiflu)	A and B	Oral capsule	75 mg twice daily*
Zanamivir (Relenza)	A and B	Oral inhalation++	2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily

+ In elderly nursing home patients, a dose reduction to 100 mg daily is recommended.
++ Zanamivir is administered by using a specially designed plastic oral inhalation device called a Diskhaler. The device and instructions for its use are included in the package with the medication.
*A dosage of 75 mg once daily is recommended for patients with creatitine clearance less than 30 mL per minute (0.5 mL per second)

Bacterial Pneumonia

Pneumonia and influenza combined are the sixth leading cause of death in the United States, and about 90 percent of these deaths occur in adults 65 years and older (12). In fact, more than 60 percent of people 65 years and older are admitted to hospitals because of bacterial pneumonia (13). Changes in pulmonary reserve, decreased mucociliary transport, decreased cough reflex, decreased elasticity of alveoli and inadequate ventilation cause older adults to be more susceptible to pneumonia (14, 15). Attention to these risk factors may help the physician assess the severity of illness at presentation and determine the need for hospitalization (16). (See Table 2). The diagnosis of pneumonia in adults is difficult since the usual clinical signs and symptoms are subtle, the initiation of antibiotic therapy is often delayed, which can contribute to higher mortality rates (17).

Table 2.

Findings Associated with Poor Prognosis in older Persons with Community-Acquired Pneumonia

Age >50 years	Temperature <35°C (95°F) or ≥ 40°C (104°F)
PaO_2 <60 mm Hg	WBC elevation >13,000 per mm3 (13 x 109 per L)
0_2 saturation <90 percent	WBC suppression <4,000 per mm3 (4 x 109 per L)
Altered mental status	Hematocrit <30 percent (0.3)
Nursing home resident	BUN ≥ 30 mg per dL (11 mmol per L)
Comorbid illness*—	Glucose ≥ 250 mg per dL (13.9 mmol per L)
Tachycardia ≥ 125 beats per minute	Sodium <130 mEq per L (130 mmol per L)
Tachypnea ≥ 30 breaths per minute	Radiographic evidence of progressing or multilobar infiltrates
Hypotension <90 mm Hg systolic	Pleural effusion

PaO_2 = partial pressure of arterial oxygen, 0_2 = oxygen,WBC = white blood cell count; BUN = blood urea nitrogen.
*—Comorbid illness includes neoplastic disease, renal failure, liver failure, congestive heart failure or cerebrovascular disease.

Diagnosis. Routine laboratory tests to determine the etiology of bronchopneumonia in the older are not of much help as in the younger adult. However, it may have prognostic significance in patients 60 years and older and therefore, is recommended for them (18). The value of a Gram stain and routine bacterial cultures of sputum from patients with pneumonia is debated. Also obtaining adequate sputum specimens in frail, older adults may be particularly difficult (18). Quantification of cultured pathogens and correlation with the Gram stain may help the physician interpret possible oropharyngeal contaminants versus true pneumopathogens (19). Blood cultures chest X rays and oxymetry samples should be obtained prior to the administration of antibiotics. The latter should be started within 4-8 hours.

Treatment. Because of increased mortality and the larger number of potential pathogens causing pneumonia in older adults, an early etiologic diagnosis is optimal to guide pharmacotherapy. Regardless of age, bacterial causes of pneumonia can only be identified in 20 to 50 percent of patients (18,20) In the absence of specific

bacterial etiology, pharmacotherapy of pneumonia is initially empiric and directed at the likely causative pathogens.

In older adults, *Streptococcus pneumoniae* is still the most common cause of pneumonia, followed by respiratory viruses, *Haemophilus influenzae,* gram-negative bacilli and *Staphylococcus aureus (*18). *Moraxella catarrhalis,* Legionella and Mycoplasma are less common but important causes of pneumonia in the elderly because these bacteriae may not be covered by traditional empiric antibiotic regimens. As a group, gram-negative bacteria are responsible for more infections in the elderly than in younger adults (1,18). Therefore, in older adults, empiric antibiotic therapy should provide coverage for gram-positive and gram-negative bacteria (1).

The selection for use of antibiotics in the older person with community acquired pneumonia must include agents with activity against the respiratory pathogens including penicillin resistant streptococcus pneumonia (21,22). We must be aware that the penicillin resistant pneumococcus is frequently resistant also to macrolides like erythromycin, azitrhomycin and clarythromycin. The initial empiric therapy of an older person with pneumonia can include a newer fluoroquinolone like levofloxacin, gatifloxacin or moxifloxacin; a macrolide or amoxicillin-clavulanate plus erythromycin. If in the patients community there are frequent penicillin resistant *S. pneumoniae* a newer fluoroquinolone should be considered unless contraindicated. If the patient needs to be hospitalized, most authors, as well as the IDSA guidelines recommend that a third or fourth generation parenteral cephalosporin plus a newer fluoroquinolone (gatifloxacin, levofloxacin or moxifloxacin) or a macrolide (azitromycin) be considered in the management of such patient.

In addition to the choice of antibiotic, physicians need to decide on the route of administration and duration of treatment. Unfortunately, little information exists regarding administration and duration of treatment. Frequently, no clear advantage is evident for the use of intravenous over oral antibiotics as long as the bioavailability and tissue penetration of the drug is adequate. Common practice has been to begin empiric intravenous therapy in hospitalized patients (19). A review of the literature suggests that a change to oral therapy can be made if the patient is hemodynamically stable, clinically improving and absorbing oral medication (19). Adequate hydration and oxygenation must also be assured for successful oral treatment. Generally, patients with S. *pneumoniae* should be treated for at least 7 days, many of them need a 10-14 days theraphy. Patients with mycoplasma or chlamydia infection and those who are immunocompromised should be treated longer (18).

Urinary Tract Infections

Urinary tract infections (UTIs) are the most frequent bacterial infection and the most common source of bacteremia in older adults (23). Factors that predispose older adults to UTIs include the use of urethral or condom catheters and neurogenic bladders with increased residual urine. Contributing factors specific to gender include prostate enlargement in men, an increased vaginal pH, vaginal atrophy due to postmenopausal estrogen depletion, and incomplete emptying of the bladder in women. These factors provide the opportunity for bacterial colonization and are likely to contribute to the higher rates of asymptomatic bacteriuria and UTIs in the elderly.(24)

Diagnosis. The same process is followed for the diagnosis of UTIs in older adults as in younger adults. An important caveat is the controversy regarding treatment of asymptomatic bacteriuria, which is common in the elderly. Most authorities advocate withholding antibiotics in-patients who are completely asymptomatic (24). Clinical findings and a urinalysis are usually sufficient for diagnosis in older adults; however, a urine Gram stain and culture should be considered to direct therapy.

Clinical manifestations. Because classic clinical manifestations of UTIs such as dysuria, fever, urinary frequency and suprapubic tenderness may be absent or masked m older adults, treating these infections in this group is a special challenge for physicians. Vague symptoms such as nausea, vomiting and decreased urinary output must be distinguished from symptoms of other common illnesses (25). Older adults with UTIs and comorbidities (e.g., diabetes) and those who are at risk for dehydration (because of fever nausea or vomiting) should be strongly considered for hospitalization.

Treatment. Treatment for UTIs should be directed at the organisms identified by Gram strain and culture. Unfortunately, polymicrobial infections occur in about 30 percent of patients and more often if the UTI is related to the use of a catheter (25). In these patients, use of a broad-spectrum antibiotic may be necessary. Most authors use on an empiric basis a fluoroquinolone like ciprofloxacin or gatifloxacin and as alternatives amoxicillin-clavulanate an oral cephalosporin or trimetroprin-sulfamethoxazole. If the patient is hospitalized parenteral therapy is preferred with a fluoroquinolone, or ampicillin plus gentamicin, a third generation cephalosporin or an antipseudomonal penicillin like piperacillin-tazobactam or ertapenem. In general, seven days is an adequate duration of therapy in older women and 14 days in older men. The duration of therapy is routinely doubled for infections considered to be serious (25).

Treatment of asymptomatic bacteriuria does not appear to reduce morbidity or mortality and may increase the likelihood of development of drug-resistant microorganisms and adverse reactions to antibiotics. Exceptions to treatment of asymptomatic bacteriuria are patients scheduled for a genitourinary procedure who have obstructive uropathy, stones or a history of recurrent symptomatic infections (23).

Infections with Resistant Bacteria

Vancomycin-resistant enterococcus (VRE). VRE presents a major problem in older patients, especially when an outbreak occurs in an institutional setting. Enterococci are the second most common organism in nosocomIal urinary tract and wound infections and the third most common cause of nosocomial bacteremia in the United States (26-28). Over the past two decades, most enterococci have become resistant to betalactam antibiotics and, recently, resistance to aminoglycosides has become widespread (28). Thus, glycopeptide antibiotics, such as vancomycin in the United States and teicoplanin (Targocid) in Europe, have become the most reliable drugs to treat infections caused by the above named enterococci. Agents like quinupristin/dalfopristin (for *E. faecium* – VRE and linezolid form VRE (*E. faecalis* and *E. faecium*) are new alternatives to treat such infections.

In 1988, the first outbreak of VRE was reported. In 1996-1997, 10 percent of isolates reported to the Centers for Disease Control and Prevention are vancomycin-resistant (26,28). Bacteremia from these isolates have a mortality rate approaching 50 percent. Multiple strains of VRE have been identified, with phenotypes vanA, van B, vanE and vanC described to date.

Therapeutic options for VRE vary by strain and resistance to other drug. The initial therapeutic options for vanA VRE were combinations of ampicillin and imipenem (Primaxin I.V.), vancomycin and ciprofloxacin (Cipro), ceftriaxone (Rocephin) with fosfomycin (Monurol), and chloramphenicol (Chloromycetin) they were used with limited success. For vanB VRE, the combination of teicoplanin (available in Europe but not in the United States) with gentamicin was successful. Quinupristin/dalfopristin (Synercid) (29-31) was used against vancomycin-resistant *Enterococcus faecium.* For UTIs, nitrofurantoin (Macrodantin) has been used against susceptible VRE. Ongoing research shows that two semisynthetic glycopeptides, as well as two new fluoroquinolones, have in vitro activity against VRE (27).

Since 1999 the availability of Quinuspristin/dlfopristin (Synercid) (29-31) as well as linelozid (Zyvox) (32-34) have provided useful therapeutic alternatives to manage these patients. The availability of linezolid in oral preparation is especially useful in the elderly, but its use must be controlled to prevent abuse and emergence of resistance (32-34).

Because of the high level of antibiotic resistance, prevention of outbreaks and spread of VRE is crucial. As with MRSA, the best way to prevent an outbreak of VRE infection is by hand washing and proper handling of bodily secretions. In addition, limiting the use of oral and parenteral vancomycin will help control the further spread of resistance. Patients who are found to be colonized with VRE should be isolated, and proper infection control should be instituted (35-36).

Methicillin-resistant Staphylococcus aureus. Methicillin-resistant *Staphylococcus aureus* (MRSA) presents a major problem for elderly patients, especially those in institutional settings. People colonized with MRSA are at increased risk of MRSA infection (25). They also have a higher risk of death from MRSA resulting from its resistance to typical antibiotics. While MRSA infection is more likely to occur in hospitalized patients than in nursing home residents, poor functional status is associated with being an MRSA carrier. Therefore, nursing homes and other institutional settings must be especially careful to prevent the spread of infection caused by this organism (30).

Hand washing, isolation of infected patients and proper handling of bodily secretions are essential to prevent the spread of MRSA. The most common reservoirs for MRSA colonization are the nasal mucosa and oropharynx. Skin contamination from persons already colonized in these areas may also be a source for MRSA infection.

While colonization by MRSA does not require systemic treatment, active infection with MRSA is treated with vancomycin (Vancomycin) as the preferred antibiotic. Vancomycin is administered intravenously in a 1-gram dose every 12 hours to normal adults. Older adults may require dosage adjustment based on renal function. Other regimens include vancomycin plus gentamicin (Garamycin) or rifampin (Rifadin). Attempts to identify the original infected person (source case) should be made by swabbing the nasopharynx of patients and staff near to the outbreak and treating those found to have MRSA infection. Staff and patients who are MRSA carriers should be isolated, and some authorities recommend treatment with topical mupirocin (Bactroban), which is applied twice daily for two weeks to the nares or other areas of skin carriage (e.g., wounds) to reduce the shedding of MRSA. Colonization recurs in about one half of treated subjects (36).

Prevention of Infections: Vaccines

Influenza vaccine. It targets the strains of influenza A and B that are most likely to cause illness during a particular season and reduce the risk of influenza infection by 30 to 70

percent among elderly persons in home settings. Preventive therapy with influenza vaccination has been shown to be about 58 percent effective in reducing influenza infection and has resulted in a 39 to 69 percent decrease in mortality from all cases during the influenza season in older adults (37-39). The influenza vaccine is usually administered as an inactivated virus preparation given intramuscularly. The optimal time for vaccination is from October to mid-November; however, the vaccination can be given throughout the influenza season and during outbreaks. Recently a live attenuated virus preparation was developed that reduced the number of infections by 19 to 24 percent when given intranasally to healthy adult volunteers (40).

Pneumococcal vaccine. It decreases the risk of pneumococcal bacteremia by 75 percent in immuno-competent persons 65 years or older (37,36,41). In nursing home residents, the vaccine is 50 to 60 percent effective in preventing pneumococcal bacteremia and 80 percent effective in preventing death from pneumonia (40,41). Pneumococcal vaccine should be used in all aging adults $\geq$65 years old.

Prevention of Urinary Tract Infections. UTI are preventable by limiting the use of urinary catheters, and providing topical estrogen therapy for women and pharmacologic or surgical relief of prostatic hypertrophy for men. Physician awareness of these competent of preventive measures is important to the care of the older adult (42).

Conclusions

We have selected a group of potentially serious infections in the aging person. We have discussed the general presentation as well as the recommendations for management. The infections presented include influenza, bacterial pneumonia, urinary tract infections as well as recommendations on the management of vancomycin resistant enterococci and methicillin resistant *S. aureus*. We conclude reminding the reader the preventive measures available to decrease the risk of such infections, vaccines, prevention of urinary catheter overuse and most important, hand washing after examing each patient.

Influenza is preventable by a vaccine and if the patient escapes vaccination we have alternatives to treat the infection with rimantadine, amantadine, zanamivir or oseltamivir.

Bacterial pneumonia by *S. pneumoniae* is very serious with high mortality in the elderly, we have a good vaccine and every adult age 65 or older should be vaccinated. Since drug resistant *S. pneumonia* (DRSP) is a high as 50%, the initial empiric therapy must cover DRSjP and the alternatives are a new fluoroquinolone alone or a third or fourth generation cephalosporin (ceftriaxone, cefotaxime, cefepime) plus a new fluoroquinolone (gatifloxacin, levotoxacin, moxifloxacin) or a macrolide (azithromycin).

Urinary tract infections are common in the aging adult. Asymptomatic bacteriuria is not treated. Treatment is usually initially empiric, with a fluoroquinolone-like ciprofloxacin. In complicated UTI's the culture results dictates the therapeutic regime; we can also decrease the risk by using urinary catheters when indicated.

Resumen

Las infecciones en el paciente envejeciente son un reto, ya que los signos clásicos de infección están ausentes o pobremente definidos. El presente artículo describe la presentación, diagnóstico, manifestaciones clínicas y tratamiento para un grupo selecto de infecciones potencialmente serias incluyendo la influenza, pneumonia bacteriana, infecciones del tracto urinario y también las infecciones causadas por bacterias multiresistentes como enterococos resistentes a vancomicina y *S. aureus* resistente a meticilina. Concluimos con la necesidad de prevención en la persona mayor con el uso de vacunas, específicamente las vacunas de influenza y antipneumococcinca, y también la prevención de las infecciones del tracto urinario. La influenza es una causa significativa de morbilidad y mortalidad, cuyos efectos dañinos pueden prevenirse en muchas personas mayores con el uso de la vacuna. Se presenta el uso de agentes como amantadina, rimantadina, zinavivir, y osealtamivir como profilaxis y/o tratamiento. La pneumonía bacteriana es una de las causas mayores de mortalidad en los envejecientes. El surgimiento del Streptococcus pneumoniae resistente a medicamentos nos lleva a considerar las nuevas fluoroquinolonas o el uso de cefalosporinas de tercera o cuarta generación en estos casos. De importancia es el uso de la vacuna antipneumocóccica entre las personas de 60 años o más. La frecuencia de las infecciones del tracto urinario entre los envejecientes posiciona a esta condición entre los de primera importancia. El reconocer en el envejeciente bacteriuria asintómatica es importante y no requiere tratamiento. Cuando se diagnostica infección del tracto urinario la mayoría de los autores usan una fluoroquinolona como tratamiento empírico.

El surgimiento de bacterias multiresistentes como el *S. aureus* resistente a meticilina y/o enterococos resistentes a vancomicina nos llevan a la necesidad de considerar agentes como quinopristin-dalfopristin, linezolid y daptomycina en el manejo de estos pacientes.

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