

Diagnostic Challenges and Opportunities in Older Adults With Infectious Diseases

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Infections remain a major threat to the well-being of our growing aged population. The correct and timely diagnosis of infections in older adults is increasingly important in the current age of antimicrobial resistance. Urinary tract infection, pneumonia, and bacteremia present particular challenges. In older patients with bacteremia, blood cultures have comparable yield as compared with younger patients. However, the routine triggers for ordering blood cultures may not be appropriate in older adults. In addition, resistance patterns of isolated pathogens may change with age. The main difficulties in diagnosing urinary tract infections in older adults are caused by an increased prevalence of asymptomatic bacteriuria and frequent use of urinary catheters. However, a combined noninvasive approach that includes history, physical examination, urinary dipstick testing, urine cultures, and simple blood tests can provide direction. In addition, specific guidelines for specific populations are available. In older patients suspected of bacterial pneumonia, bedside pulse oximetry and urinary antigen testing for *Streptococcus pneumoniae* and *Legionella pneumophila* provide direction for the clinician. Although infected older adults pose specific and unique diagnostic challenges, a thorough history and physical examination combined with minimally invasive testing will lead to the correct diagnosis in most older adults with infectious diseases, limiting the need for empiric antibiotics in this age group.

The global population is aging. By 2050, 21.4% of people are projected to be aged 60 years or older [1]. This expanding group of older adults is at increased risk of infections. Among older adults, the number of hospitalizations with an infectious disease as the primary diagnosis was estimated to be 21.4 million from 1990 through 2002 [2]. Therefore, timely and accurate diagnosis of infections in this population will be an increasingly essential skill for clinicians. However, manifestations of infections change with aging, and the differential diagnosis of various syndromes may be age-dependent [3]. Infected older adults often present with different signs and symptoms than younger adults. Classic symptoms such as fever may be either

absent or reduced in intensity, and atypical symptoms such as new or increased confusion, functional decline, falls, and loss of urinary or fecal continence may be the presenting manifestation of infection. Indeed, in one small study, infection was the leading cause of acute confusion among older adults in long-term care facilities [4]. A major issue when evaluating the existing literature is that the majority of studies comparing the presentation of infections in younger vs older adults are retrospective and rely on recorded histories. Unfortunately, obtaining a comprehensive, reliable history in older adults can be a challenge in itself [5]. Therefore, reports of a lower incidence of a particular symptom in older adults can either reflect the true absence of the symptom or lack of reporting or documentation of the symptom. In addition, for various infectious syndromes, symptoms themselves may be part of the diagnostic criteria leading to inclusion in the study. Fortunately, a thorough history and physical examination combined with minimally invasive testing will lead to the correct diagnosis in most older adults with infectious diseases, limiting the need for empiric antibiotics in this age group. In

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addition, several guidelines have been published to guide clinicians who care for the aging population [6–9].

Here, diagnostic challenges and opportunities for selected common infections in the elderly will be reviewed. In addition, a summary of current data on the use of biomarkers in infection in the elderly is provided.

BLOODSTREAM INFECTIONS AND ENDOCARDITIS

The diagnosis of a bloodstream infection (BSI) is generally straightforward if blood cultures are obtained at the appropriate time. The sensitivity and specificity of blood cultures are not influenced by the age of the patient. In hospitalized patients, the rate of false-positive blood cultures for coagulase-negative staphylococci does not appear to be increased with age [10]. Therefore, the challenges in diagnosing BSI in older adults include who should be cultured when, which pathogens are likely to be cultured, and from which source the BSI originated. For instance, per Infectious Diseases Society of America guidelines, blood cultures in febrile residents of long-term care facilities have such a low yield that routine blood cultures are not recommended unless bacteremia is highly suspected and blood cultures may help identify the offending agent when polymicrobial site-specific cultures are likely (ie, infected pressure ulcer and suspected bacteremic urinary tract infection [UTI] in a subject with an indwelling catheter) [6].

While bacteremic older adults are less likely to present with fevers, chills, and shakes, fever remains highly prevalent, reported between 77% and 97% of elderly patients [11–13]. Signs and symptoms of other organ involvement may be more common in the older adult; in one study, renal failure, acute respiratory distress, and altered consciousness were all significantly more common in older age groups with BSI [12]. Of note, urinary incontinence was identified as an independent risk factor for nosocomial BSI in older adults (odds ratio [OR], 1.65 [95% confidence interval {CI}, 1.22–2.29]), in addition to traditional risk factors that are applicable in the general population. The authors theorized that this may be secondary to direct effects of urinary incontinence—poorer hygiene and use of urinary catheters—and/or indirect effects such as more frequent exposure to healthcare providers and increased severity of illness [14]. In this context, a urinary source of bacteremia is more common in older adults, as is a lower respiratory tract source [11, 12].

The relationship between age and antimicrobial resistance in BSI varies by organism. In *Staphylococcus aureus* BSI, methicillin resistance is increasingly prevalent with increasing age (OR, 1.66, when comparing patients aged 18–60 years vs those >65 years [95% CI, 1.06–2.59]) [15, 16]. However, this trend is not seen with enterococci, in which age is not a risk factor for vancomycin resistance, and older patients are no more likely to progress

from vancomycin-resistant *Enterococcus* colonization to BSI than younger patients [17, 18]. Although residents of long-term care facilities have been proposed as a main reservoir for multidrug-resistant organisms, in patients with gram-negative BSI, increasing age itself does not predict increased risk of antimicrobial resistance [19, 20]. In patients with candidemia, age is a risk factor for non-*albicans* *Candida* species, especially *Candida glabrata*. In the Prospective Antifungal Therapy Alliance study, the mean age in patients with *C. glabrata* was 58.7 years, compared with 51.9 years in patients with *C. albicans* [21].

Two large recent studies have evaluated the impact of age on the presentation and diagnosis of infective endocarditis [22, 23]. Not surprisingly, in both studies, prosthetic valve infective endocarditis was more common in older adults. Older adults with infective endocarditis were less likely to have classic physical findings, such as splenomegaly, Osler nodes, Janeway lesions, and conjunctival hemorrhages. On the whole, embolic events were found in 15% of older adults, compared with 21% of younger adults [22]. The relative absence of these findings did not translate into a diagnostic delay; in one study the duration of symptoms prior to diagnosis was actually significantly shorter in older adults (20 vs 38 days; $P = .01$), whereas no age-related differences were seen in the frequency of causative pathogens [22, 23]. An enhanced diagnostic need for transesophageal echocardiography (TEE) with increasing age was observed; in patients ≥ 70 years of age, 20% had evidence of endocarditis on TEE only, compared with 14% in patients 50–69 years of age, and 12% in patients <50 years [22]. Summing up, BSIs may be present in older adults presenting with a variety of syndromes. Clinicians should have a low threshold for obtaining blood cultures in older patients, even in the absence of fevers in selected patients with changes in functional status (eg, new confusion), particularly in the long-term care setting. When blood cultures are positive and infective endocarditis is suspected, TEE may be required for the definitive diagnosis of infective endocarditis.

URINARY TRACT INFECTIONS AND ASYMPTOMATIC BACTERIURIA

As patients age, it is increasingly common to encounter positive urine cultures without evidence for infection. In community-dwelling older adults, the prevalence of asymptomatic bacteriuria is estimated at >20% for women ≥ 80 years, and between 6% and 15% for men >75 years [7]. In long-term care facilities, asymptomatic bacteriuria is present in 25%–50% of female and 15%–40% of male residents [24]. As antibiotics are not indicated for asymptomatic bacteriuria, it is crucial to distinguish asymptomatic bacteriuria from UTI. However, this distinction is hampered by the lack of a gold standard diagnostic test for UTI, as well as by the potential for atypical presentations in older adults. Older adults are less likely to present with classic UTI

symptoms such as dysuria and frequency compared with younger patients [25, 26]. In addition, functional symptoms such as confusion and falls may be seen in older adults with UTI [27]. On the other hand, although certain symptoms may be less common in older adults, many older adults with UTI still exhibit symptomatology, which can aid in the diagnosis. For instance, the presence of fevers, rigors, dysuria, frequency, urinary retention, and suprapubic or flank pain were associated with increased likelihood for UTI in older adults. Also, the finding of no growth on urine cultures, in a patient not on antibiotics, essentially rules out routine bacterial UTI [27]. Urinary dipstick testing for leukocyte esterase and nitrite also has a role in ruling out UTI in older adults. In nursing home residents, the negative predictive value for UTI of these 2 measures combined was 100% [28]. This has led to the recommendation not to obtain urine cultures in febrile residents of long-term care facilities unless either nitrite or leukocyte esterase is positive on dipstick [6]. Peripheral blood leukocytosis is an additional routine measurement that can be helpful. In both younger and older patients with community-acquired bacterial UTIs, >70% had white blood cell counts >10 000 cells/mm³ [29]. Simple clinical characteristics can also aid in identifying those most in need of antibiotic treatment. In a study aimed at identifying risk for bacteremia with UTI, the following 5 variables were noted to be predictive: home residence, Foley catheter, presence of bands in peripheral blood, shaking chills, and neutrophilia [30]. In conclusion, although diagnosing UTI in older adults is a considerable challenge, several routine findings can help guide the diagnostic process and inform a rational decision on whether or not to treat with antibiotics. In support of this conclusion, in a study evaluating agreement between 2 physicians to retrospectively differentiate between asymptomatic bacteriuria and UTI in 154 bacteriuric older adults, fair agreement ($\kappa = 0.49$) was observed. Notably, in half of patients in whom no agreement was reached, acute pulmonary disease was present, illustrating the potential for overlap in presentation in these 2 common situations [31].

PNEUMONIA

Correctly diagnosing bacterial pneumonia in the older adult presenting with lower respiratory tract symptoms may be a challenge. The diagnosis of viral pneumonia in older adults has been reviewed elsewhere [32]. In bacterial pneumonia, similar to UTI in older adults, some classic signs are also less frequent with increasing age. Chest pain is less commonly reported in older patients (estimates between 24% and 37%) than in younger patients with pneumonia (estimates between 45% and 67%) [33–36]. Also, older adults with pneumonia are less likely to present with fever than are younger adults. However, the majority of older adults are febrile

upon presentation with estimates ranging between 53% and 87% of patients, and cough and sputum production are similar in frequency in older adults [33–39]. Hypoxemia and increased oxygen requirements are common in older adults with pneumonia. These measures can be easily obtained by pulse oximetry at the bedside or in the office.

Most studies comparing pneumonia in various age groups require a new infiltrate on chest imaging. This limits any conclusions about differences in radiographic presentation of pneumonia in older adults, as patients who present with atypical or absent radiological findings will not be included in such cohorts. As an alternative approach, Basi et al [40] evaluated patients suspected of pneumonia without infiltrates (unconfirmed pneumonia) and compared them to those with infiltrates (confirmed pneumonia). The mean age was significantly higher (73 vs 68 years) in the unconfirmed pneumonia group. Outcomes were similar in both groups, consistent with the idea that most patients in both groups actually had pneumonia. This study suggests that older patients are less likely to present with classic radiologic findings. Similarly, patients ≥ 80 years of age were less likely to have multilobar findings on chest imaging [36]. For elderly patients with pneumonia, establishing a microbiological etiology is often limited by the inability to produce a good-quality expectorated respiratory sample. Sputum induction is an underused modality in this situation [41]. No pathogen is identified in approximately 60% of older adults with pneumonia, and the proportion of patients in whom a causative organism is not found increases with age [34–36, 42]. Blood cultures also have a relatively high yield estimated between 12% and 18%, which is not influenced by aging [34, 36, 43]. In summary, as imaging findings may be less reliable in older adults, and comorbidities may cause similar changes on radiographs; the combination of careful history, physical examination, and noninvasive testing still facilitates the diagnosis of pneumonia in most seniors.

BIOMARKERS

Erythrocyte Sedimentation Rate

Given the limitations of clinical signs, symptoms and typical changes in laboratory values (eg, leukocytosis) in infected older adults, biomarkers of infection may play a more important role in distinguishing a nonspecific presentation of infection vs a noninfectious syndrome. However, these markers are frequently elevated slightly by age itself or increased by comorbid illness often found in older adults. Therefore, the use of specific biomarkers in seniors is presented to clarify the use of such markers in populations of older adults. Although an elevated erythrocyte sedimentation rate (ESR) is a nonspecific finding, an extremely elevated ESR in an older patient should lead to further investigation [44, 45]. Workup usually results in a diagnosis such

Table 1. C-Reactive Protein in Infections in Older Adults

Outcome	No.	Age (years)	Setting	Enrolled	AUC	Cutoff (mg/L)	Sensitivity (%)	Specificity (%)	Reference
Any infection	218	≥75	Hospital	All	0.63	3	92	36	[49]
Any bacterial infection	187	≥65	Hospital	All ^c	NR	5	98	87	[53]
Any bacterial infection	187	≥65	Hospital	All ^c	NR	50	74	NR	[53]
Any bacterial infection	232	≥70	Hospital	All ^a	0.920	60	81	96	[52]
Invasive bacterial infection	172	≥75	Hospital	All ^b	0.84	10	97	29	[48]
Invasive bacterial infection	172	≥75	Hospital	All ^b	0.84	175	39	96	[48]
Bacteremia	187	≥65	Hospital	All ^c	NR	50	94	NR	[53]
Bacteremia	187	≥65	Hospital	All ^c	NR	5	94	87	[53]

Abbreviations: AUC, area under the receiver-operating characteristic curve; NR, not reported.

^a Consecutive patients were enrolled prospectively, excluding those on comfort care and those who did not provide consent.

^b Consecutive patients were enrolled prospectively, excluding those who had received antibiotics for >1 day prior to admission.

^c Cases with bacterial infection were enrolled from the hospital, and controls were community-dwelling older adults without infection.

as chronic infection, collagen vascular diseases including giant cell arteritis, or malignancy. In addition, if an elevated ESR is found in an infected patient, tracking the ESR is a simple and inexpensive way to determine response to treatment. One caveat to this approach is that lack of ESR normalization on antibiotic treatment may be secondary to undiagnosed comorbidities.

C-Reactive Protein and Procalcitonin

C-reactive protein (CRP) is an acute phase protein produced in the liver, mainly in response to interleukin 6 (IL-6) [46]. In contrast, procalcitonin (PCT) is produced by virtually all tissue types in response to invasive infection with bacteria, certain fungi, and plasmodium species [47]. A number of studies have been

performed on how to interpret CRP and PCT in older populations [48–53]. The main outcomes of these studies are summarized in Table 1 (CRP) and Table 2 (PCT). Unfortunately, various assays and cutoff values for both CRP and PCT have been reported, which limits direct comparison between studies. In addition, different outcomes as well as different populations have been studied. However, certain trends about the use of these biomarkers in an aged population can be observed. First, the more similar the infected patient is to his or her noninfected control, the less helpful biomarkers tend to be. This was shown in an emergency study in which PCT performed poorly in diagnosing infection as the cause of systemic inflammatory response syndrome, with an area under the receiver-operating

Table 2. Procalcitonin in Infections in Older Adults

Outcome	No.	Age (years)	Setting	Enrolled	AUC	Cutoff (ng/mL)	Sensitivity (%)	Specificity (%)	Reference
Any infection	218	≥75	Hospital	All	0.71	0.5	24	94	[49]
Any bacterial infection	187	≥65	Hospital	All ^a	NR	0.5	63	100	[53]
Any bacterial infection	187	≥65	Hospital	All ^a	NR	2.0	30	100	[53]
Any bacterial infection	107	65–74	ED	SIRS	0.554	NR	NR	NR	[50]
Any bacterial infection	155	≥75	ED	SIRS	0.672	NR	NR	NR	[50]
Invasive bacterial infection	172	≥75	Hospital	All ^b	0.85	0.08	97	20	[48]
Invasive bacterial infection	172	≥75	Hospital	All ^b	0.85	0.51	64	94	[48]
Bacteremia	187	≥65	Hospital	All ^a	NR	0.5	94	100	[53]
Bacteremia	187	≥65	Hospital	All ^a	NR	2.0	50	100	[53]
Bacteremia	155	≥75	ED	SIRS	0.817	0.383	96	63	[50]
Bacteremia	107	65–74	ED	SIRS	0.639	NR	NR	NR	[50]
Bacteremia	108	≥65	ED	Blood cx ^c	0.7	0.2	93	38	[51]
Bacteremia	108	≥65	ED	Blood cx ^c	0.7	0.5	57	72	[51]

Abbreviations: AUC, area under the receiver-operating characteristic curve; cx, culture; ED, emergency department; NR, not reported; SIRS, systemic inflammatory response syndrome.

^a Consecutive patients were enrolled prospectively, excluding those on comfort care and those who did not provide consent. Cases with bacterial infection were enrolled from the hospital, and controls were community-dwelling older adults without infection.

^b Consecutive patients were enrolled prospectively, excluding those who had received antibiotics for >1 day prior to admission.

^c All ED patients in whom blood cultures were obtained were enrolled.

characteristic curve of 0.554 in patients aged 65–74 years, and 0.672 in patients aged ≥ 75 years. These numbers increased to 0.639 and 0.817, respectively, when PCT was used to distinguish between older patients with or without bacteremia only [50]. Although the lack of discriminatory power in patients who are more similar to infected patients is intuitive, unfortunately, these are the patients in whom the clinical need is the most acute for a reliable biomarker.

Second, the goal of using biomarkers remains to be defined. Ruling out infection seems to be more feasible than diagnosing infection. Biomarkers may be incorporated into protocols for the responsible use of antibiotics in older adults, which can include either the decision whether to start empiric antibiotics or when to stop antibiotics.

Third, it remains unclear how much PCT and CRP add to clinical judgment. For example, in a study on 39 invasive bacterial infections among 172 acute geriatric unit admissions, the sensitivity of PCT < 0.08 $\mu\text{g/L}$ to exclude infection was 97%. However, in 23 of 27 patients with a low PCT, infection was already ruled out on clinical grounds, and 1 of the remaining 4 was a false-negative result (the patient was later diagnosed as having pyelonephritis). In this study, neither CRP nor PCT added significant gain over clinical evaluation [48].

Finally, most studies evaluate the ability of an isolated biomarker result to predict infection, whereas biomarkers probably will have the most value if combined with data from history, physical examination, imaging, and other laboratory testing. In a model to predict bacteremia in emergency room patients, both PCT and CRP were included along with other clinical variables, and in doing so the area under the curve was improved from 0.639 (CRP) and 0.737 (PCT) to 0.854 (complete predictive model) [54].

CONCLUSIONS

Infections in older adults are common and they may present in unusual ways. However, many infected older adults will present with some more typical features, which can guide the diagnostic process. Where and how to incorporate biomarkers in this diagnostic process remains to be determined. Using all available diagnostic modalities appropriately and awareness of their interpretation in older age groups will usually lead to the correct diagnosis. In doing so, a shift from emphasis on empiric treatment to a focus on diagnosis may result.

Notes

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