Staphylococcus aureus Infections and Antibiotic Resistance in Older Adults

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The prevalence of infection with Staphylococcus aureus among older adults is unknown, but clinical syndromes caused by this organism are common. Bacteremia, pneumonia, endocarditis, and bone and joint infections are encountered with relative frequency in this population, and the clinical presentation may be atypical. Underlying disease and functional debility, rather than age itself, predispose the older adult to staphylococcal carriage and infection. Infections with methicillin-resistant strains of S. aureus are acquired primarily in hospital, rather than in nursing homes or in the community. Lack of clinical suspicion for S. aureus infection and delays in appropriate therapy can be fatal. Staphylococcal infection should be considered for an older adult with risk factors for staphylococcal carriage, comorbid illness, debility, and history of recent hospitalization or nursing home stay. Choices regarding empirical therapy should be made on the basis of knowledge of local antibiotic susceptibility patterns.

Assessing the risk and impact of Staphylococcus aureus among older adults is no simple task. Elderly individuals are a heterogeneous population. There is great diversity in the burdens of comorbid illnesses, requirements for health care (which range from assistance with the basic activities of daily living to the need for skilled care provided by a nurse), and other risk factors for infection among persons who are ≥65 years old. S. aureus infection is not a reportable disease; thus, the overall prevalence among older adults is not known. However, S. aureus infections are common causes of bacteremia, endocarditis, pneumonia, septic arthritis, and vertebral osteomyelitis in the elderly population.

There has been great interest in the problem of antibiotic-resistant S. aureus, particularly among debilitated older adults. Here, the overall impact of S. aureus infections and the significance of resistance to antistaphylococcal β-lactam antibiotics in elderly persons will be reviewed. Newer issues, such as the emergence of resistance in community-acquired staphylococcal strains and the problem of vancomycin resistance, will be discussed briefly.

OVERALL IMPACT AND PREVALENCE OF S. AUREUS INFECTION AMONG OLDER ADULTS

In the United States, rates of hospitalization for infectious diseases have increased primarily in the elderly population, and more than half of all nosocomial infections occur in persons who are ≥65 years old [1, 2]. Despite advances in medical care, deaths caused by infectious diseases have also increased in older adults during the past 2 decades [3, 4]. Elderly individuals are more likely not only to be hospitalized with an infectious disease, but also to die of it.

S. aureus is the fourth-most-common hospital-acquired pathogen among older adults, following Escherichia coli, Pseudomonas aeruginosa, and enterococci, and it accounts for 9% of all nosocomial infections [2]. In addition, it is the second-most-common cause of surgical site infection, accounting for 14% of the cases of this type of infection [2]. In long-term care facilities, rates of infection are similar to those seen in hospitals [5], but the overall rate of S. aureus infection is unknown. Much information about the epidemiology of S. aureus infection among nonhospitalized elderly persons is derived.
from reports of specific clinical syndromes or from reports of outbreaks of infection with antibiotic-resistant strains [6].

**CLINICAL SYNDROMES DUE TO S. AUREUS IN OLDER ADULTS**

**Bacteremia.** Bloodstream infection is one of the top 10 causes of death in persons aged ≥65 years in the United States [3]. Attributable mortality rates associated with *S. aureus* bacteremia are reported to be several-fold higher in older adults than they are in young adults [7]. In nursing home and community settings, the mortality rate for *S. aureus* bacteremia has been reported to be >60% [8, 9]. Increasing mortality rates in older adults have been associated with increased use of such devices as prosthetic heart valves or pacemakers, with diabetes mellitus, and with a respiratory source of infection [7–10].

Increased mortality rates for *S. aureus* infection may be the result of a lack of clinical suspicion in this population. Older adults with *S. aureus* bacteremia are 25% as likely as young adults to present with fever [7]. Lack of obvious symptoms of infection could delay diagnosis and initiation of treatment and lead to increased mortality rates [7]. In older adults with community-acquired bacteremia, presentation with atypical symptoms (most commonly confusion or hypotension) has been associated with delayed treatment and poor outcome [9].

*S. aureus* bacteremia is primarily encountered in elderly hospitalized patients. In hospitals in the 1980s, *S. aureus* was the second-most-common nosocomial bloodstream pathogen in the elderly population, accounting for 18% of infections [2]. In a more recent series, staphylococcal species were the second-most-common pathogen (after *E. coli*) reported among older patients hospitalized with bacteremia that was acquired in the community or hospital [3].

In nursing home and community settings, bloodstream infections occur less often than they do in hospitals. In nursing homes, bacteremia most frequently has a urinary source, and gram-negative bacilli predominate. However, when bacteremia does occur in residents of long-term care facilities, *S. aureus* has been reported as the single most common organism [9]. In the nursing home setting, *S. aureus* is the first- or second-most-common cause of bacteremic pneumonia and the most common pathogen associated with skin- and soft-tissue–associated bloodstream infection [9]. In the community, *S. aureus* lags behind *E. coli*, *Klebsiella* species, and *Streptococcus pneumoniae* as a cause of bacteremia [10, 11].

**Respiratory tract infection.** *S. aureus* pneumonia has a notoriously poor prognosis, especially for elderly individuals. *S. aureus* pneumonia is classically found in older adults with underlying diseases, and with chronic pulmonary conditions in particular [12, 13]. Multilobar involvement, primarily of the lower lobes, with complications, such as abscess formation and empyema, are common [13].

Fortunately, staphylococcal pneumonia in the elderly populations occurs primarily in the hospital setting. After *P. aeruginosa*, *S. aureus* is the second-most-common cause of nosocomial pneumonia in older adults, accounting for 15% of the cases of infection [2]. Studies specifically devoted to *S. aureus* pneumonia report that most episodes are found in hospitalized elderly patients with significant comorbid illness [13, 14].

In long-term care facilities, the exact prevalence of *S. aureus* pneumonia is less clear. *S. aureus* accounts for a mean rate approaching 9% of cases of pneumonia in this setting, but the range is wide—from 0% to 33% [15]. Diagnosis of any pneumonia in this population is complicated by diminished fever, lack of cough, and complaint of shortness of breath [15]. Presence of tachypnea (>25 breaths/min) may be one of the earliest diagnostic indicators of pneumonia in this setting [16]. Changes in the findings of lung examinations can be misleading in residents with chronic cardiopulmonary disease. Before the initiation of empirical therapy, cultures of sputum and blood samples are not frequently performed and chest radiographs are not frequently obtained. If the results of culture are positive, the significance of *S. aureus* in sputum samples may be in doubt, because oropharyngeal colonization can be common in this population.

Attack rates of influenza vary from year to year and can influence rates of postinfluenza bacterial pneumonia in nursing homes and in the community. After *S. pneumoniae*, *S. aureus* is a common cause of postinfluenza bacterial pneumonia. It has been suggested that *S. aureus* rarely causes community-acquired pneumonia in healthy adults who live independently, except after they have influenza [13]. Thus, outside of the hospital setting, the diagnosis of *S. aureus* pneumonia should at least be considered in seriously ill nursing home residents and, during influenza season, in the healthy older adult.

**Endocarditis.** Several studies have found that *S. aureus* is the most common cause of cases of endocarditis in persons who are ≥65 years old [17, 18]. *S. aureus* endocarditis is an increasingly recognized complication of hospitalization, intravascular device use, and nosocomial bacteremia [19]. Twenty-five percent of patients with nosocomially acquired *S. aureus* bacteremia have echocardiographic evidence of endocarditis, and those patients tend to be older and without predisposing valvular disease [20].

In the older adult, endocarditis may present atypically. Presenting symptoms may be vague; classic findings, such as Janeway lesions, Osler’s nodes, and splenomegaly, are not commonly noted; murmurs, if present on admission, are often attributed to conditions common in older age [17–20]. In addition, reduced frequency of fever and leukocytosis seen in a significant proportion of older patients with endocarditis can
reduce clinical suspicion and delay diagnosis [19, 20]. Older adults have a higher mortality rate than do younger patients, perhaps because of lack of early recognition and treatment [19].

**Soft-tissue and osteoarticular infections.** Age-related changes in skin and increased prevalence of peripheral vascular disease, diabetes mellitus, and conditions that lead to diminished mobility are associated with risk of skin infection in the older adult. Thinning skin, reduced elasticity, neuropathy, decreased blood flow, and pressure contribute to breaks in skin and ulcer formation. Complications of *S. aureus* infection, such as folliculitis, carbuncles, cellulitis, and secondary wound infection, are common [21, 22]. Contiguous spread of cutaneous staphylococcal infection to adjacent bony structures can lead to the development of osteomyelitis and septic arthritis.

*S. aureus* is the most common pathogenic cause of native bone and joint infection in older adults. Increased rates of *S. aureus* vertebral osteomyelitis have been noted in persons who are ≥50 years old. These increased rates parallel increased frequency of degenerative joint disease. An obvious source of bacteremia is implicated in <50% of cases [23, 24].

In older adults, an increased frequency of osteoarthritis and rheumatoid arthritis is associated with increasing rates of septic arthritis [25]. Most cases of septic arthritis in this population are due to hematogenous seeding of an abnormal joint rather than contiguous spread. Many older patients with *S. aureus* septic arthritis do not present with fever or leukocytosis. An elevated erythrocyte sedimentation rate in an older patient may be the most reliable clue that joint pain is due to a serious and treatable infection. Complications in older patients include death caused by sepsis in ~20% of patients and development of osteomyelitis in ~40% [25].

Increased use of devices and need for surgical intervention also contribute to *S. aureus* prosthetic joint infection in the elderly population. In some studies, *S. aureus* is the second-most-common cause of prosthetic joint infections in older adults, accounting for almost one-third of episodes [26]. *S. aureus* infections are distributed equally between early and late postoperative infections.

**Urinary tract infections.** Bacteriuria with *S. aureus* is uncommon; it accounts for <2% of urinary tract infections. It is reported primarily in hospitalized older adults after they undergo surgery, catheterization, or other invasive procedures. In the community, malignancy and other causes of obstructive uropathy are associated with *S. aureus* bacteriuria. Many older patients have significant pyuria but are afebrile and asymptomatic. Bacteremia from a urinary source develops in <5% of patients with *S. aureus* bacteriuria [27]. *S. aureus* bacteriuria more often occurs as a consequence of bacteremia or endocarditis. In the older patient who is symptomatic or who has an unexplained change in clinical status, these diagnoses should be ruled out, because treatment of isolated *S. aureus* bacteriuria with oral antibiotics would be inappropriate and ineffective for bloodstream infection.

### WHY OLDER ADULTS ARE AT INCREASED RISK OF *S. AUREUS* INFECTION

**Age and the host response.** Increased rates of *S. aureus* infections among older adults cannot be attributed to a specific acquired defect in host immune responses seen with increasing age. In fact, the inflammatory response in the aged host to *S. aureus* can be normal or even accelerated compared with that in the young host [28].

**Age and the carrier state.** Antecedent *S. aureus* carriage is a significant risk factor for the development of subsequent infection with the colonizing strain [29]. Approximately 30% of the general population is asymptptomatically colonized with this potential pathogen. Persistently and heavily colonized carriers appear to be at greatest risk of developing infection with *S. aureus* [30, 31]. Increased frequency of colonization does not explain increased rates of infection in older adults—in fact, older adults are less likely to carry *S. aureus* than are children and young adults [32].

**Age, underlying illnesses, and debility.** Rates of *S. aureus* carriage and infection increase with conditions associated with disruption of cutaneous or mucosal barriers, such as those that occur in association with wounds, dermatologic conditions, the use of needles and percutaneous devices, and surgical procedures [33]. Illnesses that require the long-term use of needles, including diabetes mellitus and chronic dialysis, are associated with increased rates of *S. aureus* colonization and infection risk. Diabetes and its complications increase with increasing age and may contribute to the prevalence of *S. aureus* infection in the elderly population [34]. Among older adults with *S. aureus* bacteremia, diabetes has been reported among 25% of hospital patients, 18% of residents of long-term care facilities, and 30% of community-dwelling elderly persons [3, 9, 10]. However, in another study, which involved patients who were ≥75 years old and who had been admitted to an intensive care unit, diabetes mellitus was not a significant risk factor for *S. aureus* pneumonia [35]. Functional status also plays role in the development of *S. aureus* colonization and infection. In older adults, staphylococcal pneumonia occurs most often in debilitated patients who depend on others for their care [35]. Increased length of stay in hospitals and nursing homes has been associated with increased risk of *S. aureus* infection, and with infection with multidrug-resistant strains in particular.

Thus, there is little evidence that aging alone leads to increased risk of infection with *S. aureus*. The acquisition of *S. aureus* colonization and infection is a complicated interplay of multiple factors, including exposure to pathogenic strains, se-
verity of underlying illness, comorbid conditions, and functional dependence.

**ANTIBIOTIC-RESISTANT S. AUREUS IN OLDER ADULTS**

*Methicillin-resistant S. aureus (MRSA) and mortality.* Infection with MRSA can lead to significant morbidity and mortality. In the elderly population, attributable mortality caused by MRSA bloodstream infection may be 3 times greater than that caused by methicillin-susceptible *S. aureus* (MSSA) bacteremia [7]. The effect of age on outcome from nosocomial pneumonia due to MRSA has not been compared directly with that of pneumonia due to MSSA. However, patients with MRSA seem to be older and to have more chronic illnesses, and they often have a history of recent hospitalization. These factors likely account for higher mortality rates [36].

**MRSA in the acute-care setting.** Several prospective surveillance studies in hospitals in the United States and Europe have specifically focused on MRSA. The prevalence varies widely with geographic area, but several series have noted that ∼24%–29% of bloodstream isolates from Europe and the United States are resistant to methicillin [37–39]. Risk of acquisition of MRSA infection increases with acuity of illness. In surveys of multiple hospitals, the proportion of MRSA among *S. aureus* isolates was greater in the long-term care hospital (33%) than it was in the outpatient setting (14%) [40]. Among inpatients, MRSA has been detected most often in patients with burn wounds [40–42]. The prevalence of MRSA infections among elderly hospitalized patients is unknown; however, most patients with nosocomially acquired MRSA are older and more debilitated and most have more-severe underlying disease [36, 43, 44].

**MRSA and the long-term care setting.** Once older nursing home residents are discharged from the hospital setting, reports of documented MRSA infection are relatively uncommon. However, MRSA colonization is common; it affects 8%–46% of residents. Nursing home residents who are dependent on others for their care or who have wounds are more likely to be colonized with MRSA than are functionally independent residents. Limited studies suggest that most nursing home residents acquire their MRSA carriage in hospital rather than in the nursing home. High colonization rates in nursing homes probably reflect chronic carriage, which can persist for months to years. Thus, high rates of MRSA carriage in nursing homes likely reflect a large reservoir of persons who acquired their organism most often in hospital and remain persistently colonized for long periods of time. Increased mortality rates among MRSA-colonized residents likely reflect their poor functional status and burden of comorbid illnesses rather than death that results from MRSA [6].

Do high colonization rates translate into frequent infections in this setting? Risk factors for MRSA infection differ from risk factors for colonization. Nursing home residents with peripheral vascular occlusive disease and diabetes mellitus are more likely to acquire infection than are residents without these comorbid illnesses [45].

Most MRSA infections have been reported in the midst of an outbreak. A few prospective longitudinal studies have reported endemic rates of MRSA infection of 3%–4%. In 5 nursing homes in which colonization was common, cumulative experience of >10 years and >10,000 admissions yielded <100 MRSA infections [6]. Mortality rates associated with these infections were low. Intravenous therapy was rarely necessary, and hospital transfers did not occur frequently. When infections have been reported, skin and soft-tissue infections were most common. Thus, despite having a reservoir of MRSA carriers residing in nursing homes, reports of infection in these facilities are relatively uncommon when compared with the experience in acute-care hospitals [6].

**MRSA and the community setting.** The frequency of MRSA infection in the community is even less well characterized. Most patients with MRSA are detected when they are readmitted to the hospital. Most of these patients have had recent stays in hospitals or nursing homes [46, 47]. Colonization with multiderug-resistant strains acquired in hospital is most likely prolonged and persistent [48].

There has been recent concern that methicillin-resistant strains have arisen in the community independent of hospital strains. These community-derived strains do not represent dissemination of a single clone, are not related genetically to hospital strains, and are often susceptible to classes of antibiotics other than the β-lactams. Most infections with these unique community strains have occurred in healthy children [46].

**Glycopeptide-resistant S. aureus.** *S. aureus* strains with reduced susceptibility to glycopeptide antibiotics remain uncommon and have generally been isolated only from chronically ill patients who have required treatment with vancomycin or similar agents for prolonged periods of time. Recent reports from France detected intermediate susceptibility to vancomycin in 15 isolates of MRSA. Ten of these isolates were detected in nursing home residents. One isolate was associated with a urinary tract infection, and 3 were obtained from tracheal aspirate specimens. None of the patients had received a glycopeptide antibiotic, and the 2 strains detected were not related to other MRSA strains from the hospital [49].

**WHEN TO BEGIN TREATMENT FOR S. AUREUS INFECTION IN THE OLDER ADULT**

The decision to treat an older adult empirically for *S. aureus* infection should be made on the basis of several factors. The
clinical syndrome to be treated, severity of illness, presence of predisposing comorbid illnesses, place of residence, and history of recent procedure or stay in hospital or nursing home should influence one’s decision whether to begin therapy for *S. aureus* infection.

Any older patient who has been hospitalized after a recent surgical procedure, device insertion, or hospitalization may be at risk of nosocomially acquired *S. aureus* bloodstream infection. If the patient does not have a urinary tract infection or alternative diagnosis, initiation of iv therapy with an antistaphylococcal antibiotic should be considered, and blood samples should be obtained for culture. Given the high morbidity rates associated with *S. aureus* bloodstream infection, a bactericidal antibiotic would be preferred; an antistaphylococcal β-lactam antibiotic or vancomycin should be chosen, depending on the prevalence of MRSA. If culture of a blood sample yields positive results, a source of infection should be carefully sought. Trans-thoracic echocardiography should be performed for all patients with *S. aureus* bacteremia, regardless of whether they have a murmur or stigmata of endocarditis. Further evaluation with transesophageal electrocardiography may be necessary to evaluate the possibility of infective endocarditis. The spine should be carefully assessed for point tenderness, and radiological evidence of vertebral osteomyelitis should be sought. Large joints should be examined for decreased range of motion, pain, swelling, warmth, and erythema. Imaging studies, such as CT, may be necessary to exclude abscesses of the spleen, kidneys, or other soft tissue that may require surgical drainage.

Any older patient who requires hospitalization for bone and joint or soft-tissue infection should be treated with an iv antistaphylococcal antibiotic, regardless of the patient’s place of residence or risk factors. Appropriate cultures of blood, joint fluid, and deep-tissue samples may guide further changes in antimicrobial therapy. If the patient resides in a geographic area in which MRSA is common, and if the patient has recently had a procedure or contact with the health care system, vancomycin would be the most appropriate empirical antibiotic choice, and not a β-lactam antibiotic. For the vancomycin-intolerant patient, antibiotic choices should be made on the basis of antimicrobial susceptibilities and the severity of the infection. MRSA and MSSA are susceptible to quinupristin-dalfopristin and linezolid. Increased resistance to trimethoprim-sulfamethoxazole, ciprofloxacin, and doxycycline, as well as variable efficacy, have led to reduced enthusiasm for use of these drugs in this clinical setting.

For less-severe soft-tissue or bone infections that do not require hospitalization, oral treatment is a reasonable treatment choice. The initial antibiotic choice, once again, should be made on the basis of place of residence or exposure to the health care system. For MRSA infections in patients who are allergic to β-lactams, treatment with trimethoprim-sulfamethoxazole or doxycycline based on antimicrobial susceptibilities is appropriate. Performance of biopsy of deep tissue specimens or, in the case of chronic osteomyelitis, tract cultures can be useful to verify the etiology of infection and to ensure that the antibiotic choice is appropriate.

For the older patient who requires hospitalization for pneumonia, *S. aureus* is less common than are other bacterial etiologic agents, and decisions regarding when to treat these patients are more difficult to make. However, mortality rates are high even when the diagnosis is suspected and therapy is given promptly. *S. aureus* pneumonia is not common in healthy community-dwelling older adults. However, if an older adult requires hospital admission for pneumonia after an influenza-like illness, *S. aureus* should be more strongly considered. Ceftriaxone plus a macrolide or quinolone for empirical coverage of community-acquired pneumonia would initially cover MSSA strains. However, once cultures of sputum and blood samples confirm the diagnosis of MSSA pneumonia, nafcillin would be most the most appropriate antimicrobial agent.

In hospitalized or nursing home patients, the risk of *S. aureus* pneumonia is increased, but *S. aureus* pneumonia still remains relatively uncommon. Guidelines for treatment of nosocomial or nursing home–acquired pneumonia have not specifically recommended empirical treatment for *S. aureus*, particularly in areas where MRSA is endemic. In patients with risk factors for *S. aureus* colonization and infection, rapid review of a Gram stain of a sputum sample for gram-positive cocci in clusters can inexpensively and quickly lead to the appropriate diagnosis. Addition of vancomycin to conventional therapy or use of a broad-spectrum β-lactam antibiotic with antistaphylococcal activity in areas where MRSA is not endemic should be initiated until results of sputum and blood cultures are available.

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