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REVIEW

Bloodstream infections in older patients

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ABSTRACT

Bloodstream infections (BSIs) are both common and fatal in older patients. We describe data from studies evaluating older patients hospitalized with BSIs. Most older patients with BSIs present "typically" with either fever or leukocytosis. The most common source of BSI in older patients is the urinary tract, and accordingly, Gram-negative organisms predominate. A significant part of these BSIs may thus be preventable by removal of unnecessary urinary catheters. Increased long term mortality is reported following BSIs in older patients, however, data on other long-term outcomes, including functional capacity, cognitive decline and others are lacking. Management of BSIs may include less invasive procedures due to the fragility of older patients. This approach may delay the diagnosis and treatment in some cases. Older patients are probably under-represented in clinical trials assessing treatment of bacteremia. Physicians treating older patients should consider the relevance of these studies' outcomes.

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Infections in older patients

The growth in the number and proportion of older adults in the population is unprecedented. According to Centers for Disease Control and Prevention (CDC) data, the number of Americans aged 65 y or older is about to double to approximately 72 million during the next 25 y and by 2030, older adults will account for roughly 20% of the US population.[1]

Infections in general are more frequent in older people compared to younger adults and are associated with hospitalization and mortality.[2-4] Multiple explanations for the increased rate of infections among older patients have been suggested, including co-morbid illnesses, exposure to instrumentation and procedures, institutionalization, immunosenescence, malnutrition, and poor performance status.[5] Elderly patients in institutions are at higher risk for infections because of more pronounced impairment of defenses against infection and large number of comorbidities, in addition to higher risk for rapid dissemination of viral infections and multidrug resistant organisms.[6]

Bloodstream infections in older patients

Incidence of bloodstream infections (BSIs) increased during the last two decades, with rates reaching 166-189 per 100,000 person-years in Europe.[7] Despite the decline in the case fatality rates demonstrated over time.[8] BSIs are among the top causes of death in many European and North American countries with case fatality rates of 12-20%.[7,9,10] BSIs are more common in older people, with over 50% of cases occurring in people aged 65 y and older.[9,11] Several studies report an increase in the incidence of BSIs with age, demonstrating highest incidence among people aged 65 y and older.[9,12] Others explained the significant increase in prevalence of BSIs in patients aged 65 y and older by the increase in hospitalization rates of older patients.[13]

Older patients are at risk for health care associated or hospital acquired BSIs. In a recent large series evaluating community onset BSIs in patients aged 65 y and older, 37.5% of bacteremias were health care associated.[14] Independent risk factors for acquisition of nosocomial BSI in older patients in two retrospective studies were age, bedridden state, presence of intravascular access or gastrostomy on admission and urinary incontinence.[3,15] In a retrospective study including 1143 patients with BSIs, those with health care associated bacteremia were significantly older.[16]

We reviewed original research articles that reported on BSI in the elderly and addressed sepsis presentation, source, etiology, resistance patterns or outcomes. Where

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available, comparison to younger patients are presented. We searched Pubmed up to September 2015 for studies including the words "bacteremia" or "bacteraemia" or "bloodstream infection" along with "elderly" or "old" or "older." Older studies and non-English written studies were reviewed as abstracts. Studies addressing a specific bacteria or source of infection were not included.

Presentation of BSI

The traditional wisdom is that presentation of infection in older patients is different than in younger patients and that older patients tend to have fewer symptoms. Explanations given for this hypothesis are altered physiological responses to the infecting pathogen in this patient group, and age-related changes in temperature regulation.[6] The results of studies reporting on sepsis presentation in the elderly and in comparison with younger patients are presented below (Table 1).

Body temperature

Fever is reported in at least 75% of patients aged 65 and older in most studies.[17-21] In a recent large prospective study including 2605 patients aged 65 y and older with bacteremia, absence of fever was documented in 6.3%.[14] Moreover, in most studies no significant difference from younger patients is demonstrated in the prevalence of fever [17,19,20,22] or in median temperature on presentation.[23] Hypothermia is reported in 0.3-10%.[17,20,22,24,25]

Definition of fever and site of measurement influence the results. Darwosky et al. found that in patients aged 70 y and older sublingual temperature readings detect about one-third of fevers and that rectal temperature measurement will detect fever in up to 86% of infected patients.[26,27] In the study of Hernandez et al., who reported 6.3% absence of fever, the definition of fever was rectal or oral temperature above 37.8, while in other studies higher temperatures were considered fever.[14]

Other clinical signs of infection

Chills are reported in ~35% of older patients [17,23,25,28] and significantly less prevalent compared to younger patients.[23] Altered mental status is reported in several studies to occur in as high as ~50% of patients 65 y and older.[23,25,28,29] Other studies reported altered mental status in 12-17% in patients aged 65 y and older [17,20,22] and 21-26% in patients 85 y and older.[20,22] The variability, at least in part, can be explained by various definition of "altered mental status" (Table 2). Table 2 presents other atypical presentations of bacteremia in elderly patients.

Table 1. Presentation of BSI - fever.

Study ID	Design	Number of episodes in older patients	Age cutoff	Percentage with fever	Difference from younger	Definition of fever	Percentage with hypothermia	Definition of hypothermia
Gleckman 1982 (18)	R	192	65	87	S lower % with fever compared to <65y			
Meyers 1989 (28)	R	100	65	65		>38.3	2	<36.1
Chassagne 1992 (17)	P	71	65	80	NS	>38.5 PR several times	1.5	
Fontanarosa 1992 (25)	R	79	65	37		>38.3	10	<36.1
Leibovici 1993 1 (11)	R	656	60		S higher median temperature in >=60y compared with >=80y		NS between >=60y and >=80y	<36.5
Leibovici 1993 2 (11)	R	339	80					
Pfitzenmeyer 1995 (21)	P	46	62	74		>=38.5		
Lee 2007 1 (20)	P	406	65	86	NS % with fever compared to <65y	>38.5 tympanic	3.9	
Lee 2007 2 (20)	P	69	85	77	S lower % with fever compared to <65y		1.4	
Wester 2013 1 (22)	R	334	65	64	NS	>=38.5	0.3	<36
Wester 2013 2 (22)	R	118	85	64	NS		1.7	
Green 2014 (19)	R	38	80	79	NS	>37.2		
Yahav 2015 (23)	P	236	65		NS	>=38		

Notes. R – Retrospective, P – Prospective
S – Significant, NS – Non-significant
PR – per rectum
Unless stated, site of temperature measurement not described in original studies

Table 2. Presentation of BSI – atypical manifestations.

Study ID	Design	Number of episodes in older patients	Age cutoff	Percentage presenting with altered mental status	Definition	Difference from younger	Percentage presenting with altered general state	Definition	Difference from younger
Meyers 1989 (28)	R	100	65	52					
Chassagne 1992 (17)	P	71	65	12	Transient confusion, mild disorientation, lethargy or sudden agitation without any previous chronic history of similar mental disorders	S less frequent than <65y	57	As described by the patient	S less frequent than <65y
Fontanarosa 1992 (25)	R	79	65	52	Confusion, lethargy, or coma	S more frequent than non-bacteremic			
Pfitzenmeyer 1995 (21)	P	46	62	21.5	Confusion		12	Functional decline	
Greenberg 2005 (40)	R	238	65	22	Neurologic chief complaint				
Lee 2007 1 (20)	P	406	65	14	Glasgow Coma Scale score of if a primary central nervous system injury was present	NS			
Lee 2007 2 (20)	P	69	85	26		S higher frequency than <65y			
Rebelo 2011 1 (29)	R	31	65	39	Short portable mental status questionnaire (SPMSQ) >4				
Rebelo 2011 2 (29)	R	63	75	29					
Rebelo 2011 3 (29)	R	41	85	61					
Wester 2013 1 (22)	R	334	65	16.5	Reduced consciousness	S higher frequency than <65y	46	Decline in general health	S higher frequency than <65y
Wester 2013 2 (22)	R	118	85	21			47.5		
Yahav 2015 (23)	P	236	65	49	Reduced consciousness	S higher frequency than <65y			

Notes. R – Retrospective, P – Prospective
S – Significant, NS – Non-significant
Falls reported only by Pfitzenmeyer et al. in 10%. (21)

Laboratory markers

Leukocytosis is reported in 39-73% of patients aged 65 and older [17,21-23,25,28] and in one study was more common than in younger patients and with higher median values.[23] Leukopenia is described in ~10% of patients in most studies [17,20,22,25,28] and its prevalence is not significantly different than in younger patients.[17,20,22]

Acute kidney injury is reported to be more common in older than younger patients in some studies,[11,20,23] although not all.[13,22]

CRP >= 8 mg/dl was as common in older patients as in younger patients in one study, however median CRP levels in the group of patients aged 65-74 y were significantly lower compared to younger patients.[22] The role of procalcitonin in the diagnosis of bacteremia in older patients is yet to be defined.

If infection is suspected in the elderly and blood cultures are collected, the sensitivity and specificity of blood cultures are not influenced by age. The rate of false-positive blood cultures for coagulase-negative staphylococci in hospitalized patients does not increase with age.[30]

Septic shock

Presentation of bacteremia with septic shock is reported in as many as 39% of patients aged 85 y and older [20] and was found to be more common in older compared to younger patients, with cut offs for older age defined as 65 y [23] or 85 y[20] In several large studies, septic shock was present in 10-15% of patients aged 65 y and older.[14,22,23] In a study evaluating patients with bacteremia, severe sepsis was present in 26-33% of patients aged 50 y and older compared with 16% in younger patients and age was an independent risk factor for presentation with severe sepsis.[31]

In addition to being more common in older patients, severe sepsis and septic shock cause higher mortality in elderly reaching 50-60%. Currently, treatment recommendations are similar to that used in young adults, with worth outcomes including increased mortality and poorer quality of life. Data on treatment and outcomes of septic shock in very old are scarce, because interventional studies tend to exclude such patients.[32]

Source of BSIs

Rates of various sources of infection as presented in studies evaluating BSIs in elderly are summarized in Table 3. Excluding one study, conducted in intensive care unit (ICU) patients, in all other studies urinary tract infection (UTI) is the most common source of infection, reported in 21-59% of patients. UTI was more common in older patients: both in patients 65 y and older versus younger patients [20,33,34] and in patients 80 y and older vs. patients aged 60-80.[11,35] In nursing home residents with an indwelling catheter, risk of UTI with each day that the catheter remains in place have been reported 3-7%.[6] Prevalence of urinary catheters use in skilled nursing facilities range between 6 and 40%, depending on the population studied.[36] In a study evaluating patients with community acquired BSIs, 40% of UTI cases occurred in patients with an indwelling urinary catheter. In this study, 44% of patients 65 y and older had an indwelling urinary catheter and patients in this age group were more likely to have a urinary source of infection.[37] Even in the absence of an indwelling urinary catheter, higher rates of UTI in older patients may be secondary to incontinence or neurological disorders and to a higher rate of bacteremia associated with pyelonephritis in older people.[30,35,38]

As presented in Table 3, most studies reported respiratory tract as the source in 9-28% of patients. An abdominal source was reported in 1-20%, depending whether a biliary source was included in the definition or not. Vascular catheter was reported as the source of infection in 1-10%, with higher rates reported in studies including nosocomial BSI (20%) (3) or ICU patients (13-19%).[13] Endovascular source is reported in 1-6%. Unknown source and primary bacteremia rates are variable and depend on definitions of infection in the various studies. It has been suggested that it may be more difficult to obtain samples for culture in older, debilitated or demented patients.[39]

Microbiology of BSIs

Gram-negative bacteria are more common than Gram positive pathogens in BSIs in patients 65 y and older. In most studies evaluating both community and nosocomial BSIs in elderly, Gram-negative organisms constitute between 40%[40] to 60%[28] of BSIs in elderly. In studies including only community acquired infections, Gram negative bacteria represent up to 70% of BSIs,[20] in contrast to studies including only nosocomial BSI, in which Gram negative bacteria constitute 40-50% [3,13] but are still more common than Gram positive organisms.[41] Gram positive organisms usually represent between 30-45% of BSIs in elderly,[20,28,35] although some studies reported 55-60%.[29,40] In these studies, however, rates of methicillin resistance *Staph aureus* (MRSA) infection were higher compared to other studies in mixed population of community acquired and nosocomial BSIs. In a study including only nosocomial BSIs requiring ICU hospitalization, Gram positive organisms (~50%) were more common

Table 3. Source of infection.

Study ID	Design	Number of episodes	Age cutoff	Percentage with source									
				UTI	Respiratory	Abdominal	Catheter related	SSTI	Endovascular	Other	Unknown	Primary	Multiple sources
Esposito 1980 (85)	Retrospective	100		34	13	20					11		
Windsor 1983 (86)	Retrospective	50		24	22						20		
Meyers 1989 (28)	Retrospective	100	65	27	12	16	9	6	6		21		3
Chassagne 1992 (17)	Prospective	71	65	32	17	10		11		14			
Fontanarosa 1992 (25)	Retrospective	79	65	44	27	9		3		5	11		
Leibovici 1993 1(11)	Retrospective	656	60	34	9	5	6	7	4	12	21		
Leibovici 1993 2 (11)	Retrospective	339	80	50	10	6	1	9	2	6	15		
Pfitzenmeyer 1995 (21)	Prosspective	46	62	59	11	20			4	7			
Ismail 1997 (61)	Retrospective	191	60	25	28	13		13	1	4	5		13
Gavazzi 2002 −1 (35)	Retrospective	758	65	24	10	12	9	8		4	30		
Gavazzi 2002 −2 (35)	Retrospective	649	76	29	12	11	7	6		3	28		
Gavazzi 2002 −3 (35)	Retrospective	333	85	39	14	11	2	8		2	24		
Greenberg 2005 (40)	Retrospective	238	65	26	16		10	4			36		
Lee 2007 1 (20)	Prospective	406	65	31	8	4	4	10	3			14	
Lee 2007 1 (20)	Prospective	69	85	28	19	1	1	9	1			17	
Crane 2007 (87)	Retrospective	347	65	34	10	12						21	
Payeras 2007 (47)	Prospective	146	80	21								25	
Sogaard 2008 1 (33)	Retrospective	1092	65	36	19	10				15	19		
Sogaard 2008 2 (33)	Retrospective	909	80	43	15	11				8	24		
Blot 2009 1 (13)	Retrospective	326	65	9	16	11	19	7		4		30	5
Blot 2009 2 (13)	Retrospective	134	75	15	15	11	13	10		2		30	4
Burlaud 2010 (41)	Retrospective	167	60	Most frequent							33		
Reunes 2011 (3)	Retrospective	142	70	31	14	7	20	11	3			14	
Rebelo 2011 1 (29)	Retrospective	31	65	39	45			13		10	10		
Rebelo 2011 2 (29)	Retrospective	63	75	48	37			13		3	3		
Rebelo 2011 3 (29)	Retrospective	41	85	51	32			15		10	5		
MunozGamito 2012 1 (34)	Retrospective		65	43	11								
MunozGamito 2012 2 (34)	Retrospective		80	44	16								
Wester 2013 1 (22)	Retrospective	334	65	40	28					18	14		
Wester 2013 2 (22)	Retrospective	118	85	33	33					12	22		
Retamar 2014 (46)	Prospective	120	80	26	11	18	12	7		2	24		
Hernandez 2015 (14)	Prospective	2605	65	35	10	19	7	4	4	6	15		

than Gram negative organisms (~40%) with *Staph coagulase negative* being the most common isolate.[13]

Older patients are at increased risk for colonization with Gram negative bacteria. Nursing home residency, hospitalization, respiratory disease and poor functional status are all risk factors for Gram-negative colonization. This may explain the Gram-negative predominance in bacteremia. In addition, it may be possible that elderly are more susceptible to these bacteria due to changes in the immune system.[42] Gram negative pathogens are more common as the cause of respiratory infections in elderly compared with younger patients.[43]

E. coli is the most common pathogen in community acquired BSIs in elderly [44] and causes ~40% of these infections.[14,20,33] In a large series from Finland, it was the most common pathogen in men aged 65 y and older with BSI acquired in both community and nosocomial setting.[9] In nosocomial BSIs, *E. coli* represents 10-20% of BSIs,[3,13] while *Staphylococcus aureus* and *Staphylococci coagulase negative* assume prominence. According to SENTRY study, *S. aureus* caused ~30% of nosocomial BSI in patients 65 y and older.[44] In other studies evaluating nosocomial BSIs in elderly, *S. aureus* represented 7-24% and *S. coagulase negative* 14-25% of all these BSIs.[3,13,45] Most studies evaluating elderly with any BSI report *S. aureus* in 7-17% of BSIs[14,21,25,28,33,35,46-48] with variable rates of methicillin resistance.

E.coli is significantly more common in patients 65 y and older compared to younger patients[17,19,20,34,49] and its predominance as the causative organism of BSIs further increases with age.[11,14,35] *S. aureus* BSIs may be less common in the group of oldest old (>=80y).[14,19,20,33]

Klebsiella spp.are the cause of BSI is elderly in approximately 3% (35) to 10%,[29] *Pseudomonas aeruginosa* causes between 1-9% of BSIs, with the lower rate reported in community acquired cases[33] and higher rates in nosocomial cases.[3,13] *Acinetobacter baumanii* in elderly is reported in few studies with rates of 1-2% [3,13,28] and up to 4% in patients 75years and older in ICU setting.[13]

Enterococcus spp are the causative agent in 3-10% of BSIs in most studies.[17,20,40] Anaerobes are described in 2-5% of BSIs in most studies, Polymicrobial infection in 5-15% and fungi in 0-3% in most studies, but 4-8% in nosocomial BSIs.[3,13] The incidence of candidemia is age-specific, with the maximum rates observed at the extremes of age.[50]

In a single study in ICU setting no significant difference in pathogens was found between elderly and younger adults. The explanation was that ICU patients are homogenous enough so that age would not cause a significant difference by itself.[13]

Antimicrobial resistance

In the western world, nearly 4% of people aged 65 or older are nursing home residents and it is estimated that a third of the population aged 80 and older live in long term care facilities (LTCF).[42,51] In these institutions antibiotic resistance is a growing problem and outbreaks of infection with multidrug resistant organisms (MDROs) are frequently reported.[6,42] Long-term care facilities may play an important role in the spread of resistant organisms, including *Klebsiella pneumonia* carbapenemase (KPC)-producing Enterobacteriaceae,[52] extended spectrum β-lactamase (ESBL) producing organisms,[53] metallo-β-lactamase (MBL) producing,[54] MRSA,[55] VRE and MDR *Acinetobacter baumanii*.[56] March et al. found that among LTCF residents in 2012, 54% were colonized with $\geq$1 resistant organism.[57] Contributing factors to high rates of colonization and infection of elderly with MDROs include substantial antimicrobial exposure, frequent hospitalizations, indwelling devices, dementia and low functional status, and as a result - high rates of cross transmission in these settings.[6,58]

Dekinger et al. demonstrated that among patients aged 65 and older admitted to hospital, rates of MDROs are approximately 2-fold higher for MRSA and vancomycin resistant enterococci (VRE) and 3-fold higher for multidrug resistant (MDR) Gram negative compared to younger patients. In this study, during 2009, 57% of *Staph aureus* isolates were methicillin resistant, 25% of *enterococcal* isolates were vancomycin resistant and 14% of gram-negative isolates were multidrug resistant.[58] Van Duin described the relationship between age and antimicrobial resistance in BSIs by organism: In *Staph aureus* BSI, methicillin resistance was increasingly prevalent with increasing age. In contrast, age was not a risk factor for vancomycin resistance in *enterococci*, and the risk for progression from VRE colonization to BSI as not higher than in younger patients. Increasing age itself was not found in this study to predict increased risk of antimicrobial resistance in patients with gram-negative BSIs.[30] Pop-vicas et al. found 16% of bacteremias in patients 65 y and older to be caused by MDR Gram negative bacteria.[59] In patients with candidemia, age is a risk factor for non-albicans Candida species, especially Candida glabrata.[30]

Mortality

Over half of all deaths in many countries now occur in hospitals, with the vast majority of in hospital deaths occurring among the elderly and the very old.[6]

Mortality rates in older patients with bacteremia in various studies are given in Table 4.

Table 4. Mortality rates in older patients with bacteremia.

	Timing of mortality assessment not specified	7 d mortality	14 d mortality	28-30 d mortality	In hospital mortality	ICU mortality	60 d mortality	90 d mortality	1 year
Age cutoff 60-70	21% (61) 23% (25) 40% (28) 26% (85) 38% (48) 24% (86) 16% (34)	11% (41) 18%(11) 21% (63) 10% (33) 14% (35)	11% (87)	16% (3) 40% (11) 45% (63) 11% (14) 16% (33)	22% (3) 30% (11) 49% (13) 22% (29) 19% (22) 30% (40)	38% (13)	32% (41)	75% (11) 20% (20)	30% (22)
Age cutoff >=75	21% (34) 21% (19)	22% (11) 14% (33)	22% (46)	50% (11) 28% (46) 21% (33)	31% (11) 56% (13) 15% (22) 35% (40)	42% (13)		85% (11) 26% (20)	31% (22)

Bacteremia is associated with a higher mortality rate in older patients as compared with younger-age groups in most studies. This association was found for both in hospital / 30 d mortality, (8, 9) 90 d mortality [20] and long term mortality.[24] Age has been demonstrated as a predictor of 3 y mortality in a cohort of adult patients with BSIs.[60]

Factors contributing to this difference include senescence of both humoral and cell-mediated immune systems; reduced physiologic reserve capacity; increased incidence of underlying illnesses; poor tolerance to invasive diagnostic and therapeutic procedures; greater risk and incidence of nosocomial infections; and higher rates of adverse reactions to drugs, including antibiotics.[4,28]

Predictors of mortality in elderly in most studies include increasingage,[3,8,11,13,14,20,22,28,29,33,47,61] noncommunityacquisition,[11,14,28,61,62] poor functional status,[3,11,61,63,64] comorbidities,[14,22,29,33,47] respiratory,[13,14,28,61] abdominal,[13,14,46] neutropeniaassociated,[11,14,62] orunknown[2,11,14,29,46] sourceof infectioninoppositetoUTI[11,28,61,62] orCRBSI[28] thatweredemonstrated to protect against mortality. Specific pathogens, such as *Pseudomonas aeruginosa*,[11] *Staph aureus*,[14,46] specifically MRSA,[35] *Enterococcus* spp.[14] *S. pneumonia*,[22] and Enterobacteriaceae resistant to 3rd generation cephalosporins[14] were also associated with increased mortality. *E. coli* was demonstrated to be protective in one study.[48] In a large study from Finland, the case fatality proportions of Gram-negative BSI in people >=65 y was higher compared to younger patients and reached 13%.[9]

Another predictor of mortality is the use of inappropriate empiric antibiotic therapy [11,14,28,46-48] and age is an important risk factor of carriage of multidrug resistant organisms leading possibly to higher rates of inappropriate empirical antibiotic treatment in elderly patients.[6]

Clinical signs at presentation predicting mortality among the elderly include hypotension/ shock,[11,13,14,46,48,61] absence of fever,[14,22] low albumin,[11,41,61] elevated renal creatinine/ urea,[11,13,61] leukopenia,[22,61] change in mental status,[29,48] and in single studies other measures such as tachycardia or tachypnea,[61] elevated CRP [41] and early organ failure.[22]

Other outcomes of BSIs

During the first year after severe sepsis or infection the quality of life of survivors is impaired, and they suffer from rapid degradation in cognition and functional capacity.[65] Few studies report the following outcomes in older patients:

Length of hospital stay - In a case control study from Belgium, median length of stay was significantly longer in bacteremic patients 70 y and older compared to non-bacteremic controls, matched by year of admission and length of hospital stay.[3] Similar results were demonstrated for patients aged 65-84 with bacteremia in Norway.[22] In contrast, Blot et al. reported significantly shorter length of ICU and hospital stay in bacteremic patients aged 75 y and older compared to younger patients.[13] Tacconelli et al. reported significantly higher rates of discharge from hospital by day 7 and day 14 in patients aged 65 y and older with MRSA bacteremia compared with younger patients with MRSA bacteremia.[66] Differences in length of hospital stay may however depend on long-term care facilities availability, and thus vary between different locations.

Need for subacute care - In a cohort including mostly patients aged 60 and older with *Staph aureus* bacteremia, 54% of community-dwelling patients who survived hospitalization needed subacute care after discharge. Older age predicted need for subacute care in previously independent patients.[67] Among patients aged 75 y and older treated with drotrecogin alfa for severe sepsis, 45% were discharged home, 9% were transferred to another hospital, and 44% were transferred to a nursing home.[68]

Functional capacity and cognitive ability - severe sepsis in older patients was independently associated with substantial and persistent new cognitive impairment and

functional disability among survivors in 2 large series.[69,70] Studies evaluating these outcomes specifically in bacteremic patients are lacking.

Quality of life - Decline in quality of life was also described after sepsis in general, but not following bacteremia specifically.[71]

Other outcomes suggested to be important in older patients include cost of care, depression and site of discharge (home or institution).[72]

Management of BSIs in older patients

Some of the important aspects of management of infections in older patients have been recently reviewed and thus will not be discussed in this review. These include challenges of antimicrobial stewardship in long-term care facilities,[51] ethical dilemmas in antibiotic treatment,[73] impact of drug interactions and polypharmacy on antimicrobial therapy,[74] the role of infectious diseases consultation in older patients.[6]

Another aspect is our approach to the management of older patients, including active and invasive diagnostic work-up and treatment. In a series of patients hospitalized with *Staph aureus* bacteremia in our tertiary center in central Israel (Rabin Medical Center, Beilinson Hospital), we found that although older patients had higher mortality and complication rates, they were less likely to undergo infectious diseases consultation, transesophageal echocardiography (TEE), or imaging studies. They were also less likely be hospitalized in an ICU, have a surgical / drainage procedure, have their foreign body / catheter removed or valve replaced (unpublished data). This was demonstrated even in older patients without dementia, although without statistical significant, but not in patients with preserved functional capacity.

Low rate of echocardiography performance in elderly with *Staph aureus* bacteremia has been previously documented in patients older than 80 y with 45% of echocardiogram performance in this group. Authors assumed that because TEE is an invasive procedure some clinicians may have perceived it as too aggressive in this older cohort.[75] This stands in contradiction to the fact that TEE was found to increase significantly the diagnostic sensitivity for endocarditis specifically in elderly patients.[76]

In general, appropriate empirical antibiotic therapy has been demonstrated to improve survival in septic patients.[77] Thus, broad spectrum antibiotics are often given as empirical treatment for patients with suspected bacteremia.

However, at presentation we do not know whether the patient has a severe infection meriting early covering antibiotic treatment and the cost of a universal strategy of aggressive empirical antibiotic treatment is increased resistance in future infections. Moreover, not all patients may gain from appropriate antibiotic treatment. In patients with dementia and decubitus ulcers, appropriate therapy was not associated with survival advantage.[78] In addition, in all patients the advantage of antibiotic treatment, especially broad spectrum antibiotics, should be balanced against the risk of future resistance.[79]

Representation of the elderly in clinical trials

Older patients are probably under-represented in clinical trials in infectious diseases. Exclusion may be on the basis of age as an exclusion criteria itself or indirectly, by excluding patients due to comorbidities or need for informed consent. Avni et al. have demonstrated that patients included in randomized controlled trials (RCTs) on the treatment of community-acquired pneumonia (CAP) are significantly younger than patients included in observational studies.[80] We have recently compared (unpublished data) the characteristics of included versus excluded patients from a randomized controlled trial evaluating treatment of MRSA invasive infections.[81] Excluded patients were significantly more likely to be bedridden, dementic and had a higher Charlson comorbidity score. The major impediment to patient recruitment in the trial was the need for informed consent.

In clinical trials including patients with BSIs the problem may be even worse. As elaborated above, a large number of elderly have mental status changes as part of their clinical presentation, and thus will not be able to sign informed consent.

Some ongoing randomized controlled studies evaluating therapy for bacteremia exclude in their protocol patients aged 85-90 y (e.g., NCT02134106, NCT01970371). In a review of RCTs comparing antibiotics, frequent exclusion criteria included immune-suppression, many co-morbidities, renal and liver failure and use of concomitant medications, all more prevalent in older patients.[82]

All of the above raises questions on how evidence-based is our treatment of older patients with infectious disease generally and BSIs specifically.

In conclusion, over 50% of BSIs occur in people aged 65 y and older. Thirty days mortality of these fatal infections reach 11-50% in older patients and they are also associated with increased long term mortality and other long-term outcomes. Presentation of BSIs in elderly is probably not “atypical” as traditionally believed and most patients will have fever and/or leukocytosis. It has been suggested that prognostic scores should be adapted to older patients in terms of both validation of score’s parameters to older patients and using outcomes in addition to mortality (including cognitive decline, functional

decline, need for nursing home care, and overall quality of life).[83]

The most common source of infection is usually UTI and the most common pathogen in community acquired BSIs is E. coli. A significant part of BSIs in older patients may be preventable by removal of unnecessary urinary catheters and by adherence to infection control practices.[84]

Management of BSIs may include less invasive procedures on the background of patient's age alone, which may sometimes interfere with the diagnosis and treatment. Physicians taking care of older patients should consider the implications of refraining from diagnostic and therapeutic procedures only on the basis of age. Older patients are probably under-represented in clinical trials assessing treatment of bacteremia and the relevance of studies' results should be evaluated accordingly.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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