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ACUTE GERIATRICS

Sepsis in the older person: The ravages of time and bacteria

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Pearl is an 84 year old woman in your ED with a 2 day history of lethargy. She is usually cognitively intact and has a history of hypertension, congestive cardiac failure, mild renal impairment and Parkinson's disease. She lives in an aged care facility and mobilises with a four-wheeled walker. She has a temperature of 37.9°C and feels lethargic. She has neither other specific symptoms nor signs, although appears confused. Her blood pressure (BP) is 90 systolic and she has a pulse of 70/min.

Does Pearl have septic shock? If so, what is the source and how should we manage her?

Why talk about sepsis in the older person?

Sepsis is overwhelmingly a disease of older people (Fig. 1), with patients over 65 years of age accounting for two-thirds of sepsis cases.[1] With incidence rates increasing 20% faster than younger patients, older people account for the most rapid escalation of longitudinal incidence.[2] When presenting to the ED with sepsis, older people are more unwell, with higher levels of both potentially reversible organ dysfunction and mortality than younger people.[3] The association between age, severity of illness and comorbidities is complex. Although age, lactate and comorbidities are independently associated with mortality, each variable influences outcomes of the others.[4] For survivors, sepsis is often a life-changing illness associated with high levels of morbidity, especially if severe enough to warrant admission to the ICU. Although sepsis mortality in Australia and New Zealand has fallen steadily since 2000, the odds of being discharged to a rehabilitation facility have increased three-fold in the same period.[5] One-third of survivors in two multicentre sepsis trials had not returned to their previous level of functioning at 6 months.[6] Prompt recognition is therefore important to optimise outcomes and minimise complications.[7]

Age increases the risk of infection, bacteraemia as a result of infection and sepsis through many mechanisms (Fig. 2). Pearl may have any or all of the following:[8–10]

- Immunosenescence with marked decline in cell-mediated and humoral immune function with increasing age
- Lack of control of pro-inflammatory cytokines by anti-inflammatory mechanisms
- An increased pro-coagulant state with resultant micro-thrombotic ischaemic organ injury, and sepsis-induced apoptosis
- Comorbidities that increase exposure to infection (e.g. Pearl's Parkinson's disease resulting in decreased cough reflex with increased risk of aspiration; reduced bladder emptying; increased falls and associated wounds and so on) and diminish physiological reserve (e.g. her cardiac failure)
- Medications that may be associated with immunosuppression or reduction in cardiopulmonary responses to infection
- Increased rates of indwelling medical devices
- Increased multiresistant organisms associated with increased rates of hospitalisation, institutionalised living and antibiotic use
- Malnutrition and frailty.[11]

Identification of sepsis in the older person

Emergency physicians are taught that sepsis presents atypically in

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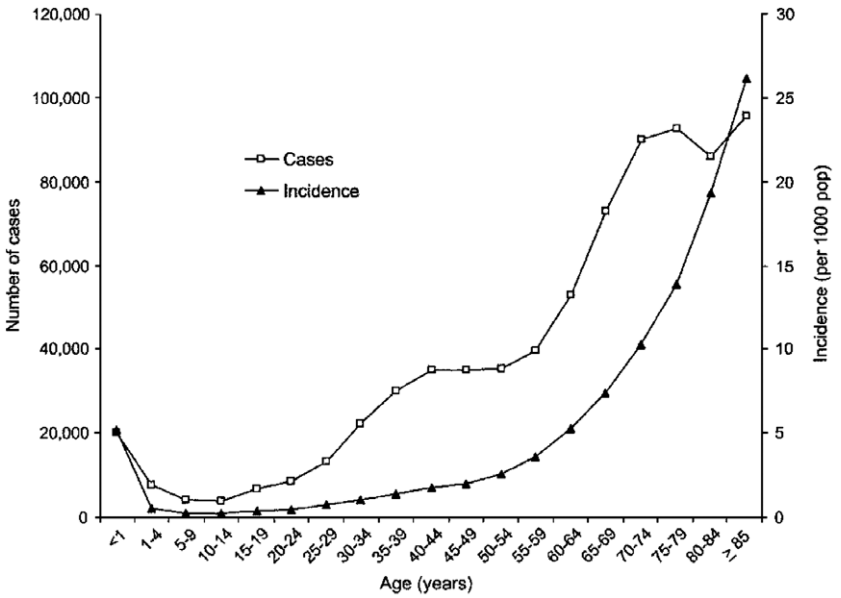

Figure 1. *Incidence of severe sepsis by age (national estimates for the United States). (Reproduced from Angus* et al.,[1] *with permission.)*

older people. In reality, because sepsis is mostly seen in older people, this is non-sensical and based on outdated teaching of what sepsis is and should look like. Older patients with bacteraemia do exhibit fewer clinical signs than younger patients[12] and sepsis may be one of many causes of non-specific presentations such as reduced mobility or an unexplained fall. But this is not the same as saying these presentations are atypical, when they may in fact be typical of the bulk of sepsis we see in our practice.

Attention should be paid to sepsis risk factors in the history, such as recent hospitalisation, invasive procedures, frequent presentations and immunosuppression (disease or medication-related).

Fever is absent in up to 50% of frail older persons with serious infections.[12–14]

Hypothermia, rigors, sweating, altered mental status, leukopenia and lymphopenia, although reported to be significantly less common than in younger people with bacteraemia, still have high specificity for bacteraemia in older adults.[12]

Identification of septic shock (i.e. sepsis-related tissue hypoperfusion) may be delayed due to failure to assess circulation appropriately. In older persons, the usual response of tachycardia may be blunted due to reduced responsiveness of myocardium to catecholamines or beta-blockade; alternately atrial fibrillation (AF) and congestive cardiac failure may occur with sepsis and the associated tachycardia may wrongly be ascribed solely to AF, delaying recognition and management.[15] Older patients may have a relatively increased baseline BP compared to the younger population,[16] with attendant under-appreciation of relative hypotension. This is compounded by the finding that automated BP machines may overestimate BP in the setting of stiffening of arteries.[16]

Common causes of sepsis in older adults are summarised in Table 1. Unfocused laboratory and imaging tests are poor surrogates for careful history and physical examination. Because identification of both bacteraemia and sepsis is difficult, a large amount of research effort has been spent on finding biomarker, rapid bacterial polymerase chain reaction or bedside assessments of microcirculatory function to aid sepsis recognition. At present no single test can, in isolation, reliably identify sepsis in a useful time frame, and the diagnosis in the ED is a clinical one.

Risk stratification and prognostication of older patients with sepsis

A number of tools have been suggested to risk-stratify patients with sepsis (Table 2); however, their prognostic performance is lower in older age groups.[34] In older persons, Systemic Inflammatory Response Syndrome (SIRS) criteria and the quick Sepsis-related Organ Failure Assessment (qSOFA) demonstrate a sensitivity for prediction of 30 day mortality of only 65% and 28%, respectively, using cut-points of ≥2.[31] However, qSOFA has a significantly higher specificity than SIRS, at 94% and 49% for 30 day mortality, respectively.[31] The Glasgow tachYpnoea Morbidity score has recently been suggested as a measure to improve prognostic capacity in older people with sepsis, with a sensitivity of 80% for 30 day mortality when using a cut-point of ≥1.[31] However, this score has been assessed at only a single centre and requires external validation. Scoring systems incorporating age and comorbid illness burden such as the Mortality in ED Sepsis (MEDS) and Predisposition Insult Response Organ failure (PIRO) scores have better predictive value in the ED than SOFA, which addresses only physiological derangements.[32] These scoring systems typically treat age as a dichotomous variable (e.g. ≥65 years); however, in reality the association with increased mortality to age is continuous. In addition, there are complex interactions between chronological age, comorbid illness burden and physiological reserve, which render any definitional threshold arbitrary when applied to the individual.

Management

As with all resuscitative decisions, goals of care should be established together with the older person or their alternate health decision-maker and be guided by physiological decline, comorbidities and individual life values. Such discussions should include the high likelihood for a patient like Pearl of further

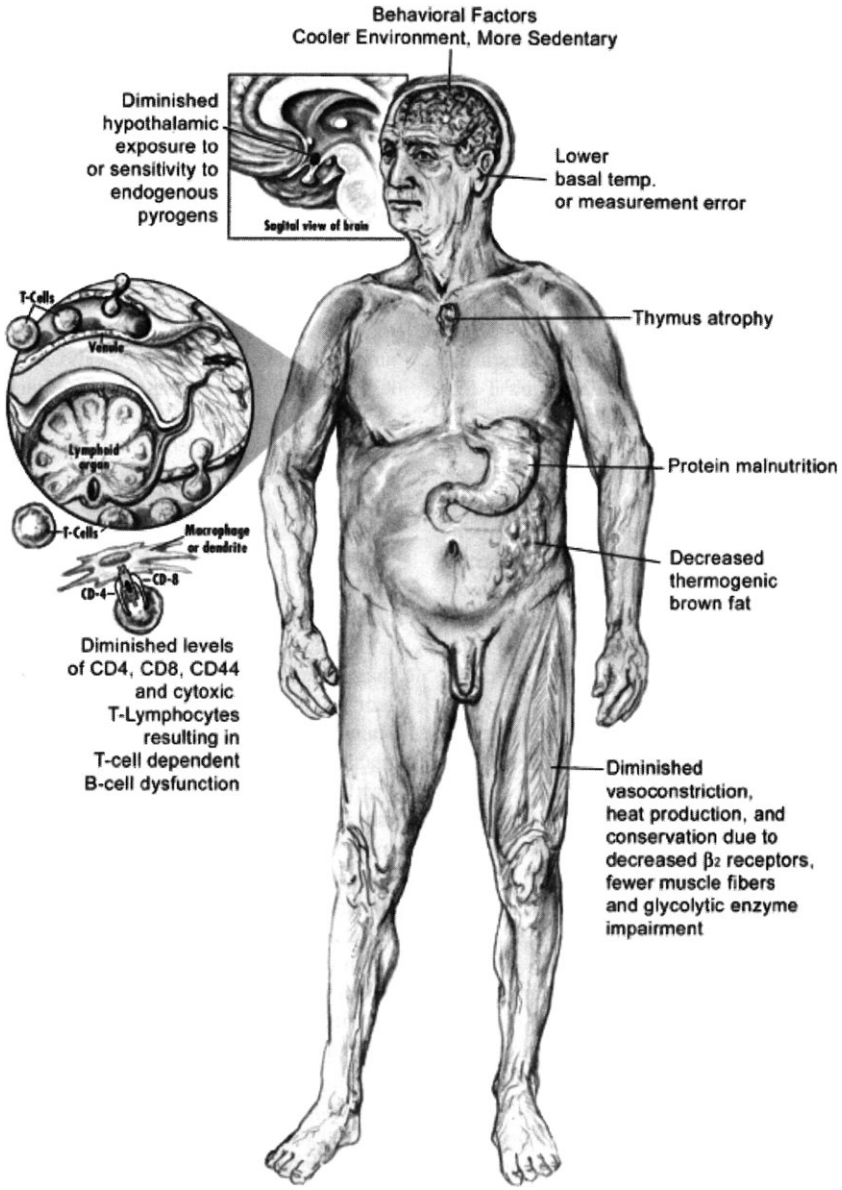

Figure 2. *Factors associated with sepsis susceptibility in aging adults. (Reproduced from Katz* et al.,[8] *with permission.)*

permanent functional decline if she were to survive this episode.[35] However, these discussions often take time, particularly if the person is lacking decision-making capacity and alternate health decision-makers are not present; therefore, they may be more appropriately completed after the initial administration of antibiotics and commencement of fluid resuscitation. This allows for background information on comorbidity, functional status and patient preferences to be appraised so an informed discussion about the potential benefits and harms of more invasive therapy can take place.

Where an interventional approach is adopted, management needs to encompass early antibiotics; timely fluid resuscitation and early vasopressor support where indicated; source control; management of comorbidities or complications; and a multidisciplinary approach to care, particularly where surgical source control is required. Timely management and resuscitation has been demonstrated to result in more than 16% absolute risk reduction of mortality in older persons with septic shock.[36] In a recent evaluation of 50 000 ED patients, of which 75% were over 60 years of age, each hour delay in completing a 3 h bundle was associated with increased mortality (odds ratio for death until completion of 3 h bundle, 1.04/h, 95% confidence interval 1.02–1.05; $P < 0.001$). Bundle elements included blood cultures before antibiotics, and lactate measurement.[37]

Antibiotics

Improved survival is associated with early administration of effective antibiotics in patients with sepsis, with a target of administration within 1 h of ED arrival for those with sepsis or septic shock.[38] Although prompt treatment for critically ill patients makes intuitive sense, there is conflicting evidence to support time-based targets in the ED setting.[39] A 'time effect' may be due to missed or delayed diagnosis in sicker patients who have non-specific presentations.[40,41] However, Ferrer *et al.* reported increased adjusted mortality for every hour of antibiotic delay in 18 000 severe sepsis and septic shock patients.[42] Seymour *et al.* additionally described an increased mortality per hour delay of antibiotic administration in 50 000 severe sepsis and septic shock patients presenting to 185 EDs across New York state. Patients receiving antibiotics between 3 and 12 h incurred a 14% increased odds of in-hospital death compared to those who received antibiotics within the first 3 h (odds ratio 1.14; 95% confidence interval 1.07–1.21; $P < 0.001$).[37]

Given that localising symptoms are commonly absent in older patients with sepsis such as Pearl, it is necessary to initially administer empiric broad-spectrum antibiotics and then de-escalate when the source of infection becomes apparent. Given the higher incidence of multiresistant organisms and polymicrobial sepsis in older adults, it is particularly critical to collect at least two sets of blood cultures prior to administration of intravenous antibiotics.[38]

TABLE 1. *Common sources of sepsis in older adults presenting to ED*

Source of sepsis		Predominant causative organisms	Predisposing risk factors	Diagnosis	Mortality rate
Pneumonia	Community-acquired pneumonia (CAP)[17–19]	*Streptococcus pneumoniae*; *Haemophilus influenza*; influenza; *Mycoplasma pneumoniae*; *Staphylococcus aureus*; *Legionella* spp.	Alcoholism; underlying respiratory disease; immunosuppression	Cough, fever and dyspnoea absent in 66% of older persons with pneumonia; 50% present with acute confusion; chest radiography; urinary antigen testing for *Pneumococcus* and *Legionella*	CURB-65: Confusion; uremia; respiratory rate ≥30 breaths/min; BP, systolic <90 mmHg or diastolic ≤60 mmHg; age ≥65 years: low mortality if 0 or 1; moderate if 2; high if ≥3. Comorbidities, particularly cancer, advanced liver disease, renal impairment and collagen vascular disease, have been identified as the strongest predictor of mortality in older adults with CAP[20]
	Healthcare acquired	MRSA; *Pseudomonas aeruginosa*; *Klebsiella pneumoniae*	Hospital admission for 2 or more days in preceding 3 months		
	Aspiration[21–23]	Polymicrobial; *Staphylococcus aureus*; *Streptococcus pneumoniae*; gram-negative bacilli; anaerobes	Dementia; deterioration in swallow; cerebrovascular accident; Parkinson disease; malnutrition; poor oral hygiene; antipsychotic drug use		
UTI[17]	Cystitis; pyelonephritis	*Escherichia coli*; *Enterococcus*; *Klebsiella; Providencia*; *Proteus*; polymicrobial if catheter-associated	Indwelling catheter; increased post-void residual (neurogenic bladder from stroke, dementia or Parkinson disease; OR urinary outlet obstruction from prostatic hypertrophy)	Acute confusion is a common presenting feature; acute dysuria is specific for UTI; malodourous or cloudy urine are not reliable signs of UTI. Rates of asymptomatic bacteriuria range from 6 to 16% of community dwelling women to 25 to 55% of aged care facility residents.[24,25] Failure to	In-hospital mortality for UTI associated sepsis is 30%

TABLE 1. *Continued*

Source of sepsis		Predominant causative organisms	Predisposing risk factors	Diagnosis	Mortality rate
				appreciate the high incidence of asymptomatic bacteriuria may result in premature diagnostic closure and inappropriate antibiotic choice in older patients with sepsis.	
Skin source	Cellulitis	*Staphylococcus aureus*; *Streptococcus* spp.	Wounds – log-roll to exclude sacral pressure injury; venous stasis; lymphoedema	Cellulitis is common in this population and is predominantly a clinical diagnosis. However, bilateral lower limb involvement of cellulitis is extremely rare and should prompt consideration of cellulitis mimics, particularly chronic venous eczema.[26]	If associated with sepsis, emergent exclusion of necrotising fasciitis is recommended as this has high mortality; if associated with a chronic wound, underlying osteomyelitis may be present
Meningitis/ encephalitis		*Streptococcus pneumoniae*; herpes simplex encephalitis	Predisposing conditions including otitis media, sinusitis, pneumonia	Differentiation from delirium may be challenging, particularly given the lower incidence of neck stiffness and rash. Timely diagnosis of meningitis in febrile older adults with altered mental status is challenging because indiscriminate lumbar puncture is low yield.[27]	Herpes simplex encephalitis

TABLE 1. *Continued*

Source of sepsis		Predominant causative organisms	Predisposing risk factors	Diagnosis	Mortality rate
Intra-abdominal causes[28]	Appendicitis	*Escherichia coli*; *Klebsiella*; *Enterococcus*; *Enterobacter*; *Pseudomonas*; *Bacteroides fragilis*; *Streptococci*	No prior history of appendectomy	Atypical presentations are typical; CT abdomen useful	2–14%; morbidity 40%
	Diverticulitis		History of diverticulosis	In older adults, generalised peritonism more common than localised peritonism	17% if associated perforation
	Cholecystitis/ cholangitis		Choledocholithiasis; iatrogenic strictures; neoplasms	Cholangitis: Charcot's triad in 55–70%, jaundice, abdominal pain, fevers; in older persons hypotension and confusion common	Cholecystitis: 15–20% if associated empyema, gangrenous gallbladder, perforation or abscess; cholangitis: 10%
	Mesenteric ischaemia		Age; ischaemic heart disease; peripheral vascular disease; hypertension; multiple comorbidities	Abdominal pain disproportionate to physical examination; increased serum lactate; CT abdomen; exploratory laparotomy	Mortality ~70% if bowel gangrenous

Optimal dosing of antibiotics is critical to achieving rapid therapeutic drug concentrations to facilitate pathogen clearance in sepsis. Pearl will have altered muscle mass, total body water, renal function and serum albumin compared to a younger female.[17] However, sepsis itself is associated with changes to pharmacokinetics and pharmacodynamics of antibiotics, which may predispose to subtherapeutic drug concentrations.[17] Therefore, antimicrobial dosing may be complex in this cohort, and should start at maximum recommended dose with subsequent adjusting for baseline renal or hepatic insufficiency as appropriate.[17]

Fluid resuscitation and vasopressors

Pearl is hypotensive and has renal and cardiac dysfunction. Perhaps because of clinician concerns of iatrogenic fluid overload in patients like Pearl, sepsis studies have consistently identified under-resuscitation with fluids.[16] Given preload dependence of stroke volume and increased vascular capacitance in sepsis, adequate fluid resuscitation has long been held to improve survival and limit organ dysfunction.[16] Initial fluid recommendations continue to be 30 mL/kg of crystalloid therapy over the first 3–6 h after identification of the patient with septic shock. However, administration of intravenous fluids beyond physiological requirements, where stroke volume can no longer be increased, results in tissue oedema, organ dysfunction and increased mortality.[43] Current research is exploring the potential benefits from lower fluid volumes and earlier institution of vasopressor support.[44] Focussed ultrasound can assist in identification of a static dilated inferior vena cava or cardiac dysfunction, where early institution of inotropic support may be beneficial.[16,45] Where ultrasound is not available, response of BP to bilateral passive leg raising may be assessed.[43] In practice, we currently recommend judicious use of fluid boluses titrated to clinically appropriate end points.

TABLE 2. *Clinical scoring systems for risk stratification of sepsis in older persons*

Clinical scoring system	Cut-point for increased risk of mortality with sepsis	Included variables		Cut-points or assigned points for individual variables
Systemic Inflammatory Response Syndrome (SIRS)[29]	≥2 criteria	Temperature		>38°C or <36°C
		Heart rate (/min)		>90
		Respiratory rate (RR; breaths/min) or p_aCO_2 (mmHg)		RR >20 or p_aCO_2 <32
		White blood cell count (/mm^3) or % immature bands		>12 000 or <4000 or >10% immature bands
Quick Sepsis-related Organ Failure Assessment (qSOFA)[30]	≥2 criteria	Respiratory rate (breaths/min)		≥22
		GCS score		<15
		Systolic BP (mmHg)		≤100
Glasgow tachYpnoea Morbidity[31]	≥1 criterion	GCS score		<15
		Respiratory rate (breaths/min)		>20
		Charlson Comorbidity Index		>3
Predisposition Insult Response Organ failure (PIRO)[32]	<5 = 0% mortality 5–9 = 5% 10–14 = 5% 15–19 = 37% ≥20 = 80%	Predisposition	Age	<65 = 0; 65–80 = 1; >80 = 2
			COPD history	1
			Liver disease history	2
			Nursing home resident	2
			Malignancy	Without metastases = 1; with metastases = 2
		Infection	Skin and soft tissue	0
			Any other infection	2
			Pneumonia	4
		Response	Respiratory rate >20	3
			Bands >5%	1
			Heart rate >120	2
		Organ dysfunction	Systolic BP	>90 mmHg = 0; 70–90 = 2; <70 = 4
			Blood urea nitrogen >7.1 mmol/L	2
			Respiratory failure/ hypoxaemia	3
			Lactate >4	3
			Platelet count <150 × 10^9/L	2
Mortality in ED Sepsis (MEDS)[33]	28 day mortality rate with MED score of:[33] 1 = 1.1%	Predisposition	Age >65 years	3
			Nursing home resident	2
			Rapidly terminal comorbid illness	6

TABLE 2. *Continued*

Clinical scoring system	Cut-point for increased risk of mortality with sepsis	Included variables		Cut-points or assigned points for individual variables
	2 = 4.4%			
	3 = 9.3%			
	4 = 16%			
	5 = 39%	Infection	Lower respiratory infection	2
		Response	Bands >5%	3
		Organ dysfunction	Tachypnea or hypoxaemia	3
			Septic shock	3
			Platelet count <150 000/mm^3	3
			Altered mental status	2

A recent trial suggested that in patients with chronic hypertension, targeting a mean arterial pressure of 80–85 mmHg resulted in a lower requirement for renal replacement therapy, albeit with no change in mortality.[46] However, another trial suggested that in those >75 years, mortality was reduced when targeting a mean arterial pressure of 60–65 *versus* 75–80 mmHg, with lower risk of AF and lower doses of vasopressors.[47] Therefore, current guidelines continue to support a target mean arterial pressure of 65 mmHg in older persons with sepsis.[38]

Source control

Rapid source control, particularly for intra-abdominal abscesses, gastrointestinal perforation, ischaemic bowel, cholangitis, cholecystitis, necrotising soft-tissue infection and implanted device infections, is critical after initial resuscitation. Survival reduces if delays to source control occur beyond 6 h.[38] This highlights the need for a multidisciplinary approach to management of sepsis in older people, with early involvement of surgeons where indicated.

Conclusion

The identification of sepsis in the older person requires a high index of suspicion and careful history and physical examination. Early management with appropriate antibiotics and fluid resuscitation with vasopressor support where indicated, with a multidisciplinary team approach, is associated with marked improvement in morbidity and mortality. However, given the high associated morbidity, high rates of increased dependence and high mortality of sepsis in older adults, it is important for ED physicians to ensure that a shared decision-making approach is taken to ensure that ongoing management is consistent with individual patient goals of care.

Competing interests

SPJM is a section editor for *Emergency Medicine Australasia*.

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit. Care Med.* 2001; **29**: 1303–10.
2. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. *Crit. Care Med.* 2006; **34**: 15–21.
3. Warmerdam M, Stolwijk F, Boogert A *et al*. Initial disease severity and quality of care of emergency department sepsis patients who are older or younger than 70 years of age. *PLoS One* 2017; **12**: e0185214.
4. Phillips GS, Osborn TM, Terry KM, Gesten F, Levy MM, Lemeshow S. The New York sepsis severity score: development of a risk-adjusted severity model for sepsis. *Crit. Care Med.* 2017: 1.
5. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA* 2014; **311**: 1308–16.
6. Yende S, Austin S, Rhodes A *et al*. Long-term quality of life among survivors of severe sepsis: analyses of two international trials. *Crit. Care Med.* 2016; **44**: 1461–7.
7. Nasa P, Juneja D, Singh O, Dang R, Arora V. Severe sepsis and its impact on outcome in elderly and very elderly patients admitted in intensive care unit. *J. Intensive Care Med.* 2012; **27**: 179–83.
8. Katz E, Carpenter C. Fever and immune function in the elderly. In: Meldon S, Ma OJ, Woolard R, eds. *Geriatric Emergency Medicine*.

New York: McGraw-Hill, Medical Publication Division, 2004; 55–69.
9. Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. *Clin. Infect. Dis.* 2005; **41**(Suppl 7): S504–12.
10. Nasa P, Juneja D, Singh O. Severe sepsis and septic shock in the elderly: an overview. *World J. Crit. Care Med.* 2012; **1**: 23–30.
11. Arendts G, Burkett E, Hullick C, Carpenter CR, Nagaraj G, Visvanathan R. Frailty, thy name is. *Emerg. Med. Australas.* 2017; **29**: 712–6.
12. Chassagne P, Perol MB, Doucet J *et al*. Is presentation of bacteremia in the elderly the same as in younger patients? *Am. J. Med.* 1996; **100**: 65–70.
13. Henschke PJ. Infections in the elderly. *Med. J. Aust.* 1993; **158**: 830–4.
14. Musgrave T, Verghese A. Clinical features of pneumonia in the elderly. *Semin. Respir. Infect.* 1990; **5**: 269–75.
15. Sehgal V, Bajwa SJ, Consalvo JA, Bajaj A. Clinical conundrums in management of sepsis in the elderly. *J. Transl. Int. Med.* 2015; **3**: 106–12.
16. Perera T, Cortijo-Brown A. Geriatric Resuscitation. *Emerg. Med. Clin. North Am.* 2016; **34**: 453–67.
17. Liang SY. Sepsis and other infectious disease emergencies in the elderly. *Emerg. Med. Clin. North Am.* 2016; **34**: 501–22.
18. Fernandez-Sabe N, Carratala J, Roson B *et al*. Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics, and outcomes. *Medicine* 2003; **82**: 159–69.
19. Marrie TJ. Community-acquired pneumonia in the elderly. *Clin. Infect. Dis.* 2000; **31**: 1066–78.
20. Conte HA, Chen YT, Mehal W, Scinto JD, Quagliarello VJ. A prognostic rule for elderly patients admitted with community-acquired pneumonia. *Am. J. Med.* 1999; **106**: 20–8.
21. Manabe T, Teramoto S, Tamiya N, Okochi J, Hizawa N. Risk factors for aspiration pneumonia in older adults. *PLoS One* 2015; **10**: e0140060.
22. Chong CP, Street PR. Pneumonia in the elderly: a review of the epidemiology, pathogenesis, microbiology, and clinical features. *South Med. J.* 2008; **101**: 1141–5.
23. Quagliarello V, Ginter S, Han L, Van Ness P, Allore H, Tinetti M. Modifiable risk factors for nursing home-acquired pneumonia. *Clin. Infect. Dis.* 2005; **40**: 1–6.
24. Nicolle LE. Asymptomatic bacteriuria in the elderly. *Infect. Dis. Clin. North Am.* 1997; **11**: 647–62.
25. Rodhe N, Lofgren S, Matussek A *et al*. Asymptomatic bacteriuria in the elderly: high prevalence and high turnover of strains. *Scand. J. Infect. Dis.* 2008; **40**: 804–10.
26. Hirschmann JV, Raugi GJ. Lower limb cellulitis and its mimics: part II. Conditions that simulate lower limb cellulitis. *J. Am. Acad. Dermatol.* 2012; **67**: 177 e1–9.
27. Shah K, Richard K, Edlow JA. Utility of lumbar puncture in the afebrile vs. febrile elderly patient with altered mental status: a pilot study. *J. Emerg. Med.* 2007; **32**: 15–8.
28. Podnos YD, Jimenez JC, Wilson SE. Intra-abdominal sepsis in elderly persons. *Clin. Infect. Dis.* 2002; **35**: 62–8.
29. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit. Care Med.* 1992; **20**: 864–74.
30. Singer M, Deutschman CS, Seymour CW *et al*. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016; **315**: 801–10.
31. Gonzalez Del Castillo J, Julian-Jimenez A, Gonzalez-Martinez F *et al*. Prognostic accuracy of SIRS criteria, qSOFA score and GYM score for 30-day-mortality in older non-severely dependent infected patients attended in the emergency department. *Eur. J. Clin. Microbiol. Infect. Dis.* 2017; **36**: 2361–9.
32. Macdonald SP, Arendts G, Fatovich DM, Brown SG. Comparison of PIRO, SOFA, and MEDS scores for predicting mortality in emergency department patients with severe sepsis and septic shock. *Acad. Emerg. Med.* 2014; **21**: 1257–63.
33. Shapiro NI, Howell MD, Talmor D, Donnino M, Ngo L, Bates DW. Mortality in emergency department sepsis (MEDS) score predicts 1-year mortality. *Crit. Care Med.* 2007; **35**: 192–8.
34. de Groot B, Stolwijk F, Warmerdam M *et al*. The most commonly used disease severity scores are inappropriate for risk stratification of older emergency department sepsis patients: an observational multi-centre study. *Scand. J. Trauma Resusc. Emerg. Med.* 2017; **25**: 91.
35. Poulsen JB, Moller K, Kehlet H, Perner A. Long-term physical outcome in patients with septic shock. *Acta Anaesthesiol. Scand.* 2009; **53**: 724–30.
36. El Solh AA, Akinnusi ME, Alsawalha LN, Pineda LA. Outcome of septic shock in older adults after implementation of the sepsis 'bundle'. *J. Am. Geriatr. Soc.* 2008; **56**: 272–8.
37. Seymour CW, Gesten F, Prescott HC *et al*. Time to treatment and mortality during mandated emergency care for sepsis. *N. Engl. J. Med.* 2017; **376**: 2235–44.
38. Rhodes A, Evans LE, Alhazzani W *et al*. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med.* 2017; **43**: 304–77.
39. de Groot B, Ansems A, Gerling DH *et al*. The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study. *Crit. Care* 2015; **19**: 194.
40. Waterer GW, Kessler LA, Wunderink RG. Delayed administration of antibiotics and atypical presentation in community-acquired pneumonia. *Chest* 2006; **130**: 11–5.
41. Marti C, John G, Genne D *et al*. Time to antibiotics administration and outcome in community-acquired pneumonia: secondary analysis of a randomized controlled trial. *Eur. J. Intern. Med.* 2017; **43**: 58–61.
42. Ferrer R, Martin-Loeches I, Phillips G *et al*. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from

the first hour: results from a guideline-based performance improvement program. *Crit. Care Med.* 2014; **42**: 1749–55.
43. Boyd JH, Sirounis D. Assessment of adequacy of volume resuscitation. *Curr. Opin. Crit. Care* 2016; **22**: 424–7.
44. Macdonald SPJ, Taylor DM, Keijzers G *et al.* REstricted Fluid REsuscitation in Sepsis-associated Hypotension (REFRESH): study protocol for a pilot randomised controlled trial. *Trials* 2017; **18**: 399.
45. Sekiguchi H, Harada Y, Villarraga HR, Mankad SV, Gajic O. Focused cardiac ultrasound in the early resuscitation of severe sepsis and septic shock: a prospective pilot study. *J. Anesth.* 2017; **31**: 487–93.
46. Asfar P, Meziani F, Hamel JF *et al.* High versus low blood-pressure target in patients with septic shock. *N. Engl. J. Med.* 2014; **370**: 1583–93.
47. Lamontagne F, Meade MO, Hebert PC *et al.* Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. *Intensive Care Med.* 2016; **42**: 542–50.