Sepsis in Older Adults in Long-Term Care Facilities: Challenges in Diagnosis and Management

Thomas T. Yoshikawa, MD, Bernardo J. Reyes, MD,† and Joseph G. Ouslander, MD†*

Despite the current understanding of the pathophysiology of sepsis and advances in its treatment, the rate of sepsis is increasing globally. Sepsis is a common cause of hospitalization in older adults, and infections are among the most common diagnoses among residents transferred to the hospital from long-term care facilities (LTCFs). LTCFs and hospitals are facing financial and regulatory requirements to reduce potentially preventable emergency department visits, hospitalizations, and hospital readmissions due to infections and other causes. In addition, the human and financial costs of these events are substantial. Current criteria for early identification of sepsis have low sensitivity and specificity among LTCF residents. Early diagnosis must focus on changes in clinical, mental, and functional status, and vital signs including pulse oximetry. Laboratory data can increase the suspicion of sepsis, but the availability of testing and timing of results limits its usefulness in most LTCFs.While new diagnostic criteria for sepsis are being developed and validated in the LTCF setting, clinical practice and decision support tools are available to guide management. Most LTFCs do not have the capabilities to manage sepsis based on current guidelines despite availability of qualified nursing staff and clinicians. Thus excluding circumstances in which a resident's desire is palliative or hospice care without transfer to a hospital, most LTCFs will continue to transfer residents with severe infections at risk for evolving into sepsis to an acute hospital setting. **J Am Geriatr Soc 67:2234-2239, 2019.**

From the *Geriatric and Extended Care Service, Department of Veterans Affairs Greater Los Angeles Healthcare System, and Department of Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; and the †Department of Integrated Medical Sciences, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, Florida.

Address correspondence to Bernardo Reyes, MD, Department of Integrated Medical Sciences, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL 33431. E-mail: reyesb@health.fau.edu

DOI: 10.1111/jgs.16194

BACKGROUND

The clinical syndrome of sepsis has been known for more than 2000 years. It was described by Hippocrates and Galen, and later better understood during the germ theory era by Ignaz Semmelweis, Joseph Lister, Robert Koch, and Louis Pasteur.[1] Despite current understanding of the microbiology and complex pathophysiology of sepsis, as well as therapeutic intervention of antibiotics, critical care unit patient monitoring, and infection control and preventive measures, the rate of sepsis appears to be increasing globally. More importantly, although the death rates per individual cases may be diminishing, the total number of deaths due to sepsis is increasing because more patients are affected.[2] Equally relevant is that sepsis occurs disproportionately in older adults with more than 50% of cases occurring in those aged 65 and older.[3,4] In addition, the outcomes of sepsis are worst in older adults, with higher rates of mortality, organ dysfunction, cognitive impairment, permanent disabilities, and long-term institutionalization.[5-7]

Data from the National Center for Health Statistics indicate the five most common causes of hospitalization for adults aged 85 and older are (in descending order)[1] congestive heart failure,[2] pneumonia,[3] urinary tract infection,[4] septicemia (sepsis), and stroke.[5] Infection, including sepsis, accounted for three of the five most frequent reasons for needing acute care admissions.[8,9] Such data support the observation that older adults residing in long-term care facilities (LTCFs; includes nursing homes, nursing facilities, and skilled nursing facilities) are at greater risk for infections and infections complicated by sepsis. LTCF residents, when compared with non-LTCF older adults, are 7 times more likely to have a sepsis diagnosis (14% vs 1.9%), have higher rates of intensive care unit admissions (40% vs 21%), longer hospital length of stay (median = 7 vs 5 d), and greater in-hospital mortality (37% vs 15%).[10]

PATHOPHYSIOLOGY OF SEPSIS AND THE IMPACT OF AGING

An excellent review on the pathophysiology of sepsis in older adults is available.[11] Briefly, it is now understood the sepsis syndrome is an inflammatory process as a result of a dysregulated immunologic response to different insults.

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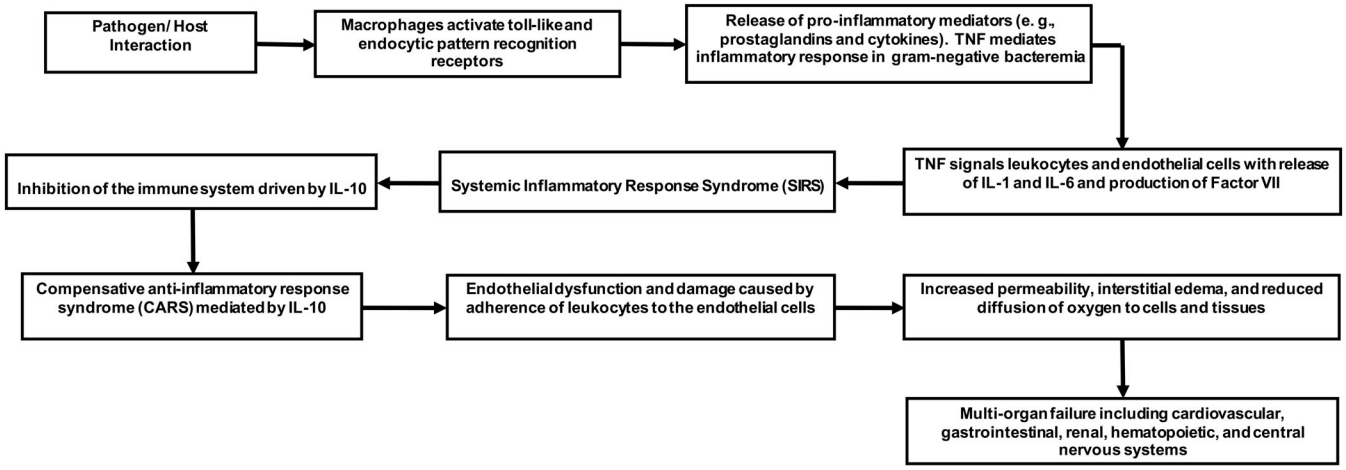

Figure 1. Pathophysiology of sepsis. IL, interleukin; TNF, tumor necrosis factor.

Figure 1 provides a summary of this pathophysiologic process. As inflammation becomes more systemic, neutrophils that adhere to endothelial cells are activated causing endothelial dysfunction and damage that results in fibrin deposition, increased permeability, interstitial edema, and reduced diffusion of oxygen to cells and tissues. Moreover, mitochondria have impaired oxygen metabolism causing cellular energy failure. Activation of the coagulation system and inhibition of the fibrinolytic pathway further enhance tissue hypoperfusion. If these processes are not halted, the alterations will lead to multiorgan failure including cardiovascular, gastrointestinal, renal, hematopoietic, and central nervous systems.[11]

With aging, all components of the immune system (innate immunity, T cells, B cells) are altered to some degree.[12] These age-related alterations may either enhance or fail to halt the processes involved in the sepsis syndrome. In addition, sepsis produces greater inhibition of the mitochondrial respiratory chain and more severe mitochondrial damage that leads to greater cellular apoptosis in older adults compared with young adults. The effects of aging on sepsis-associated apoptosis support the observation of increased incidence of multiorgan failure and death from sepsis in older adults.[12]

MAJOR ISSUES AND CHALLENGES OF DIAGNOSIS AND TREATMENT OF SEPSIS LTCFS

A 2018 editorial published[13] in response to a study using a variety of clinical tools and parameters to identify sepsis in LTCF residents before requiring hospitalization[14] outlined many important reasons why those who care for LTCF residents need to be aware and knowledgeable about early diagnosis and treatment of sepsis including the following:

1. The human and financial costs of emergency department visits, hospital admissions, and readmissions from LTCFs are substantial, with a significant proportion of them considered potentially avoidable.
2. As value-based payment models increase, LTCFs will need to be able to manage acute changes in condition without hospital transfer when clinically appropriate, safe, and feasible.
3. Infections that can lead to sepsis represent at least one-third of all readmissions from LTCFs, and infections including sepsis are the most common admitting diagnosis for residents transferred to the hospital from an LTCF.
4. New federal regulations require LTCFs to have an infection control practitioner and an antimicrobial stewardship program.

There are numerous challenges in diagnosis, decisions on site of management, and disposition of LTCF residents suspected or exhibiting clinical manifestations of sepsis. First, the definitions and criteria for sepsis have undergone several modifications. In the early 1990s, the definition of sepsis was limited to an inflammatory process related to infection that was called "sepsis" that could be complicated by organ dysfunction, called "severe sepsis," and "septic shock" if there was the presence of persistent tissue hypoperfusion (expressed in the form of hypotension, lactic acidosis, or need for vasopressors) despite appropriate fluid resucitation.[15-17]

The most recent definition of sepsis is the *presence of life-threatening organ dysfunction caused by a dysregulated host response to infection*, and the term "severe sepsis" is no longer used because organ dysfunction is a default state. The criteria to diagnose sepsis also have evolved in the past decades. One of the major limitations that clinicians face is that sepsis is a syndrome without a validated diagnostic test.[16] The previous diagnostic criteria for sepsis was based on the identification of an infection associated with the presence of two or more components of the systemic inflammatory response syndrome (SIRS) that included the presence of abnormalities in heart rate, respiratory rate, temperature, and white blood cell count.

By 2016, a task force proposed new criteria to diagnose sepsis based on the fact that SIRS had an "*excessive focus in inflammation*" instead of focusing on organ dysregulation caused by infection. For that reason, the same task force recommended the use of systemic organ failure assessment (SOFA) and its abbreviated version quick SOFA (qSOFA)[16] Since then, SOFA and qSOFA have become the standard to identify those at risk for adverse outcomes associated with sepsis.

Second, older patients frequently demonstrate atypical or absent clinical manifestations of diseases including infections.[18] Diseases may present simply as abnormalities in physical and/or cognitive function, rather than more specific manifestations of that particular disease or disorder. Residents in LTCFs are generally the most physically and cognitively

impaired, thus limiting the usefulness of clinical findings as signs or indicators of any underlying infection or sepsis syndrome. Moreover, regular and routine clinical assessment is not the norm for care provided in such settings. Vital signs are not performed daily in long-stay residents; nursing staff may not be adequately trained to identify early findings of an infection or sepsis; and clinicians (physicians, nurse practitioners, physician assistants) may not be immediately available on site to evaluate the resident to determine more carefully if an infection or sepsis is present.

Third, if either a known infection appears to be transforming into sepsis, or early findings suggestive of sepsis are noted in an LTCF resident, making decisions on the most appropriate disposition (ie, manage in-house or transfer the resident to an acute care facility) is a multifactorial and complex process. Issues to consider include these questions: (1) What is the clinical status and stability of the resident? (2) Does the facility have rapid access to needed laboratory tests and imaging studies? (3) Can the staff in the LTCF adequately assess and monitor the resident as well as provide necessary and appropriate therapeutic resources for managing serious infections and/or sepsis on a 24/7 basis? (4) Is there an advance directive that will assist in the level of healthcare intervention(s) that can be implemented in the resident?

These issues may seem incongruous to the mission of most LTCFs because (up to now) care in LTCFs was primarily focused on chronic care to promote function and quality of life, and short-term rehabilitation. However, due to changes in health policy and reimbursement, many LTCFs are accepting and caring for increasing numbers of patients discharged from the hospital who require subacute care including close monitoring and continuation of some level of acute therapies. These issues make early diagnosis and management of infections that may evolve into sepsis a significant challenge for LTCFs.

CLINICAL CHALLENGES IN EARLY DIAGNOSIS OF SEPSIS IN LTCF RESIDENTS

Early diagnosis of any disease including sepsis in older LTCF residents requires a different approach to clinical assessment. Because typical clinical manifestations of diseases are often not present in residents of LTCFs, the diagnostic paradigm must focus on *changes* in clinical and functional status and certain parameters ("vital parameters") including vital signs, pulse oximetry, mental status, and impairments of basic activities of daily living. Abnormalities of these vital parameters may not be consistently present in older adults. Hence it is essential to compare newly obtained vital parameters when the LTCF resident's clinical condition changes and determine whether there is a *change* from baseline vital parameters. A typical example is fever. A temperature of 100°F or higher is often considered a fever. However, it has been documented repeatedly that body temperature may not rise above accepted levels defined as fever in older LTCF residents.[19,20] When one examines if there is a change in body temperature (because baseline body temperature in older LTCF residents may be below 98°F), often a rise in body temperature is noted. If a body temperature increases 2°F from baseline, this is considered a "febrile" response.

Similarly, an older adult may have a baseline heart rate of 60 beats/minute and then experiences an increased heart rate to 90 beats/minute. The 90 beats/minute may not qualify as tachycardia based on standard criteria, yet the resident is experiencing a sudden increase in heart rate. Conversely, changes in some vital parameters may not be present when a resident becomes ill. For example, cardiac conduction disease and/or drug therapy (eg, β-blockers and cholinesterase inhibitors) may prevent tachycardia. In addition, certain laboratory parameters are commonly abnormal in older LTCF residents. Hence not only should clinicians in LTCFs evaluate for abnormal values in an LTCF resident's vital parameters when there appears to be a change in the resident's clinical condition, but also determine if there are changes in these vital parameters from baseline or conditions that may mask these changes from becoming clinically apparent.

The implications of these factors are critical for identifying infections that may evolve into sepsis. Current SIRS criteria require presence of suspected site infection (eg, cough, dysuria, cellulitis or wound, abdominal pain), and *abnormalities* of two[2] or more of the following parameters: body temperature, pulse, blood pressure, and respiratory rate (or oxygen saturation).[18] In the LTCF population, *changes* from baseline in these parameters could be considered rather than simply comparing them with published normal values. However, the qSOFA has not been validated in LTCFs, but a higher score is associated with mortality from sepsis.[21] A major limitation of qSOFA is that the Glasgow Coma Scale is not frequently used in LTCFs.[14] The "100-100-100" criteria have also been recommended to suspect "early sepsis," but its sensitivity only reaches 79% within the 12 hours preceding resident transfer to hospital due to sepsis.

Overall, the existing criteria to diagnose sepsis have significant limitations when they are used in LTCF settings. Although the use of changes in "vital parameters" has not been validated, the general concept of "change in condition" has proven to be sensitive enough for early identification of acute illness. Further studies are needed to identify which combination of "vital parameters" and/or changes in these parameters have the highest early sensitivity and specificity to diagnose sepsis in LTCFs. Such new criteria could be used by providers of different levels of training at the bedside.

In addition to vital parameters, baseline laboratory tests could be obtained including complete blood count with white blood cell differential count, blood urea nitrogen/serum creatinine, urinalysis, blood lactate (if available), and liver functions tests. Targeted imaging such as chest and abdominal radiographs could also help facilitate the diagnostic evaluation in those residents suspected of chest and/or abdominal pathologies. Nonetheless, timing of reporting results of tests is a common challenge in an LTCF. This is especially true for the less commonly ordered tests such as lactate levels that have been used as one of the diagnostic tests for sepsis and requires special collection techniques (Table 1).

Implementation of the suggested diagnostic interventions in LTCFs will require a different paradigm in LTCFs, if early diagnosis of sepsis or pre-sepsis is to be attained. Many LTCFs obtain routine vital signs weekly, and more often only when it is obvious there is a change in the resident's clinical status. However, given that clinical manifestations of an infection or sepsis may be atypical, delayed, or

Table 1. Steps of Appropriate Collection Techniques to Measure Serum Lactate[a]

- No tourniquet use
- Patient should be at complete rest avoiding exercise of the arm and hand before collecting sample
- Within 15 minutes of draw, separate the plasma by centrifugation for 10 minutes
- Immediately chill specimen after centrifuge

[a]Balakrishnan et al.[31]

absent in an LTCF resident, monitoring vital parameters on a more frequent schedule of all residents may be important in early identification of sepsis. Any notable changes identified by the nursing staff should prompt contacting a healthcare provider of these abnormalities. Criteria for changes that should prompt notification of a physician or advance practice clinician are available.[22-24] Because the treatment of sepsis requires resources that might not be available in LTCFs, efforts should focus on identifying those who could develop sepsis. As stated earlier, a major limitation is the lack of validated criteria to make early identification possible.

NEXT STEPS AND RECOMMENDATIONS

Clinicians in LTCFs clearly face a conundrum in managing infections and possible sepsis. LTCFs and hospitals are under increasing financial and regulatory requirements to reduce unnecessary emergency department visits, hospitalizations, and hospital readmissions. The Centers for Medicare & Medicaid Services is focusing on reducing potentially avoidable hospitalizations related to six conditions: pneumonia, urinary tract infections, congestive heart failure, dehydration, skin ulcers and cellulitis, and chronic obstructive lung disease and asthma. From a clinical standpoint, any of these conditions could lead to or be a manifestation of sepsis. In some instances, managing these conditions in the LTCF is safe and feasible. However, if the clinical conditions indicate greater severity, significant deviations of vital parameters from baseline, and/or the LTCF is not equipped (staff, laboratory tests, other resources) to manage such LTCF residents, then transfer to a higher level of care should be considered.

The main challenge that practitioners in LTCFs will encounter in the near future is the development of clinical tools for early and rapid identification of septic residents or those at risk for developing sepsis. Such tools should be sensitive enough to avoid delays in recognition and early treatment or transfer to an acute care facility, but specific enough to avoid unnecessary therapeutic interventions and/or transfers. Currently, available screening tests for sepsis such as the qSOFA as well as the "100-100-100 early detection tool"[14,21] have not been tested or validated extensively in the LTCF settings. In a recent retrospective study of 236 LTCF residents,[14] the sensitivity and specificity of several screening tools to identify nursing facility residents at high risk for developing sepsis 12 hours before hospitalization were examined. The most sensitive and specific screening tools were the 100-100-100 and qSOFA detection tools (Table 2). A major limitation of these findings is the small number of patients with sepsis included in the study, and the need to substitute the Glasgow Coma Scale for other nonstandardized assessments of mental status. Therefore, whether these or other screening tools can be validated in a prospective and larger study, particularly in an LTCF setting, remains to be determined. Serum level of procalcitonin was used as an indicator for respiratory infections and sepsis.[25,26] However, studies of procalcitonin in LTCF residents are too few to reach definitive conclusions.[27,28]

Figure 2 suggests a clinical approach and workflow for residents with suspected sepsis in LTCFs. The clinical practice and decision support tools from the Interventions to Reduce Acute Care Transfers (INTERACT) has resources to identify early changes in condition such the STOP and WATCH.[22] Although tools like the STOP and WATCH are very sensitive, their specificity is low. Once an resident is identified as having a change in condition, close observation and initial work-up should be in place to determine if such a change in condition is due to an infection or other causes such as dehydration. Until currently available screening tools are validated and/or better tools and data become available, one approach to the challenge of identifying and managing infections that might progress to sepsis is carefully assessing the *changes* in vital parameters (if such data are available) and /or applying qSOFA and 100-100-100 as early screening tools (the latter tools if all vital parameters are not readily available). Artificial intelligence was used to define differing phenotypes of sepsis, demonstrating the heterogeneity of the condition.[29] Use of artificial intelligence embedded in electronic medical records looking for changes in vital parameters by collecting and analyzing longitudinal data on routine assessments may play an important role in the early identification of risk for sepsis as well as a number of other conditions in the LTCF population.

In addition or concurrently, the INTERACT program[22] and other similar programs and tools[23,24] should be used when managing acute changes in condition in clinical practice and determining if and when antimicrobial treatment is indicated. As a practical matter, most LTCFs (even those with availability of qualified nurses, physicians, and advanced practice providers, and laboratory and pharmacy support) are not capable of implementing recommendations for the management of sepsis.[30] In most LTCFs, it is not possible to obtain rapid results for lactic acid, procalcitonin

Table 2. Sensitivity and Specificity of Established Criteria for Sepsis in Long-term Care Facilities[a]

Sepsis screening tool	13-72 h to hospitalization, %	≤12 h before hospitalization, %
SIRS		
Sensitivity for sepsis	10	36
Specificity for sepsis	94	86
qSOFA		
Sensitivity for sepsis	7	27
Specificity for sepsis	96	88
100-100-100		
Sensitivity for sepsis	28	79
Specificity for sepsis	84	69

Abbreviations: qSOFA, quick sequential organ failure assessment; SIRS, systemic inflammatory response syndrome.
[a]Sloane et al.[14]

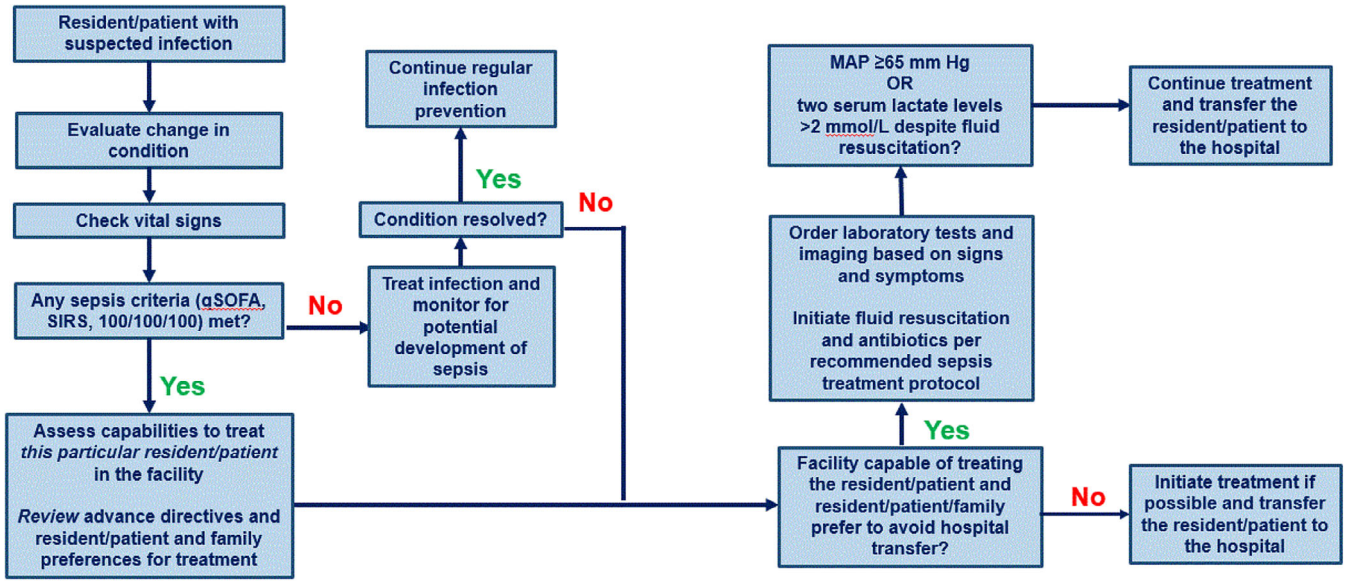

Figure 2. Clinical approach and workflow for patients with suspected sepsis in long-term care facilities. MAP, mean arterial pressure; qSOFA, quick sepsis-related organ failure, SIRS, systemic inflammatory response syndrome.

levels, and critical laboratory tests, to check frequent vital parameters, and to initiate within an hour and maintain intravenous fluids and antimicrobial agents in those critically ill LTCF residents. Thus unless a resident is terminally ill or on hospice care, has an advanced directive limiting hospitalization, or refuses to be transferred to the hospital, LTCFs should consider transferring residents with an infection that is at risk for evolving into sepsis to be managed in the hospital setting.

ACKNOWLEDGMENTS

Conflict of Interest: Joseph G. Ouslander is a full-time employee of Florida Atlantic University (FAU) and has received support through FAU for research on INTERACT from the National Institutes of Health, the Centers for Medicare & Medicaid Services, The Commonwealth Fund, the Retirement Research Foundation, the Florida Medical Malpractice Joint Underwriting Association, PointClickCare, Medline Industries, and Think Research. He and his wife had ownership interest in INTERACT Training, Education, and Management ("I TEAM") Strategies, LLC, which had a license agreement with FAU for use of INTERACT materials and trademark for training during the time of the study, and they now receive royalties from Pathway Health that currently holds the license. Dr. Ouslander serves as a paid advisor to Pathway Health, Think Research, and Curavi. Work on funded INTERACT research is subject to the terms of conflict of interest management plans developed and approved by the FAU Financial Conflict of Interest Committee. Thomas T. Yoshikawa and Bernardo J. Reyes have declared no conflicts of interests for this article.

Author Contributions: All the authors made substantial contributions to the conception and design, drafted the article and revised it critically for important intellectual content, and gave final approval of the version to be published.

Sponsor's Role: The authors did not receive funding support for their contributions.

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