TAKING STOCK OF INFECTIONS AND ANTIBIOTIC RESISTANCE IN THE ELDERLY AND LONG-TERM CARE FACILITIES: A SURVEY OF EXISTING AND UPCOMING CHALLENGES

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Treating elderly patients with infections represents one of the greatest challenges to health-care providers. Older adults are the largest growing sector of the population and suffer excessively from infectious diseases such as pneumonia, urinary tract infections (UTIs), and skin and soft-tissue infections. Often because of disabilities, the elderly require treatment of infectious diseases in long-term care facilities (LTCFs). As a result of antibiotic use, LTCFs have become “reservoirs of resistance” and multi-drug resistant (MDR) pathogens are frequently recovered. Clinicians also need to be aware of the impairment of immune function and other emerging chronic infections (HIV, HCV) that are now present in the elderly. Despite vigilance regarding this issue, delays in diagnosis and initiation of therapy are common. This article reviews the changing landscape of infections in the elderly and the challenge these syndromes present in the context of an increasing older population that requires dedicated resources.

Introduction:

Aging and infectious diseases

Our society is aging rapidly. By 2030, the population of adults > 65 years old will double in the United States (US) and the population older than 85 years old will likely triple [1, 2]. Globally, individuals aged 60 years or older currently constitute 10% of the world’s population. Moreover, this value is projected to increase to 22% in 2050 [3]. Because aging and functional limitations increase with each ensuing decade, more than 40% of the elderly will spend at least some time in a nursing home or long-term care facility, LTCF [4–8]. Nearly half of the 2.2 million people in the US who turned 65 years old in 1990 will enter an LTCF at least once before they die [2]. At the present time, our societies’ economic infrastructures are poorly prepared for this major change in demographics. We are soon to suffer an *aging tsunami*. With this in mind, our goal is to summarize the changing landscape of infectious disease syndromes in the elderly and highlight the new challenges infectious diseases and clinical microbiology will meet in 2011 and beyond.

An overview of infections in the elderly and LTCFs

Infectious diseases are one of the principal causes of morbidity and mortality in the elderly, especially those in

LTCFs. In LTCFs, the mean age of residents who suffer from an infectious disease syndrome is > 80 years and the risk of developing an infection is 32.7% [9]. In direct terms, 4–10 infections occur per 1000 patient days in an LTCF [10, 11]. This translates to about 1 infection/year (and 1 course of antibiotics). In addition, LTCFs provide a unique living situation; the pattern of socialization in LTCFs is distinctly different. Residents have meals in common, come into close physical contact, and often share living quarters.

Because LTCFs function by taking care of elderly patients who do not have the means to care for themselves and are a less costly alternative to hospitalization, infectious diseases clinicians are treating many serious infections in the LTCF. As a result of antibiotic use, LTCFs are recognized as sources of organisms resistant to multiple antibiotics (i.e. “reservoirs of resistance”) [12, 13]. Regrettably, excessive use of antibiotics has created serious threats to our therapeutic armamentarium. LTCFs are faced with methicillin-resistant *Staphylococcus aureus*, MRSA. Currently, colonization by MRSA has reached staggering proportions in LTCFs [13–18]. Furthermore, multidrug resistant (MDR) Gram-negative pathogens (especially *Escherichia coli*, *Klebsiella pneumoniae* and *Acinetobacter baumannii* harboring extended-spectrum beta-lactamases/cephalosporinases that confer resistance to cefotaxime, ceftazidime, ceftriaxone and carbapenemases (e.g. KPCs and OXA enzymes) that result in resistance to

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Fig. 1. The continued introduction of new drugs will foster the emergence of different mechanisms of resistance

imipenem, meropenem, ertapenem and doripenem) are frequently reported [19–21]. As more and broader spectrum antibiotics are used, the prevalence of *Clostridium difficile* is also increasing (Fig. 1) [12, 22–25].

Functional outcomes also change with age and underlying diseases. Many elderly suffer from diabetes, crippling osteoarthritis, terminal or untreatable cancer, cardiovascular and cerebro-vascular disease, and frailty. Moreover, dementia, instability of gait, falls, and swallowing disorders also increase with age. These conditions add to morbidity and higher mortality from infectious diseases [5, 26–29]. Lastly, there are specific communal challenges that occur in infections in the elderly. The process of socialization is different in an LTCF. As a result, if the proper infection control measures are not followed, infection spreads, often by MDR pathogens.

The changing spectrum infections in the elderly: The immunology of aging, HIV, HCV, RTIs, UTIs and ABSSTIs

Infections to which the elderly patients were particularly vulnerable are respiratory tract infections (RTIs, e.g., bronchitis, bacterial pneumonia, and influenza), UTIs, intra-abdominal infections (particularly *C. difficile*), and acute bacterial skin and soft tissue infections (ABSSTI). Now, the infectious diseases physician must also consider chronic viral infections such as human immunodeficiency virus (HIV), hepatitis C virus (HCV) and varicella zoster virus (VZV). The syndromes of infection in the elderly

are changing and older adult individuals are the largest group of “immuno-compromised” patients that physicians now treat.

Immunology of aging

Despite significant strides, the immunology of aging is still poorly understood [3]. Little is really known about immunosenescence or how specific T-cell subsets respond to antigenic challenges with age [30–33]. As an example, it is recognized that there are impairments of adaptive and innate immunity (T and B lymphocytes), but this is yet to be precisely defined in the elderly. Moreover, cellular immune responses and antibody production are impaired. It is not known why there is reduced surface expression or function of toll-like receptor (TLR1/2); diminished TLR1/2 activity relates to increased risk of disease due to specific pathogens (e.g. *Listeria*, *Mycobacterium tuberculosis* and reactivation of VZV).

HIV is an emerging consideration in the elderly

According to the CDC (<http://www.cdc.gov/hiv/topics/surveillance/basic.htm#aidsage>), the number of persons aged 50 years and older living with HIV/AIDS is increasing. By 2015, more than one-half of all HIV-infected individuals in the US will be > 50 years old. Recent data in the US reveal that persons aged 50 and older accounted for 15% of new HIV/AIDS diagnoses, 24% of persons living with HIV/AIDS (increased from 17% in 2001), 19% of all AIDS di-

agnoses, 29% of persons living with AIDS, and 35% of all deaths of persons with AIDS. The rates of HIV/AIDS among persons 50 and older were 12 times as high among blacks (51.7/100,000) and 5 times as high among Hispanics (21.4/100,000) compared with whites (4.2/100,000). Currently, there are more than 60,000 HIV+ people who are above 50 years of age in the US (<http://www.cdc.gov/hiv/topics/surveillance/basic.htm#aidsage>). In addition, the number of people > 65 years old with HIV has grown 10-fold in the last 10 years. In the last decade, the number of new AIDS cases rose twice as fast in persons > 50 than in persons < 50.

What is responsible for the change in demographics of HIV infection in the elderly? The life expectancy of HIV-infected persons receiving highly active antiretroviral therapy (HAART) is now extended and approaches that of the general population. In addition, an ever-increasing number of individuals aged ≥ 50 years with HIV infection is expected in the coming years, as a result of both increased survival of patients with treated disease and delayed recognition of individuals with occult HIV disease.

Age also influences the course of HIV infection. In a study performed by Viard et al., the influence of age on the CD4 cell response to highly active antiretroviral therapy (HAART) was examined in 1956 patients in the EuroSIDA study [34]. The investigators found a profound impact of age on CD4 cell count and concluded that younger age may favor CD4 cell restoration because of preserved thymic function. In addition, the CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe) and other related studies showed that older individuals (45–64 years old) had lower 10-year survival whether pre-HAART or during HAART therapy [35–38]. The limited data available about combined antiretroviral therapy in the older adult seem to show an overlapping virological success rate, but a slower and blunted immune recovery compared with younger patients. In addition, the best way to deliver antiretroviral therapy and reconstitute the immune system in this older adult HIV population is still unclear. An emerging area of interest is the impact of disease- and therapy-related complications.

The areas discussed above (HIV and immunosenescence) reveal a fundamental question in immunology: *what are the immunologic defects that occur with age?* [39–48] These questions approach the problem of frailty, both in the non-HIV and the HIV-infected patients [49, 50]. A major challenge is to examine these immunological parameters as they will relate to clinical outcomes in the older adult. We expect that HIV as a comorbidity will add to the use of antibiotics in LTCFs as these patients will experience even more frequent episodes of infections with MDR pathogens.

HCV in the elderly

The burden of chronic HCV infection in older adult persons is also expected to increase significantly (<http://www.cdc.gov/hepatitis/Statistics.htm#section1>). In addition, chronic HCV infection may be more severe in the older adult than in younger adults [51, 52]. Most of the older adults with chronic HCV infection have acquired the disease earlier in life. These patients often present with complications of liver disease, mainly cirrhosis and hepatocellular carcinoma (HCC). It is estimated that, each year, HCC will develop in 1–2% of patients with chronic HCV infection and cirrhosis. The risk of HCC increases significantly with age, probably owing to age-related changes in the ability to repair DNA and to the prolonged interval from the time of infection (<http://www.cdc.gov/hepatitis/Statistics.htm#section1>). The interval between infection and diagnosis of HCC may be shorter when the infection is acquired at an older age.

The CDC estimates that approximately 4.1 million (1.6%) Americans are infected with HCV (<http://www.cdc.gov/hepatitis/Statistics.htm#section1>). Of those infected, 75 to 85% will have complications, and in up to 20% of those people, these infections may progress to cirrhosis or HCC. One percent to 5% of those chronically infected may die of their disease. HCV infection is most prevalent among those born during 1945–1965, the majority of whom were likely infected during the 1970s and 1980s when rates were

Table 1. Summarizes the unique challenges of taking care of older adult veterans with HIV

Age-related decline in immune function	Comorbidities
Increasing numbers of medications	Diabetes (endocrine insulin resistance)
Drug interactions	Hypertension
Adverse events	Cardiovascular diseases and lipid abnormalities; risk of myocardial infarction
Lower adherence	Cerebrovascular and neurological disorders (depression and dementia)
	Renal dysfunction
	Hepatic dysfunction; coinfection with HCV
	Psychiatric disorders
	Osteoporosis

highest (because of intravenous drug use). The clinical and economic impact of HCV in the older adult is also poorly studied and the influence of co-infection with HIV is uncertain. As in the case with HIV, the effects this illness will have on the incidence of bacterial infections are expected to be significant.

Varicella zoster virus, VZV

“Shingles” is caused by reactivation of latent VZV. The incidence and severity of shingles and postherpetic neuralgia (PHN) increase with age in association with a progressive decline in cell-mediated immunity to VZV. The triggers for reactivation of VZV are poorly understood, and protection may involve external boosting, internal boosting, or other mechanisms [53–57].

Risk factors associated with VZV include increasing age and impaired cell-mediated immunity. The lifetime risk for HZ has been estimated to range from 10% to 20% in the general population [53]. More than 66% of all VZV cases occur in people who are 50 years of age and older according to epidemiologic studies conducted in the US [55]. Furthermore, it is estimated that nearly one-half of individuals reaching 85 years of age will have an episode of HZ.

VZV vaccines (Oka/Merck varicella-zoster virus, VZV, Zostavax[®] vaccine) can elicit significant antibody titers and increase in cell-mediated immunity to VZV in immunocompetent older adults. In a landmark paper, the authors showed that the zoster vaccine (0.5 ml of the investigational live attenuated Oka/Merck VZV vaccine) markedly reduced morbidity from herpes zoster and PHN among older adults [58]. In this clinical trial involving thousands of adults 60 years old or older, the VZV vaccine prevented shingles in about half (51%) of the people and PHN in 67% of the study participants. While the vaccine was most effective in people 60–69 years old, it also provided some protection for older groups. Surprisingly, compliance with this vaccine among the elderly is poor. Since the pain and discomfort of VZV and PHN are substantial, one would anticipate that more patients would be vaccinated [54, 58].

RTIs (influenza, RSV), UTIs and ABSSTI in the elderly

Among the most fatal infectious diseases syndromes in the elderly are RTIs. Community-acquired pneumonia (CAP) by *Streptococcus pneumoniae* was one of the most important diagnostic considerations in the past. Now the incidence of *S. pneumonia* is decreasing as other pathogens need to be considered (e.g. *Legionella*, *Chlamydia*, *Mycoplasma*, *Hemophilus*, and *Moraxella*, etc.). Elderly patients also suffer from nursing-home- or hospital-acquired pneumonia (NHAP, HAP), and they are at risk for aspira-

tion as well. In these latter three syndromes, Gram-negative pathogens need to be included in the decision to use empiric therapy. In HAP, the geriatrician must consider Gram-negative pathogens such as *Pseudomonas aeruginosa* and drug-resistant *S. aureus* as causative agents. The inclusion of *P. aeruginosa* and *S. aureus* (especially methicillin resistant, MRSA) greatly expands the number, type, and complexity of antibiotics that must be given to the elderly.

More challenging than determining the etiology is how to treat these infections. Many clinicians treat RTIs in LTCFs with antibiotics often used in community-acquired infections. However, the evidence for traditionally recommended 7- to 14-day duration of antibacterial therapy for CAP is not well established in the elderly. Recently, a group in Europe assessed the effectiveness and safety of ≤ 7 days versus ≥ 10 days of therapy for CAP with the same antibacterial regimens, in the same daily dosages [59, 60]. Five randomized control trials (RCTs) involving adults (including outpatients and inpatients that did not require intensive care) and two RCTs were also included in this analysis. Interestingly, differences were not found between short- and long-course regimens. A systematic review of RCTs comparing short-course and extended-course antibiotic regimens for CAP was performed at the San Francisco VA by Li et al. [3]. This group found that adults with mild to moderate CAP can be safely and effectively treated with an antibiotic regimen of 7 days or less. The authors concluded that reduction in antibiotic use may limit the increasing rates of antibiotic resistance, decrease cost, and improve patient adherence and tolerability.

Residents of LTCFs will experience episodes of influenza, RSV, or other respiratory viral illness. Influenza is particularly worrisome as the risk of a poor outcome correlates with advanced age and ability to respond to vaccine. Influenza continues to cause mortality and serious morbidity in elderly persons (persons ≥ 65 years of age [30, 61–66]. Currently available influenza vaccines are most effective only against infecting strains of virus that have matching hemagglutinins (HA) to the vaccine strains of similar antigenic characteristics. When the infecting virus has had minor changes in the HA (antigenic drift), the vaccine may provide partial protection. A major change in the viral HA (antigen shift) results in lack of vaccine protection.

Elderly persons have markedly diminished abilities to produce antibody in sufficient quantity after the administration of bacterial and viral vaccines [67, 68]. Despite significant controversy as to the effectiveness of the influenza vaccine, there is general consensus that elderly patients are to be immunized with the flu vaccine to avoid respiratory complications and post-influenza bacterial pneumonia [69–72]. Now, clinicians also need to be aware of the novel H1N1 variant of influenza. Current clinical experience dictates that novel H1N1 is not as much of a threat to elderly patients as seasonal H1N1. However, the number of patients exposed so far has been limited and conclu-

sions as to virulence in the elderly need to be tempered by more data.

While all infections pose unique and often lethal risks for older adults, perhaps none is more treatable than those associated with the use of bladder catheters (catheter-associated urinary tract infections or CAUTIs). Each year, over 5 million adults in hospitals and nursing homes in the US have urinary catheters inserted. In fact, catheter-associated urinary tract infections (CAUTIs) remain the most common cause of nosocomial infections in hospitals, amounting to about 40% of all infections. Unfortunately, clear indications for the use of catheters remain poorly defined and appear to be at least in part a treatment of “convenience”. Many of the urinary tract infections (UTIs) that are caused in the elderly are associated with the use of catheters.

ABSSTIs are extraordinarily important in the elderly. A special category of ABSSTIs that is often ignored is the infection in patients undergoing vascular surgery. These ABSSTIs include infections of the site of surgery, prosthetic grafts, vascular ulcers and diabetic foot infections. Each of these infections represents a serious health concern, particularly among individuals with comorbid conditions who are at an increased risk of morbidity and mortality. Surgical-site infections in the elderly occur primarily as a result of contamination by skin organisms during surgery, whereas prosthetic-graft infections result typically from a progressive wound infection. Vascular infections, like those elsewhere in the body, reflect an imbalance between the host and bacteria. Efforts to limit or prevent the likelihood of patients developing these infections center on reducing the bacterial “load” by means of antibiotic prophylaxis and decolonization. One of the most concerning and problematic pathogenic bacteria encountered in vascular surgical patients is MRSA. Strains of MRSA can cause significant surgical-site infections and may require the use of vancomycin, daptomycin, or linezolid for treatment. Local resistance patterns and surveillance efforts are essential to ensure appropriate empiric antibiotic selection for prophylaxis or treatment.

LTCFs as “reservoirs of resistance”: Impact of resistant infections

LTCFs serve as reservoirs of resistance and the impact of resistant pathogens in these centers is greatly feared. Since 1975 there have been many reports of antibiotic resistance that has been detected in LTCFs.

As stated above, the most problematic pathogens here are MRSA, penicillin-resistant pneumococcal infections, mupirocin-resistant *S. aureus*, trimethoprim sulfa-resistant, Gram-negative rods, and aminoglycoside-resistant enterococci and Gram-negative rods [1, 2, 9, 12, 15, 20, 21, 29]. In studies looking at LTCFs, quinolone resistance in *P. aeruginosa* often complicates treatment as does amoxicillin clavulanic-acid-resistant *E. coli*. Cefazidime-resistant *E. coli* and *Klebsiella* are also seen. Among those that are cefazidime resistant are extended-spectrum β -lactamases of

the TEM-12, TEM-26, SHV varieties [73–75]. In addition, it has also become common now to recover Gram-negative bacteria that have plasmid-borne AmpC β -lactamases. Many of these non-TEM or non-SHV extended β -lactamases are responsible for the phenotypic emergence of resistance to advanced generation cephalosporins (i.e., ceftazidime and cefepime). There are also many resistant Gram-positive infections in long-term care (i.e. MRSA). The rates of colonization of infections range from 20–55%.

MRSA has proven to be particularly challenging. Rates of colonization and infection range from 25% to 50%, and 3% of residents colonized get infected. Colonization by MRSA is often a hallmark of significant short-term disability. In a study by Niclaes et al., the relative risk of dying within 6 months was greater for MRSA carriers than that for non-carriers [76].

Nearly a decade ago, a study was done in Cleveland examining cefotaxime-resistant bacteria colonizing older people admitted to an acute care hospital. Of the 190 surveillance cultures obtained from 143 patients, 26 cefotaxime-resistant Gram-negative isolates from 22 patients were recovered. The prevalence rate of cefotaxime-resistant isolates on admission was 13.3% (19/143). A logistic regression model using cefotaxime colonization as the dependent variable found that multiple comorbidities, admission to a surgical service, diagnosis of infection on presentation, and transfusion history were factors associated with the presence of colonization. These four clinical items accurately classified 74% of patients colonized. Surprisingly, antibiotic use and LTCF residence were not associated with the presence of colonization by cefotaxime-resistant organisms. These data raise awareness that there are community- and LTCF-dwelling older patients colonized with Gram-negative enteric bacilli resistant to third-generation cephalosporins on admission to the hospital. The “reservoir of resistant bacteria” in older people is no longer confined to LTCFs [12].

Studies have also shown that there is spread of *E. coli* with high levels of cefotaxime resistance between community, LTCF and hospital institutions [77]. In this prospective surveillance study, 151 *E. coli* isolates resistant to cefazidime and cefotaxime were examined from three hospitals, eight LTCFs, and a day care center. Co-resistance to ciprofloxacin, gentamicin, tobramycin, cefepime, amoxicillin/clavulanate and tmp/smx was found. The background of these isolates contained CTX-M-15, -14, -32, linked to *ISEcp1* and *IS26* elements. Other clusters of mobile resistance genes (*tetA*, *aac6'1b*, *dfrA*, *sul*, *aac3IIb*) were also detected. The greatest cluster of resistant isolates was from UTIs in elderly adults.

Why are we faced with this problem?

Owing to advances in the care of the elderly, the transfer of patients through the medical system and from tertiary and quaternary care institutions occurs very frequently. Unfor-

tunately, lapses in infection control occur frequently. Poor infection control and the excess use of broad-spectrum antibiotics that select for resistant strains are common. Risk factors associated with recovery of resistant strains (percutaneous endoscopic gastrostomy feeding tubes, pressure ulcers, malnutrition, immunosuppression [age- and medication-related], prior antibiotic use) are also more prevalent. Moreover, there is a cycle of institutionalization and hospitalization that seems insurmountable. This leaves the clinician with many unresolved questions. What is the frequency of cross transmission in the elderly in LTCFs? Is there evolution from previously susceptible organisms? If cross-transmission, what are the best methods to limit horizontal spread? Should we invest in targeted or generalized surveillance? Can we or should we identify unrecognized reservoirs? From an analysis of these data, it is this author's opinion that antibiotic resistance in LTCFs approaches prevalence rates comparable to those in intensive care units. Therefore, the clinical and economic impact of infections due to MRSA and MDR GNRs is substantial and will present one of the greatest challenges to the institutionalized elderly. Our agenda for research in this important area needs to be defined.

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