Society of Critical Care Medicine and the Infectious Diseases Society of America Guidelines for Evaluating New Fever in Adult Patients in the ICU

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RATIONALE: Fever is frequently an early indicator of infection and often requires rigorous diagnostic evaluation.

OBJECTIVES: This is an update of the 2008 Infectious Diseases Society of America and Society (IDSA) and Society of Critical Care Medicine (SCCM) guideline for the evaluation of new-onset fever in adult ICU patients without severe immunocompromise, now using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.

PANEL DESIGN: The SCCM and IDSA convened a taskforce to update the 2008 version of the guideline for the evaluation of new fever in critically ill adult patients, which included expert clinicians as well as methodologists from the Guidelines in Intensive Care, Development and Evaluation Group. The guidelines committee consisted of 12 experts in critical care, infectious diseases, clinical microbiology, organ transplantation, public health, clinical research, and health policy and administration. All task force members followed all conflict-of-interest procedures as documented in the American College of Critical Care Medicine/SCCM Standard Operating Procedures Manual and the IDSA. There was no industry input or funding to produce this guideline.

METHODS: We conducted a systematic review for each population, intervention, comparison, and outcomes question to identify the best available evidence, statistically summarized the evidence, and then assessed the quality of evidence using the GRADE approach. We used the evidence-to-decision framework to formulate recommendations as strong or weak or as best-practice statements.

RESULTS: The panel issued 12 recommendations and 9 best practice statements. The panel recommended using central temperature monitoring methods, including thermistors for pulmonary artery catheters, bladder catheters, or esophageal balloon thermistors when these devices are in place or accurate temperature measurements are critical for diagnosis and management. For patients without these devices in place, oral or rectal temperatures over other temperature measurement methods that are less reliable such as axillary or tympanic membrane temperatures, noninvasive temporal artery thermometers, or chemical dot thermometers were recommended. Imaging studies including ultrasonography were recommended in addition to microbiological evaluation using rapid diagnostic testing strategies. Biomarkers were recommended to assist in guiding the discontinuation of antimicrobial therapy. All recommendations issued were weak based on the quality of data.

CONCLUSIONS: The guidelines panel was able to formulate several recommendations for the evaluation of new fever in a critically ill adult patient, acknowledging that most recommendations were based on weak evidence. This highlights the need for the rapid advancement of research in all aspects of this issue–including better noninvasive methods to measure core body temperature, the use of diagnostic imaging, advances in microbiology including molecular testing, and the use of biomarkers.

KEY WORDS: diagnosis; evaluation; fever; guidelines; infection; temperature measurement

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Fever, a frequent early indicator of infection, occurs in 26–88% of adult ICU patients, depending on the definition used and characteristics of the cohort studied (1). The range of potential etiologies of fever is vast and includes both infectious and noninfectious causes (2). Noninfectious causes of fever should be considered in the differential diagnosis (**Table 1**), but because early treatment initiation may improve outcomes of infections, initial evaluation of patients with new-onset fever is usually directed at potential microbial causes, and this is the primary focus of this guideline.

TABLE 1.
Noninfectious Causes of New Fever in ICU Patients

Acalculous Cholecystitis
Acute myocardial infarction
Adrenal insufficiency
Atelectasis
Blood product transfusion
Cytokine release syndrome
Dressler syndrome (pericardial injury syndrome)
Drug fever
Fat emboli
Fibroproliferative phase of acute respiratory distress syndrome
Gout
Heterotopic ossification
Immune reconstitution inflammatory syndrome
Intracranial bleed
Jarisch-Herxheimer reaction
Malignant hyperthermia
Neuroleptic malignant syndrome
Nonconvulsive status epilepticus
Pancreatitis
Pulmonary infarction
Pneumonitis without infection
Serotonin syndrome
Stroke
Thyroid storm
Transplant rejection
Tumor lysis syndrome
Venous thrombosis
Withdrawal from certain substances including alcohol, opiates, barbiturates, benzodiazepines

This is an update, now using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, of the 2008 Infectious Diseases Society of America and Society (IDSA) and Society of Critical Care Medicine (SCCM) guideline for the evaluation of new-onset fever in adult ICU patients without severe immunocompromise (3). Any recommendation from the 2008 guideline not specifically addressed in this update remains in place. In this document, we address microbiologic studies, imaging procedures, and the use of biomarkers in the diagnostic evaluation of fever with initial onset after ICU admission, focusing on detection of potential infectious etiologies. It should be noted that not all febrile episodes dictate a need for investigation, that is, those in which a noninfectious etiology is obvious such as fever occurring immediately in the postoperative state. For those fevers that do require investigation, a good history and physical examination will often reveal potential sources of infection. Diagnostic studies should then be sent with those potential sources in focus rather than reflexively sending cultures for all possible sources. Although much of this document and its recommendations may be applicable to severely immunocompromised patients, such as organ transplant recipients and those with severe neutropenia, these populations are not directly addressed here. The variability and complexities of different types of immunocompromise make this a task that cannot be accomplished in the context of a generally applicable guideline.

The guideline is intended for use by members of multidisciplinary care teams managing mixed populations of critically ill patients in the ICU, including intensivists, infectious diseases specialists, advanced practice providers, clinical pharmacists, nurses, respiratory therapists, and policymakers.

METHODOLOGY

The SCCM and IDSA reconvened a taskforce to update the 2008 version of the guideline for evaluation of new fever in critically ill adult patients (3). The taskforce included expert clinicians as well as methodologists from the Guidelines in Intensive Care, Development and Evaluation Group. The guidelines committee consisted of 12 experts in critical care, infectious diseases, clinical microbiology, organ transplantation,

public health, clinical research, and health policy and administration.

The panel was divided into five subgroups focusing on fever determination, treatment, imaging, microbiological evaluation, and rapid diagnostic testing. Group leaders were responsible to develop Population, Intervention, Comparison, and Outcomes (PICOs) questions for their group. The final list of PICO questions was approved by consensus of the taskforce members. The taskforce members then provided all potentially relevant outcomes for each PICO. Electronic voting was used to prioritize outcomes according to importance to patients and clinicians on a scale from 1 to 9 (not important to critical); only outcomes with an average score of 7 and above were selected. In all, 26 PICOs were included (**supplement**, http://links.lww.com/CCM/H386).

All task force members followed all conflict-of-interest procedures as documented in the American College of Critical Care Medicine (ACCM)/SCCM Standard Operating Procedures Manual and the IDSA. There was no industry input or funding to produce this guideline.

A professional medical librarian developed the search strategies for the PICO questions. We searched Cochrane Central and MEDLINE databases for relevant studies published in the English language from inception through December 2018. We updated the searches through June 2022 just before our final submission as recommended by the ACCM.

We aimed to include recent (10 yr old or less) relevant systematic reviews or update outdated reviews when newer data were available. In the absence of a published meta-analysis for a specific PICO question, we used the random-effects model to pool the effect sizes across randomized controlled trials (RCTs) or observational studies, when applicable. For interventions, we presented the pooled results as relative risk (RR) and 95% CI for binary outcomes and mean difference (MD) and 95% CI for continuous outcomes. All analyses were performed using RevMan software (Review Manager [RevMan] Version 5.4, The Cochrane Collaboration, 2020). For diagnostic tests, we used the random-effects bivariate analysis and hierarchical standard receiver operating curve (ROC) methods to present pooled sensitivity and specificity using Open Meta-Analyst software (Center for Evidence Synthesis in Health, Brown University; http://www.cebm.brown.edu/openmeta/doc/openMA_help.html#self) (4, 5).

Risk of bias for individual RCTs was assessed using the Cochrane Collaboration risk of bias assessment tool (6).

Guideline methodologists assessed the quality of the body of evidence using the GRADE methodology and rated quality as high, moderate, low, or very low based on the following domains: risk of bias, inconsistency, indirectness, imprecision, publication bias, and other criteria (7, 8). Methodologists used GRADEpro guideline development tool online software (https://gradepro.org/) to produce evidence summary tables (9).

We used the evidence-to-decision (EtD) framework to formulate recommendations. Recommendations and their respective EtD are provided in supplement (http://links.lww.com/CCM/H386). The task force met monthly and completed the electronic EtD forms for each PICO to formulate a recommendation. Factors considered when determining the direction and strength of recommendation were: quality of evidence, magnitude of effect, patient values and preferences, resources, cost, acceptability, and feasibility (10). For strong recommendations, we used the wording "we recommend" and for weak recommendations, we used "we suggest." When the taskforce was confident that desirable outweighed undesirable effects, a strong recommendation for an intervention was made while a strong recommendation against an intervention was made when undesirable outweighed desirable effects. A weak recommendation for or against an intervention was made when the taskforce was less confident about the balance between desirable and undesirable effects, respectively. Best-practice statements were made only when suggested GRADE criteria for best-practice statements were met (11). Best practice statements had to be clear, answer an important actionable question where the benefit would be unequivocally large, and evidence would be difficult to collect or summarize. An explicit rationale for the benefit was provided.

After finalizing a preliminary recommendation, members of the taskforce received electronic links to indicate their agreement or disagreement. Consensus required 80% agreement by at least 75% of the voting panel. Recommendations and best-practice statements are listed in **Table 2**.

TABLE 2.
Consensus Recommendations

1. Central temperature monitoring methods, including thermistors for pulmonary artery catheters, bladder catheters, or esophageal balloon thermistors, are preferred when these devices are in place or accurate temperature measurements are critical to diagnosis and management. For patients without these devices in place, we suggest using oral or rectal temperatures over other temperature measurement methods that are less reliable (such as axillary or tympanic membrane temperatures, noninvasive temporal artery thermometers, or chemical dot thermometers) (weak recommendation, very low-quality evidence).
2. For critically ill patients with fever, we suggest avoiding routine use of antipyretic medications for the specific purpose of reducing the temperature (weak recommendation, moderate quality evidence).
3. For critically ill patients with fever who value comfort by reducing temperature, we suggest using antipyretics over nonpharmacologic methods to reduce body temperature (weak recommendation, low-quality evidence).
4. For patients who develop fever during ICU stay, we recommend performing a chest radiograph (best-practice statement).
5. For patients who have recently undergone thoracic, abdominal, or pelvic surgery, we recommend performing CT (in collaboration with the surgical service) as part of a fever workup if an etiology is not readily identified by initial workup (best practice statement).
6. For critically ill patients with fever in whom other diagnostic tests have failed to establish an etiology, we suggest either performing an ^{18}F-fluorodeoxyglucose positron emission tomography/CT if the risk of transport is deemed acceptable (weak recommendation, very low-quality evidence).
7. The panel found insufficient evidence to issue a recommendation regarding the use of WBC scan for patients with fever without an established etiology.
8. For critically ill patients with fever and no abdominal signs or symptoms or liver function abnormalities, and no recent abdominal surgery, we recommend against the routine use of a regular abdominal ultrasound or point-of-care ultrasound (POCUS) as an initial investigation (best-practice statement).
9. In patients with fever and recent abdominal surgery or in any patient with either abdominal symptoms or suspicion of an abdominal source (e.g., abnormal physical examination/POCUS, increased transaminases, or alkaline phosphatase, and/or bilirubin), we recommend performing a formal bedside diagnostic ultrasound of the abdomen (best-practice statement).
10. For critically ill patients with fever and an abnormal chest radiograph, we suggest performing a thoracic bedside ultrasound when sufficient expertise is available to more reliably identify pleural effusions and parenchymal or interstitial lung pathology (weak recommendation, low-quality evidence).
11. Insufficient evidence was found to issue a recommendation regarding the use of thoracic bedside ultrasound for patients with fever without chest radiograph abnormalities.
12. For ICU patients with fever without an obvious source and who have a central venous catheter, we recommend simultaneous collection of central venous catheter and peripherally drawn blood cultures to allow calculation of differential time to positivity (Best practice statement).
13. In patients with fever in the ICU in whom central venous catheter cultures are indicated, we recommend sampling at least two lumens (best-practice statement).
14. For critically ill patients with a new fever of unclear origin, we suggest that if rapid molecular tests on blood are performed, they should only be used with concomitant blood cultures (weak recommendation, very low-quality evidence).
15. When performing blood cultures in adult ICU patients, we recommend collecting at least two sets of blood cultures (ideally 60 mL of blood total) one after the other, from different anatomical sites, without a time interval between them (best practice statement).
16. For febrile ICU patients with pyuria and in whom urinary tract infection is suspected, we recommend replacing the urinary catheter and obtaining urine cultures from the newly placed catheter (best-practice statement).
17. For critically ill patients with a new fever and suspected pneumonia, or new upper respiratory infection symptoms (e.g., cough), we suggest testing for viral pathogens using viral nucleic acid amplification test panels (weak recommendation, very low-quality evidence).

(*Continued*)

TABLE 2. (*Continued*)
Consensus Recommendations

18. There was insufficient evidence to allow a recommendation on performing routine blood testing for viral pathogens in immunocompetent patients in the ICU (e.g., herpesviruses, adenovirus).
19. For critically ill patients with a new fever, we recommend testing for severe acute respiratory syndrome coronavirus 2 by PCR based on levels of community transmission (best-practice statement).
20. If the probability of bacterial infection is deemed low to intermediate in a critically ill patient with a new fever and no clear focus of infection, we suggest measuring procalcitonin (PCT) in addition to bedside clinical evaluation vs bedside clinical evaluation alone (weak recommendation, very low-quality evidence).
21. If the probability of bacterial infection is deemed high in a critically ill patient with a new fever and no clear focus of infection, we suggest not measuring PCT to rule out bacterial infection. (Weak recommendation, very low-quality evidence).
22. If the probability of bacterial infection is deemed low to intermediate in a critically ill patient with a new fever and no clear focus of infection, we suggest measuring C-reactive protein (CRP) in addition to bedside clinical evaluation vs bedside clinical evaluation alone (weak recommendation, very low-quality evidence).
23. If the probability of bacterial infection is deemed high in a critically ill patient with a new fever and no clear focus of infection, we suggest not measuring CRP to rule out bacterial infection (weak recommendation, very low-quality evidence).
24. If the probability of bacterial infection is deemed low to intermediate in a critically ill patient with a new fever and no clear focus of infection, we suggest measuring serum PCT or CRP to rule out bacterial infection (weak recommendation, very low-quality evidence).

FEVER DEFINITION

The normal body temperature range is subject to a variety of factors such as age, gender, diurnal variation, and sampling site (12). In addition, evidence indicates that the normal body temperature has been decreasing in the human population by 0.03°C per birth decade over the last 157 years (13).

The United States Centers for Disease Control and Prevention definition of fever in the diagnosis of hospital-acquired infections is a measured temperature of greater than 38°C (14). The Infectious Diseases Society of America (IDSA) has defined fever in individuals greater than 65 years old residing in long-term care facilities as a single oral temperature greater than 37.8°C, repeated temperature measurements greater than 37.2°C (oral) or greater than 37.5°C (rectal), or an increase from baseline greater than 1.1°C (15). In patients with neutropenia due to chemotherapy, fever is defined by both the IDSA and the National Comprehensive Cancer Network as a single oral temperature measurement greater than or equal to 38.3°C or greater than 38.0°C sustained over at least 1 hour (16). The SCCM and IDSA have previously defined fever in ICU patients as the presence of a single temperature measurement greater than or equal to 38.3°C (3). We used this SCCM/IDSA definition of fever for this guideline.

Not all patients with infection manifest fever and, in fact, the absence of fever in patients with infection is associated with worse outcomes (17, 18). Consequently, the recommendations in this guideline may generally apply to ICU patients with suspected infection regardless of the presence of temperature elevation.

MEASURING BODY TEMPERATURE IN CRITICALLY ILL PATIENTS

Recommendation

1. Central temperature monitoring methods, including thermistors for pulmonary artery catheters, bladder catheters, or esophageal balloon thermistors, are preferred when these devices are in place or accurate temperature measurements are critical to diagnosis and management. For patients without these devices in place, we suggest using oral or rectal temperatures over other temperature measurement methods that are less reliable (such as axillary or tympanic membrane temperatures, noninvasive temporal artery thermometers, or chemical dot thermometers) (weak recommendation, very low-quality evidence).

Rationale: Any device used to measure temperature in a patient should provide reliable, reproducible, safe, and convenient results. This assumes that all devices are calibrated and maintained according to manufacturers' specifications. The thermistor of a pulmonary artery catheter, a bladder catheter, or an esophageal

probe is considered the gold standard method for measuring core body temperature to which other devices are compared (19–22). Many ICU patients will not have a device in place to directly measure core body temperature and will need to have temperature measurements taken by other devices.

The question as to agreement between peripheral (oral and tympanic membrane) and central thermometers was addressed by a meta-analysis published in 2015 (23). One finding was that nonvascular central thermometers (esophageal and bladder) had clinically acceptable limits of agreement with the pulmonary artery thermistors (23). Although this meta-analysis categorized rectal thermometers as central thermometers, rectal temperatures were found to be a few tenths of a degree different from the central temperature comparator and were not predictably consistent (23). Oral and tympanic membrane temperature measurements did not accurately estimate body temperature and were often 1 or 2 degrees higher or lower than the actual core body temperature. Both oral and tympanic membrane thermometers are poor screening tools for monitoring temperature (23).

When accurate temperature measurement will influence diagnosis and management, a central thermometer is preferred. A rectal thermometer could be used but is often impractical in the ICU setting. Oral measurements are safe and convenient for alert and cooperative patients, but these temperature measurements can be distorted by mouth breathing or hot or cold fluids or gases in or near the mouth. In critically ill patients, oral temperature measurements are often impractical due to endotracheal intubation or the inability of the patient to cooperate. Both thermometers are better than the alternatives when a central thermometer is not available.

Tympanic membrane temperature reflects the temperature of the hypothalamus (core). Through an otoscopic probe, infrared ear thermometry detects radiant energy and core body temperature. Multiple studies have shown consistently poor agreement between tympanic membrane thermometer measurements and pulmonary artery or esophageal thermistors (20–22, 24–28). Tympanic membrane thermometers are not accurate if there is inflammation or blockage of the auditory canal. Furthermore, there can be inaccurate readings obtained if the operator does not completely engage the otoscope with the tympanic membrane.

The same infrared technology used in tympanic membrane thermometers has been used in noninvasive temporal artery thermometers which provides an estimate of the core body temperature. These estimates have not been reliable (29), as they have been found to be influenced by environmental temperature and sweating, and like axillary measurements, they should not be relied on.

Chemical dot thermometers have been evaluated in critically ill intubated patients. These are single-use plastic strips with 50 heat-sensitive dots (temperature sensors) that represent temperature increments of 0.1 degrees. Inconsistent agreement between such devices and pulmonary catheter thermistors should limit their use in critically ill patients (27).

ANTIPYRETIC MEDICATION IN CRITICALLY ILL PATIENTS

Recommendations

2. For critically ill patients with fever, we suggest avoiding the routine use of antipyretic medications for the specific purpose of reducing the temperature (weak recommendation, moderate quality evidence).
3. For critically ill patients with fever who value comfort by reducing temperature, we suggest using antipyretic medications over nonpharmacologic methods to reduce body temperature (weak recommendation, low-quality evidence).

Rationale: In the ICU, fever is often therapeutically reduced to decrease metabolic demand, especially in critically ill patients with limited physiologic reserves (30). A systematic review and meta-analysis of 13 RCTs including 1,963 non-neurocritically ill patients were examined to inform these guidelines (31). Fever management reduced body temperature (8 RCTs, n = 1,139, MD –0.41; 95% CI [–0.66 to –0.16]; $p < 0.001$; I^2 = 94%, low quality), but did not improve 28-day mortality (11 RCTs, n = 1,745 patients, RR 1.03; 95% CI [0.79–1.35]; p = 0.82; I^2 = 45%, low quality), hospital mortality (3 RCT, n = 877, RR 0.97; 95% CI [0.73–1.30]; p = 0.85; I^2 = 0%, moderate quality) or shock reversal (2 RCTs, n = 229, RR 1.11; 95% CI [0.76–1.62]; p = 0.59; I^2 = 19%, very low quality). The panel issued a weak recommendation against the routine use of antipyretics in febrile ICU patients. However, in selected cases where patients or family members value reducing temperature for symptomatic relief, the panel issued a weak recommendation favoring the use of antipyretic medications to treat fever. In certain patient

populations, (neurologically injured or post cardiac arrest) the theoretical benefit of antipyretic therapy may outweigh the risk, but there is little evidence to support a recommendation for routine use of antipyretic medications in these populations.

IMAGING STUDIES IN CRITICALLY ILL PATIENTS WITH FEVER

Recommendations

4. For patients who develop a fever during ICU stay, we recommend performing a chest radiograph (best practice statement).

Rationale: No RCTs have been performed to examine the role of chest radiography in the diagnostic workup of febrile patients in the ICU. Imaging of the lungs is a component of the diagnosis of pneumonia in the ICU. Bedside chest radiography is a routinely available, low-cost, and noninvasive test. Pneumonia is a common cause of fever in patients in the ICU, and the most common infection in ICU patients who develop a fever (32). Therefore, it is reasonable to perform bedside chest radiography on most febrile ICU patients, especially when pneumonia is suspected. Patients for whom bedside chest radiography might not be indicated include those with a clear alternative source for fever, and those for whom higher quality chest imaging, such as multiple-view standing chest radiography or cross-sectional imaging, is available. A limitation of bedside chest radiography is the low positive predictive value of an abnormal result for diagnosis of pneumonia in ICU patients (33).

5. For patients who have recently undergone thoracic, abdominal, or pelvic surgery, we recommend performing CT (in collaboration with the surgical service) as part of a fever workup if an etiology is not readily identified by the initial workup (best-practice statement).

Rationale: There is insufficient evidence to allow for a recommendation to inform the diagnostic value of CT for the diagnosis of underlying causes of fever in ICU patients. However, there was consensus among the panel that it is reasonable for surgical patients to undergo CT imaging of the operative area when fever first occurs several days after surgery and an alternative cause is not readily identified. There is currently insufficient data regarding the timing of performing CT imaging in the immediate postoperative setting; this decision should be made in collaboration with the surgical services. Stability of the patient and risk of adverse events during transportation should be taken into consideration. In addition to surgical risk factors, indications for CT imaging in febrile ICU patients may include host factors such as immunocompromised state and for specific follow-up of abnormalities on plain radiography. A benefit of CT imaging is the potential to identify sources of fever for which direct diagnostic and/or therapeutic intervention is possible (e.g., percutaneous drainage of an intra-abdominal abscess) (34, 35).

6. For critically ill patients with fever in whom other diagnostic tests have failed to establish an etiology, we suggest performing an ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT if the risk of transport is deemed acceptable (weak recommendation, very low-quality evidence).
7. The panel found insufficient evidence to issue a recommendation regarding the use of WBC scans for patients with fever without an established etiology.

Rationale: Several studies evaluated the diagnostic value of nuclear imaging in the diagnosis of fever of unknown origin, with an estimated sensitivity of 85–100% and specificity of 23–90% (35, 36). None had a sufficient sample size of ICU patients with appropriate controls to allow for a recommendation (37, 38). Limited data including a small meta-analysis support the use of ^{18}F-FDG PET/CT in selected febrile ICU patients in whom other diagnostic workup has failed to reveal a source of fever (39, 40).

8. For critically ill patients with fever and no abdominal signs or symptoms or liver function abnormalities, and no recent abdominal surgery, we recommend against the routine use of a formal abdominal ultrasound or point-of-care ultrasound (POCUS) as an initial investigation (best practice statement).
9. In patients with fever and recent abdominal surgery or in any patient with either abdominal symptoms or suspicion of an abdominal source (e.g., abnormal physical examination/POCUS, increased transaminases, or alkaline phosphatase, and/or bilirubin), we recommend performing a formal bedside diagnostic ultrasound of the abdomen (best-practice statement).

Rationale: POCUS in critical care settings is a useful tool to further complement the physical examination, and its use is recommended when available. For guidance on how to best use general bedside ultrasound in critical ill patients, the reader is referred to dedicated guidelines (41). Diagnostic abdominal ultrasound has not been studied in the evaluation of fever in critically

ill patients, and the impact its routine use may provide when absent abdominal symptoms or liver test abnormalities are incompletely defined. Whether to pursue a diagnostic ultrasound or CT imaging first for critically ill patients with fever depends on various factors. Diagnostic ultrasound has advantages over other imaging modalities, including its lack of radiation, general availability, and safety. Its main disadvantages are a more limited abdominal evaluation, and the need for an onsite experienced sonographer, since competence and experience may influence results. Even though in general, ultrasonography has been considered a low-cost procedure, the need for onsite competence may translate into higher costs. Abdominal ultrasound can potentially diagnose acalculous cholecystitis, cholelithiasis, liver or kidney abscesses, perforated bowel, ascites, and/or appendicitis as potential sources of fever. In surgical patients, it can also identify surgical wound abscesses, and determine if they are amenable to drainage. Acalculous cholecystitis an important, albeit uncommon, cause of fever in critically ill patients, is frequently unrecognized (42). When there is right upper quadrant pain, this diagnosis may be suspected; however, this is commonly absent in critically ill patients. In patients with elevated alkaline phosphatase, or bilirubin, the use of abdominal ultrasound may be helpful in the diagnosis of the underlying cause of a febrile episode. In surgical patients, where the yield may be higher, it may help in identifying the source of the fever, or the need for another diagnostic procedure. There is a lack of data on false-positive and false-negative results from diagnostic abdominal ultrasound in patients with fever without abdominal signs or symptoms, precluding a firm recommendation to support the routine use of diagnostic abdominal ultrasound.

Recommendations

10. For critically ill patients with fever and an abnormal chest radiograph, we suggest performing a thoracic bedside ultrasound when sufficient expertise is available to reliably identify pleural effusions and parenchymal or interstitial lung pathology (weak recommendation, low-quality evidence).
11. Insufficient evidence was found to issue a recommendation regarding the use of thoracic bedside ultrasound for patients with fever without chest radiograph abnormalities.

Rationale: POCUS can improve reliability of the physical examination findings and in critical care settings is a useful tool to further complement the physical examination, and its use is recommended when available. Diagnostic lung ultrasound (LUS) has advantages over other imaging modalities, including its lack of radiation, safety, low cost, and accessibility. It has been studied systematically in the evaluation of critically ill patients with fever and respiratory symptoms (43). Studies have evaluated its use in the diagnosis of acute respiratory failure or suspected pneumonia in emergency departments (44–47). There have been some studies in critically ill patients, but none solely for the evaluation of fever (48, 49). LUS can detect parenchymal or interstitial lung pathology with reasonable sensitivity and specificity (41, 44–47). Sonographic consolidation is highly specific (50). LUS can also reliably identify pleural effusions, identify septations, and aid in sampling or drainage, if needed (41). However, unlike other imaging modalities, such as CT, LUS cannot visualize the entire lung, and in mechanically ventilated patients, evaluation is even more limited. The presence of atelectasis may lower specificity, and the competence and experience of the sonographer may influence results. In immunocompromised individuals, LUS may be insufficient to rule out pulmonary parenchymal disease, and CT imaging is preferable. However, in experienced hands, LUS can be superior (45, 46, 51) or complementary to conventional chest radiography for evaluation of pulmonary infiltrates, pleural effusions, or other thoracic processes in critically ill patients, and potentially carry a lower risk given that patient transport would not be needed. As such, it can be considered when sufficient expertise is available, as a safe imaging modality in patients with fever and an abnormal chest radiograph, regardless of respiratory symptoms. The role of the LUS in the evaluation of critically ill patients with fever without an abnormal chest radiograph has not been studied in clinical trials and as such its role is unclear; in such situations, its use could be considered on case-by-case basis.

BLOOD CULTURES IN CRITICALLY ILL PATIENTS WITH FEVER

Recommendations

12. For ICU patients with fever without an obvious source and who have a central venous catheter, we recommend simultaneous collection of central venous catheter and

peripherally drawn blood cultures to allow calculation of differential time to positivity (best practice statement).

Rationale: In general, collection of blood cultures through central venous catheters should be avoided, as central venous catheter-collected blood cultures are associated with higher rates of contamination than those collected by peripheral venipuncture. Contaminated blood cultures can be clinically confusing, potentially leading to overuse of antibiotics and drawing healthcare teams' attention away from actual causes of fever in patients in the ICU. Strategies to reduce the higher contamination rates from catheter blood cultures include use of antiseptic barrier caps on central venous catheter hubs and only obtaining cultures after the removal of the old needleless connector or through a new connector (52). Differential time to positivity (TTP) can be used to define catheter-associated bacteremia. Blood cultures are simultaneously collected via a central venous catheter and peripheral venipuncture; if both are ultimately positive for the same organism with the former being positive two or more hours earlier than the peripheral specimen, a diagnosis of catheter-associated bacteremia is supported (53–55). One meta-analysis showed high sensitivity/specificity of differential TTP overall (albeit lower performance with S. aureus bacteremia and candidemia) (56).

13. In patients with fever in the ICU in whom central venous catheter cultures are indicated, we recommend sampling at least two lumens (best-practice statement).

Rationale: Blood cultures collected through central venous catheters are associated with higher rates of contamination than those collected by venipuncture. However, in many ICU patients, multiple peripheral venipunctures are not feasible. One study showed that blood cultures should be collected through all catheter lumens to establish a diagnosis of catheter-related bloodstream infection; failure to separately collect blood from each lumen may lead to missed detection of bacteremia (57).

Recommendation

14. For critically ill patients with a new fever of unclear origin, we suggest that if rapid molecular tests on blood are performed, they should only be used with concomitant blood cultures (weak recommendation, very low-quality evidence).

Rationale: The traditional method to detect bacteria as well as *Candida* species and related yeasts in blood has been and remains conventional blood cultures. Some laboratories, investigators, and/or companies have developed rapid molecular and other tests for detecting bacteria in blood. In the studies reviewed, the sensitivity of such rapid tests was 83% (95% CI, 61–94%) and the specificity was 96% (95% CI, 84–99%) (58–67). In the United States, there are two Food and Drug Administration-cleared tests for rapid direct detection of bacteria or *Candida* species and related yeasts in blood, both from Ts2Biosystems (Lexington, MA), the T2Candida Panel which detects *Candida albicans, Candida tropicalis, Pichia kudriavzevii, Nakaseomyces glabrataa* and *Candida parapsilosis*, and the T2Bacteria panel which detects *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli*; results are generated in 3–5 hours. Other rapid direct-from blood nucleic acid amplification tests (NAATs) are available outside of the United States. An advantage of such tests is that they are more rapid than blood cultures; however, blood cultures are still needed because they detect a wider spectrum of microorganisms and yield isolates for susceptibility testing. Also, blood cultures are not always meaningful when deferred (e.g., while awaiting a positive or negative result from a rapid test) because antibiotics given in the interim may render them falsely negative. It is possible that NAATs may reveal a pathogen while blood cultures are negative because of antecedent antibiotic treatment; this may or may not be clinically helpful. Collecting a rapid direct-from blood NAAT plus blood cultures adds cost to care; value in febrile ICU patients should be demonstrated in implementation science studies. Ideally, rapid diagnostic tests should yield results in a shorter time than 3 hours, include a wider array of potential pathogens than currently available and provide information about antibiotic susceptibility; point-of-care diagnostics deployed near or in ICUs might be an interesting option. Implementation science studies of futuristic novel diagnostics are needed to demonstrate value.

Recommendation

15. When performing blood cultures in adult ICU patients, we recommend sequentially collecting at least two sets of blood cultures (ideally 60 mL of blood total), from different anatomical sites, without a time interval between them (Best practice statement).

Rationale: Blood cultures are the most used method to detect bacteria and *Candida* species and related yeasts in blood. Blood cultures should be properly collected, ideally via peripheral venipuncture, with appropriate skin preparation and preferably by a dedicated venipuncture team, to mitigate contamination (68). Proper filling of blood culture bottles (10 mL per bottle) is important; subpar filling can decrease yield. At a minimum, an aerobic and anaerobic bottle should be included in each set (69). At least two sets should be collected, each from a separate site, to help with interpretation of results, to provide sufficient blood for analysis, and to help in the identification of skin commensals. Contamination is likely if only a single blood culture set is positive for a microorganism that is a common contaminant (e.g., *Staphylococcus epidermidis*). Collection of blood cultures should not substantially delay (i.e., < 45 min in patients with sepsis) the start of antimicrobial therapy in febrile ICU patients if such therapy is indicated (70). Collection of two aerobic and one anaerobic blood culture bottles (i.e., three bottles) per set has been shown to improve yield compared to two bottles per set in a study population that did not exclusively involve febrile ICU patients (69). Blood culture sets may be collected sequentially (i.e., one after the other) without a purposeful pause between them (71).

CULTURING URINE

Recommendation

16. For febrile ICU patients with pyuria and in whom urinary tract infection (UTI) is suspected, we recommend replacing the urinary catheter and obtaining urine cultures from the newly placed catheter (best-practice statement).

Rationale: Although UTI can cause fever in ICU patients, members of the panel considered that the presence of urinary tract symptoms (if ascertainable)/signs and pyuria (defined as 5–10 WBC/hpf) on urinalysis should be used to justify urine culture. In cases of asymptomatic bacteriuria, positive urine cultures may lead to overuse of antibiotics and draw healthcare teams away from actual causes of fever in patients in ICUs. In those with urinary catheters, asymptomatic bacteriuria may result in false diagnoses of catheter-associated urinary tract infection (CAUTI), with potential effects on CAUTI reporting. In patients who are unable to attest to symptoms and have no other obvious source or suspicion of infection, the urinary catheter should be replaced. A urinalysis should be sent from a newly placed catheter and if WBCs are present, a urine culture should then be obtained (72).

TESTING FOR VIRAL PATHOGENS

Recommendation

17. For critically ill patients with new fever and suspected pneumonia, or new upper respiratory infection symptoms (e.g., cough), we suggest testing for viral pathogens using viral NAAT panels (weak recommendation, very low-quality evidence).

Rationale: It is important to diagnose the etiology of pneumonia so that treatment can be appropriately targeted, and appropriate strategies put into place to prevent transmission of infectious agents to healthcare providers and other patients. If there is concern about nosocomial acquisition based on local epidemiology, viral testing should be considered at any time during a patient's hospitalization. In patients with pneumonia, it is assumed that deep tracheal aspirates will be sent for bacterial stains and culture. Viral studies should also be conducted if pneumonia is considered, as viruses may coinfect patients with a bacterial etiology. The spectrum of viruses causing pneumonia in the ICU will vary based on patient-level details (e.g., immunization status, exposure history, underlying disease and immune system status, travel history), time of the year and even specific year, geographic location, and whether the patient is admitted with pneumonia directly to the ICU from the community, or instead has been hospitalized with a nonpneumonic illness before developing pneumonia. There are multiple viruses that can cause pneumonia in febrile patients in ICUs, including but not limited to influenza, respiratory syncytial virus, adenovirus, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and occasionally human metapneumovirus, seasonal coronaviruses, rhinovirus, parainfluenza virus, herpes simplex virus, cytomegalovirus, varicella-zoster virus, Middle East respiratory syndrome coronavirus, Sin Nombre virus, and measles virus, among others. Upper respiratory tract sampling is sufficient for most cases, but in some instances, viruses such as influenza viruses and SARS-CoV-2 may only be detected in lower respiratory tract samples, such as those obtained by bronchoalveolar lavage or endotracheal tube aspirate. There are many

commercial multiplex NAAT panels available for testing respiratory specimens; specific panel compositions vary, and clinicians will likely use the specific panel available at their center. Potential value of panel-based testing was recognized, as testing for viruses one-by-one will likely increase cost and oftentimes it is not clinically clear a priori which virus might be present. Users should be aware that not all potential causes of pneumonia are encompassed by such panels and that it is possible to detect viruses in a febrile ICU patient that are present but are noncontributory to patient's illness. Ideally, viral respiratory NAAT panels should be rapidly performed, with results used to rapidly direct appropriate use of antimicrobials; implementation science studies are needed to demonstrate safety and value of such an approach. The panel's summary of relevant literature is presented in the supplement (http://links.lww.com/CCM/H386) (73–84). Future implementation science studies should also evaluate the value of lower respiratory tract panels that include viruses, bacteria, and fungi, which were not analyzed here.

18. There was insufficient evidence to allow a recommendation on performing routine blood testing for viral pathogens in immunocompetent patients in the ICU (e.g., herpesviruses, adenovirus).

Rationale: Review of the literature did not identify a specific study that answered this question; hence, the panel was unable to issue a recommendation. In most adult patients in the ICU, fever is not related to systemic herpesvirus (e.g., herpes simplex virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus) or adenovirus infection, so blood testing for these viruses with NAATs is not indicated, although there was no study identified that specifically addressed this topic. And although asymptomatic CMV reactivation in immunocompetent ICU patients is increasingly recognized, treatment for CMV in this population does not improve outcomes.

RECOMMENDATION

19. For critically ill patients with a new fever, we recommend testing for SARS-CoV-2 by PCR based on levels of community transmission (best practice statement).

Rationale: Identifying patients infected or not infected with SARS-CoV-2 among those with fever and pneumonia in the ICU is important. Because of the concern of nosocomial acquisition, COVID-19 testing should be considered at any time during a patient's hospitalization. Testing for SARS-CoV-2 using a NAAT on a nasopharyngeal swab, mid-turbinate swab, anterior nasal swab, saliva, or a combined anterior nasal/oropharyngeal swab, and if negative and a COVID-19 lower respiratory tract infection is suspected, lower respiratory secretions (e.g., sputum, tracheal aspirate, bronchoalveolar lavage fluid) should be considered (85); the reader is referred to the COVID-19 molecular diagnostic testing guideline from the IDSA https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics (86).

RAPID BIOMARKER TESTING

Recommendations

20. If the probability of bacterial infection is deemed low to intermediate in a critically ill patient with a new fever and no clear focus of infection, we suggest measuring procalcitonin (PCT) in addition to bedside clinical evaluation versus bedside clinical evaluation alone (weak recommendation, very low-quality evidence).
21. If the probability of bacterial infection is deemed high in a critically ill patient with a new fever and no clear focus of infection, we suggest not measuring PCT to rule out bacterial infection (weak recommendation, very low-quality evidence).
22. If the probability of bacterial infection is deemed low to intermediate in a critically ill patient with a new fever and no clear focus of infection, we suggest measuring C-reactive protein (CRP) in addition to bedside clinical evaluation versus bedside clinical evaluation alone (weak recommendation, very low-quality evidence).
23. If the probability of bacterial infection is deemed high in a critically ill patient with a new fever and no clear focus of infection, we suggest not measuring CRP to rule out bacterial infection (weak recommendation, very low-quality evidence).
24. If the probability of bacterial infection is deemed low to intermediate in a critically ill patient with a new fever and no clear focus of infection, we suggest measuring either serum PCT or CRP to rule out bacterial infection (Weak recommendation, very low-quality evidence).

Rationale: Biomarkers such as PCT and CRP deployed with rapid turnaround times, have been used as adjuncts in the early diagnosis of sepsis while awaiting microbiologic culture results (87–89). When used in conjunction with clinical assessment, these biomarkers may guide antimicrobial therapy, especially its discontinuation, and thus reduce unnecessary antimicrobial exposure in hospitalized patients, including those in the ICU (90–93). To date, major guidelines

recommend against routine use of biomarkers in the setting of sepsis and septic shock, out of respect for uncertain benefit and cost and availability issues (94). In the setting of fever and lower likelihood of infection, however, there may be a role in obtaining a baseline value to assist in the discontinuation of antimicrobial therapy.

PCT is a precursor hormone of calcitonin produced by the parafollicular cells of the thyroid gland and neuroendocrine cells of the lung and the intestine that are thought to discriminate the systemic response due to bacterial causes from viral and noninfectious etiologies. More recent retrospective studies have shown that PCT may be elevated during severe viral illness including influenza and COVID-19, potentially making the discriminating power for predicting the causative microorganisms less useful (95–97). PCT begins to rise four hours after exposure to bacteria, reaching a maximum level after six to eight hours (98). Serum levels of PCT are associated with the severity of the infection, and decrease rapidly after antibiotic treatment (99). PCT test results are usually available within one hour with point-of-care testing devices or in routine laboratories. PCT values in healthy individuals are less than 0.05 ng/mL.

CRP is an acute-phase protein synthesized in the liver that rises in response to inflammation or infection because of its cell-membrane-binding capability which occurs following attachment to the phosphocholine in exposed cell membranes during cell injury, and phosphocholine in polysaccharides from cell envelopes of bacterial pathogens present in infections (100). Plasma CRP levels start to rise 12–24 hours after an acute inflammatory or infectious insult, reaching a maximum value after 48 hours. Levels of CRP are typically below 5 mg/L and the typical cutoff for CRP is 10 mg/L. Like PCT, CRP test results are available within minutes with point-of-care assays, or within an hour with laboratory-based assays. Laboratory assays are quantitative and therefore, suitable for the serial monitoring of patients (101, 102). Unlike PCT, CRP concentrations can be affected by neutropenia, immunodeficiency, and the use of nonsteroidal anti-inflammatory drugs.

In deciding whether to use CRP or PCT under these conditions, the literature does not strongly favor one over the other. A recent systematic review and meta-analysis evaluated the diagnostic accuracy of PCT and CRP in the diagnosis of sepsis in adults (103). Nine studies were analyzed, involving 495 patients in the sepsis and 873 in the nonsepsis groups. With regards to the diagnostic accuracy of PCT for sepsis, the overall area under the summary receiver operator characteristic (SROC) curve was 0.85 (95% CI, 0.82–0.88), with a sensitivity and specificity of 0.80 (95% CI, 0.69–0.87) and 0.77 (95% CI, 0.60–0.88), respectively, and a diagnostics odd ratio (DOR) of 12.50 (95% CI, 3.65–42.80). With CRP, the overall area under the SROC curve was 0.73 (95% CI, 0.69–0.77), with a sensitivity and specificity of 0.80 (95% CI, 0.63–0.90) and 0.61 (95% CI, 0.50–0.72), respectively, and a DOR of 6.89 (95% CI, 3.86–12.31). The authors concluded that there is a moderate degree of value of PCT and CRP for diagnosis of sepsis in adult patients, and that the diagnostic accuracy and specificity of PCT are higher than those of CRP. This systematic review and meta-analysis had limitations, including inclusion of various types of studies (prospective, retrospective, cross-sectional and cohort studies), differences in inclusion and exclusion criteria, use of only English or Chinese articles, use of pooled data and different cutoff values for PCT and CRP, and use of different sampling times of PCT and CRP (103). In addition, there was heterogeneity between the included studies for the pooled estimated diagnostic accuracy of CRP and PCT, which might be related to the different sepsis patient populations and states of illness. Further studies are needed to define the optimal cutoff points for PCT and CRP and the diagnostic indexes in different disease stages.

Several RCTs have demonstrated that PCT-based algorithms safely reduce antibiotic use in stable, low-risk patients with respiratory infections (104, 105). This use of PCT is different than our recommendations but can help with de-escalation. In ICU patients with suspected sepsis, clinicians should not initially withhold antibiotics, but PCT levels of less than 0.5 μg/L or levels that decrease by greater than or equal to 80% from peak levels may guide antibiotic discontinuation once patients stabilize (106–110). The Stop Antibiotics on Procalcitonin Guidance Study demonstrated a reduction in both antibiotic exposure and mortality in critically ill patients (110).

More recently, a meta-analysis of 11 RCTs involving 4,482 patients (111) reported that PCT-guided antibiotic treatment in ICU patients with infection and sepsis patients resulted in improved survival and lower antibiotic treatment duration. The latest and

largest systematic review and meta-analysis to date of 16 studies and greater than5000 patients showed that PCT-guided antibiotic discontinuation appeared to decrease antibiotic utilization by 1 day and improve mortality (112). However, support for their findings was tempered by low-certainty evidence given the substantial risk of bias, indirectness of effect, and unknown application of antibiotic stewardship programs in control arms. Also, the majority of the PCT trials excluded severely immunocompromised patients.

In summary, PCT and CRP provide only supportive and complementary information to clinical assessment. Decisions on initiating, altering, or discontinuing antimicrobial therapy should not be made solely based on changes in PCT or CRP levels. Measuring PCT or CRP in critically ill patients with a new fever and no clear focus of infection with low to intermediate clinical probability of bacterial infection is recommended in addition to bedside clinical evaluation, but not in patients with high clinical probability of bacterial infection.

CONCLUSIONS

Although important advances have been made in dealing with patients with new onset of fever while receiving critical care, knowledge gaps remain multiple and large. This demonstrates the need for rapid advancement of research in all aspects of this issue—including better noninvasive methods to measure core body temperature, the use of diagnostic imaging, advances in microbiology including molecular testing, and the use of biomarkers.

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REFERENCES

1. Egi M, Morita K: Fever in non-neurological critically ill patients: A systematic review of observational studies. *J Crit Care* 2012; 27:428–433
2. Achaiah NC, Ak AK: *Fever in the Intensive Care Patient*. In: *StatPearls* [Internet]. Treasure Island, FL, StatPearls Publishing, 2023
3. O'Grady NP, Barie PS, Bartlett JG, et al; American College of Critical Care Medicine: Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. *Crit Care Med* 2008; 36:1330–1349
4. Leeflang MM, Deeks JJ, Gatsonis C, et al; Cochrane Diagnostic Test Accuracy Working Group: Systematic reviews of diagnostic test accuracy. *Ann Intern Med* 2008; 149:889–897

5. Reitsma JB, Glas AS, Rutjes AW, et al: Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005; 58:982–990
6. Higgins JP, Altman DG, Gotzsche PC, et al; Cochrane Bias Methods Group: The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343:d5928
7. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group: GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336:924–926
8. Balshem H, Helfand M, Schunemann HJ, et al: GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; 64:401–406
9. Guyatt GH, Oxman AD, Santesso N, et al: GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *J Clin Epidemiol* 2013; 66:158–172
10. Andrews J, Guyatt G, Oxman AD, et al: GRADE guidelines: 14. Going from evidence to recommendations: The significance and presentation of recommendations. *J Clin Epidemiol* 2013; 66:719–725
11. Guyatt GH, Schunemann HJ, Djulbegovic B, et al: Guideline panels should not GRADE good practice statements. *J Clin Epidemiol* 2015; 68:597–600
12. Geneva II, Cuzzo B, Fazili T, et al: Normal body temperature: A systematic review. *Open Forum Infect Dis* 2019; 6:ofz032
13. Protsiv M, Ley C, Lankester J, et al: Decreasing human body temperature in the United States since the industrial revolution. *Elife* 2020; 9:e49555
14. Garner JS, Jarvis WR, Emori TG, et al: CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; 16:128–140
15. High KP, Bradley SF, Gravenstein S, et al: Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 48:149–171
16. Freifeld AG, Baden LR, Brown AE, et al; National Comprehensive Cancer Network: Fever and neutropenia clinical practice guidelines. *J Natl Compr Canc Netw* 2004; 2:390–432
17. Yamaga S, Shime N, Sonneville R, et al: Risk factors for sepsis-associated encephalopathy. *Intensive Care Med* 2017; 43:1548–1549
18. Kane WJ, Hassinger TE, Elwood NR, et al: Fever is associated with reduced mortality in trauma and surgical intensive care unit-acquired infections. *Surg Infect (Larchmt)* 2021; 22:174–181
19. Dinarello CA, Cannon JG, Wolff SM: New concepts on the pathogenesis of fever. *Rev Infect Dis* 1988; 10:168–189
20. Erickson RS, Kirklin SK: Comparison of ear-based, bladder, oral, and axillary methods for core temperature measurement. *Crit Care Med* 1993; 21:1528–1534
21. Erickson RS, Meyer LT: Accuracy of infrared ear thermometry and other temperature methods in adults. *Am J Crit Care* 1994; 3:40–54
22. Schmitz T, Bair N, Falk M, et al: A comparison of five methods of temperature measurement in febrile intensive care patients. *Am J Crit Care* 1995; 4:286–292
23. Niven DJ, Gaudet JE, Laupland KB, et al: Accuracy of peripheral thermometers for estimating temperature: A systematic review and meta-analysis. *Ann Intern Med* 2015; 163:768–777
24. Milewski A, Ferguson KL, Terndrup TE: Comparison of pulmonary artery, rectal, and tympanic membrane temperatures in adult intensive care unit patients. *Clin Pediatr (Phila)* 1991; 30(4 Suppl):13–16; discussion 34-15
25. Nierman DM: Core temperature measurement in the intensive care unit. *Crit Care Med* 1991; 19:818–823
26. Moran JL, Peter JV, Solomon PJ, et al: Tympanic temperature measurements: Are they reliable in the critically ill? A clinical study of measures of agreement. *Crit Care Med* 2007; 35:155–164
27. Farnell S, Maxwell L, Tan S, et al: Temperature measurement: Comparison of non-invasive methods used in adult critical care. *J Clin Nurs* 2005; 14:632–639
28. Poveda VB, Nascimento AS: Intraoperative body temperature control: Esophageal thermometer versus infrared tympanic thermometer. *Rev Esc Enferm USP* 2016; 50:946–952
29. Furlong D, Carroll DL, Finn C, et al: Comparison of temporal to pulmonary artery temperature in febrile patients. *Dimens Crit Care Nurs* 2015; 34:47–52
30. Young P, Saxena M, Bellomo R, et al; HEAT Investigators: Acetaminophen for fever in critically ill patients with suspected infection. *N Engl J Med* 2015; 373:2215–2224
31. Sakkat A, Alquraini M, Aljazeeri J, et al: Temperature control in critically ill patients with fever: A meta-analysis of randomized controlled trials. *J Crit Care* 2021; 61:89–95
32. Vincent JL, Rello J, Marshall J, et al; EPIC II Group of Investigators: International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; 302:2323–2329
33. Fernando SM, Tran A, Cheng W, et al: Diagnosis of ventilator-associated pneumonia in critically ill adult patients—a systematic review and meta-analysis. *Intensive Care Med* 2020; 46:1170–1179
34. Barkhausen J, Stoblen F, Dominguez-Fernandez E, et al: Impact of CT in patients with sepsis of unknown origin. *Acta Radiol* 1999; 40:552–555
35. Velmahos GC, Kamel E, Berne TV, et al: Abdominal computed tomography for the diagnosis of intra-abdominal sepsis in critically injured patients: Fishing in murky waters. *Arch Surg* 1999; 134:831–836; discussion 836-838
36. Lee SW, Kim SJ, Seo Y, et al: F-18 FDG PET for assessment of disease activity of large vessel vasculitis: A systematic review and meta-analysis. *J Nucl Cardiol* 2019; 26:59–67
37. Kampe KK, Rotermund R, Tienken M, et al: Diagnostic value of positron emission tomography combined with computed tomography for evaluating critically ill neurological patients. *Front Neurol* 2017; 8:33
38. Kluge S, Braune S, Nierhaus A, et al: Diagnostic value of positron emission tomography combined with computed tomography for evaluating patients with septic shock of unknown origin. *J Crit Care* 2012; 27:316.e1–316.e7
39. Huang CK, Huang JY, Ruan SY, et al: Diagnostic performance of FDG PET/CT in critically ill patients with suspected infection: A systematic review and meta-analysis. *J Formos Med Assoc* 2020; 119:941–949

40. Simons KS, Pickkers P, Bleeker-Rovers CP, et al: F-18-fluorodeoxyglucose positron emission tomography combined with CT in critically ill patients with suspected infection. *Intensive Care Med* 2010; 36:504–511
41. Frankel HL, Kirkpatrick AW, Elbarbary M, et al: Guidelines for the appropriate use of bedside general and cardiac ultrasonography in the evaluation of critically ill patients—Part I: General ultrasonography. *Crit Care Med* 2015; 43:2479–2502
42. Treinen C, Lomelin D, Krause C, et al: Acute acalculous cholecystitis in the critically ill: Risk factors and surgical strategies. *Langenbecks Arch Surg* 2015; 400:421–427
43. Winkler MH, Touw HR, van de Ven PM, et al: Diagnostic accuracy of chest radiograph, and when concomitantly studied lung ultrasound, in critically ill patients with respiratory symptoms: A systematic review and meta-analysis. *Crit Care Med* 2018; 46:e707–e714
44. Staub LJ, Mazzali Biscaro RR, Kaszubowski E, et al: Lung ultrasound for the emergency diagnosis of pneumonia, acute heart failure, and exacerbations of chronic obstructive pulmonary disease/asthma in adults: A systematic review and meta-analysis. *J Emerg Med* 2019; 56:53–69
45. Chavez MA, Shams N, Ellington LE, et al: Lung ultrasound for the diagnosis of pneumonia in adults: A systematic review and meta-analysis. *Respir Res* 2014; 15:50
46. Ye X, Xiao H, Chen B, et al: Accuracy of lung ultrasonography versus chest radiography for the diagnosis of adult community-acquired pneumonia: Review of the literature and meta-analysis. *PLoS One* 2015; 10:e0130066
47. Long L, Zhao HT, Zhang ZY, et al: Lung ultrasound for the diagnosis of pneumonia in adults: A meta-analysis. *Medicine (Baltim)* 2017; 96:e5713
48. Lichtenstein DA, Lascols N, Meziere G, et al: Ultrasound diagnosis of alveolar consolidation in the critically ill. *Intensive Care Med* 2004; 30:276–281
49. Mongodi S, Via G, Girard M, et al: Lung ultrasound for early diagnosis of ventilator-associated pneumonia. *Chest* 2016; 149:969–980
50. Bach PB, Schrag D, Nierman DM, et al: Identification of poor prognostic features among patients requiring mechanical ventilation after hematopoietic stem cell transplantation. *Blood* 2001; 98:3234–3240
51. Hew M, Corcoran JP, Harriss EK, et al: The diagnostic accuracy of chest ultrasound for CT-detected radiographic consolidation in hospitalised adults with acute respiratory failure: A systematic review. *BMJ Open* 2015; 5:e007838
52. Mermel LA: Drawing blood cultures through intravascular catheters: Controversy and update. *Infect Control Hosp Epidemiol* 2019; 40:457–459
53. Raad I, Hanna HA, Alakech B, et al: Differential time to positivity: A useful method for diagnosing catheter-related bloodstream infections. *Ann Intern Med* 2004; 140:18–25
54. Mermel LA, Allon M, Bouza E, et al: Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 49:1–45
55. Buetti N, Marschall J, Drees M, et al: Strategies to prevent central line-associated bloodstream infections in acute-care hospitals: 2022 update. *Infect Control Hosp Epidemiol* 2022; 43:553–569
56. Dhaliwal M, Daneman N: Utility of differential time to positivity in diagnosing central line associated bloodstream infections: A systematic review and meta-analysis. *Clin Infect Dis* 2023:ciad225
57. Guembe M, Rodriguez-Creixems M, Sanchez-Carrillo C, et al: How many lumens should be cultured in the conservative diagnosis of catheter-related bloodstream infections? *Clin Infect Dis* 2010; 50:1575–1579
58. Bloos F, Bayer O, Sachse S, et al: Attributable costs of patients with candidemia and potential implications of polymerase chain reaction-based pathogen detection on antifungal therapy in patients with sepsis. *J Crit Care* 2013; 28:2–8
59. Bloos F, Sachse S, Kortgen A, et al: Evaluation of a polymerase chain reaction assay for pathogen detection in septic patients under routine condition: An observational study. *PLoS One* 2012; 7:e46003
60. Ginn AN, Hazelton B, Shoma S, et al: Quantitative multiplexed-tandem PCR for direct detection of bacteraemia in critically ill patients. *Pathology (Phila)* 2017; 49:304–308
61. Gupta MD, Kaur H, Ray P, et al: Ribosomal RNA-based pan-bacterial polymerase chain reaction for rapid diagnosis of septicaemia in intensive care unit patients. *Indian J Med Microbiol* 2016; 34:219–221
62. McCann CD, Moore MS, May LS, et al: Evaluation of real-time PCR and pyrosequencing for screening incubating blood culture bottles from adults with suspected bloodstream infection. *Diagn Microbiol Infect Dis* 2015; 81:158–162
63. McMullan R, Metwally L, Coyle PV, et al: A prospective clinical trial of a real-time polymerase chain reaction assay for the diagnosis of candidemia in nonneutropenic, critically ill adults. *Clin Infect Dis* 2008; 46:890–896
64. McMullan R, Metwally L, Troughton JA, et al: The impact of a PCR assay for candidemia on antifungal drug prescribing in critical care: An interrupted time series pilot study. *J Infect* 2010; 61:81–85
65. Moore MS, McCarroll MG, McCann CD, et al: Direct screening of blood by PCR and pyrosequencing for a 16S rRNA gene target from emergency department and intensive care unit patients being evaluated for bloodstream infection. *J Clin Microbiol* 2016; 54:99–105
66. Peters RP, van Agtmael MA, Gierveld S, et al: Quantitative detection of Staphylococcus aureus and Enterococcus faecalis DNA in blood to diagnose bacteremia in patients in the intensive care unit. *J Clin Microbiol* 2007; 45:3641–3646
67. Rowther FB, Rodrigues CS, Deshmukh MS, et al: Prospective comparison of eubacterial PCR and measurement of procalcitonin levels with blood culture for diagnosing septicemia in intensive care unit patients. *J Clin Microbiol* 2009; 47:2964–2969
68. He M, Huang S, Xiong J, et al: Improving adherence to facility protocol and reducing blood culture contamination in an intensive care unit: A quality improvement project. *Aust Crit Care* 2020; 33:546–552
69. Patel R, Vetter EA, Harmsen WS, et al: Optimized pathogen detection with 30- compared to 20-milliliter blood culture draws. *J Clin Microbiol* 2011; 49:4047–4051

70. Alhazzani W, Lewis K, Jaeschke R, et al: Conflicts of interest disclosure forms and management in critical care clinical practice guidelines. *Intensive Care Med* 2018; 44:1691–1698
71. Miller JM, Binnicker MJ, Campbell S, et al: A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 update by the Infectious Diseases Society of America and the American Society for Microbiology. *Clin Infect Dis* 2018; 67:813–816
72. Hooton TM, Bradley SF, Cardenas DD, et al; Infectious Diseases Society of America: Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis* 2010; 50:625–663
73. Cameron RJ, de Wit D, Welsh TN, et al: Virus infection in exacerbations of chronic obstructive pulmonary disease requiring ventilation. *Intensive Care Med* 2006; 32:1022–1029
74. Legoff J, Zucman N, Lemiale V, et al: Clinical significance of upper airway virus detection in critically ill hematology patients. *Am J Respir Crit Care Med* 2019; 199:518–528
75. Vanspauwen MJ, van Mook WN, Bruggeman CA, et al: Human metapneumovirus in bronchoalveolar lavage fluid of critically ill patients with suspected pneumonia. *Intensive Care Med* 2012; 38:728–729
76. Smith CA, Conroy LT, Pollock M, et al: Detection of herpes viruses in respiratory secretions of patients undergoing artificial ventilation. *J Med Virol* 2010; 82:1406–1409
77. Schnell D, Legoff J, Mariotte E, et al: Molecular detection of respiratory viruses in immunocopromised ICU patients: Incidence and meaning. *Respir Med* 2012; 106:1184–1191
78. Siow WT, Koay ES, Lee CK, et al: The use of polymerase chain reaction amplification for the detection of viruses and bacteria in severe community-acquired pneumonia. *Respiration* 2016; 92:286–294
79. Schnell D, Gits-Muselli M, Canet E, et al: Burden of respiratory viruses in patients with acute respiratory failure. *J Med Virol* 2014; 86:1198–1202
80. Daubin C, Vincent S, Vabret A, et al: Nosocomial viral ventilator-associated pneumonia in the intensive care unit: A prospective cohort study. *Intensive Care Med* 2005; 31:1116–1122
81. Legoff J, Guerot E, Ndjoyi-Mbiguino A, et al: High prevalence of respiratory viral infections in patients hospitalized in an intensive care unit for acute respiratory infections as detected by nucleic acid-based assays. *J Clin Microbiol* 2005; 43:455–457
82. Loubet P, Voiriot G, Houhou-Fidouh N, et al: Impact of respiratory viruses in hospital-acquired pneumonia in the intensive care unit: A single-center retrospective study. *J Clin Virol* 2017; 91:52–57
83. Lopez Roa P, Rodriguez-Sanchez B, Catalan P, et al: Diagnosis of influenza in intensive care units: Lower respiratory tract samples are better than nose-throat swabs. *Am J Respir Crit Care Med* 2012; 186:929–930
84. Piralla A, Mariani B, Rovida F, et al: Frequency of respiratory viruses among patients admitted to 26 intensive care units in seven consecutive winter-spring seasons (2009-2016) in Northern Italy. *J Clin Virol* 2017; 92:48–51
85. Boger B, Fachi MM, Vilhena RO, et al: Systematic review with meta-analysis of the accuracy of diagnostic tests for COVID-19. *Am J Infect Control* 2021; 49:21–29
86. Hanson KE, Caliendo AM, Arias CA, et al: The Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: Molecular diagnostic testing. *Clin Infect Dis* 2021:ciab048
87. Wacker C, Prkno A, Brunkhorst FM, et al: Procalcitonin as a diagnostic marker for sepsis: A systematic review and meta-analysis. *Lancet Infect Dis* 2013; 13:426–435
88. Gupta BK, Das BP, Mhaske VR, et al: Diagnostic accuracy of various biomarkers of sepsis (Serum Pro-Calcitonin, High-Sensitivity C-reactive Protein, and C-reactive Protein) and band cell percentage in critically Ill patients: A prospective, observational, cohort study. *Anesth Essays Res* 2020; 14:615–619
89. Leticia Fernandez-Carballo B, Escadafal C, MacLean E, et al: Distinguishing bacterial versus non-bacterial causes of febrile illness—a systematic review of host biomarkers. *J Infect* 2021; 82:1–10
90. Schuetz P, Briel M, Christ-Crain M, et al: Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: An individual patient data meta-analysis. *Clin Infect Dis* 2012; 55:651–662
91. Heyland DK, Johnson AP, Reynolds SC, et al: Procalcitonin for reduced antibiotic exposure in the critical care setting: A systematic review and an economic evaluation. *Crit Care Med* 2011; 39:1792–1799
92. Elnajdy D, El-Dahiyat F: Antibiotics duration guided by biomarkers in hospitalized adult patients; A systematic review and meta-analysis. *Infect Dis (Lond)* 2022; 54:387–402
93. Arulkumaran N, Khpal M, Tam K, et al: Effect of antibiotic discontinuation strategies on mortality and infectious complications in critically ill septic patients: A meta-analysis and trial sequential analysis. *Crit Care Med* 2020; 48:757–764
94. Evans L, Rhodes A, Alhazzani W, et al: Surviving sepsis campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Crit Care Med* 2021; 49:e1063–e1143
95. Gautam S, Cohen AJ, Stahl Y, et al: Severe respiratory viral infection induces procalcitonin in the absence of bacterial pneumonia. *Thorax* 2020; 75:974–981
96. Carbonell R, Moreno G, Martin-Loeches I, et al: Prognostic value of procalcitonin and C-reactive protein in 1608 critically ill patients with severe influenza pneumonia. *Antibiotics (Basel)* 2021; 10:350
97. Tong-Minh K, van der Does Y, Engelen S, et al: High procalcitonin levels associated with increased intensive care unit admission and mortality in patients with a COVID-19 infection in the emergency department. *BMC Infect Dis* 2022; 22:165
98. Hamade B, Huang DT: Procalcitonin: Where are we now? *Crit Care Clin* 2020; 36:23–40
99. Paudel R, Dogra P, Montgomery-Yates AA, et al: Procalcitonin: A promising tool or just another overhyped test? *Int J Med Sci* 2020; 17:332–337
100. Volanakis JE: Human C-reactive protein: Expression, structure, and function. *Mol Immunol* 2001; 38:189–197
101. Vallance H, Lockitch G: Rapid, semi-quantitative assay of C-reactive protein evaluated. *Clin Chem* 1991; 37:1981–1982
102. Zecca E, Barone G, Corsello M, et al: Reliability of two different bedside assays for C-reactive protein in newborn infants. *Clin Chem Lab Med* 2009; 47:1081–1084

103. Tan M, Lu Y, Jiang H, et al: The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: A systematic review and meta-analysis. *J Cell Biochem* 2019; 120:5852–5859
104. Christ-Crain M, Stolz D, Bingisser R, et al: Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: A randomized trial. *Am J Respir Crit Care Med* 2006; 174:84–93
105. Schuetz P, Christ-Crain M, Thomann R, et al; ProHOSP Study Group: Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: The ProHOSP randomized controlled trial. *JAMA* 2009; 302:1059–1066
106. Hochreiter M, Kohler T, Schweiger AM, et al: Procalcitonin to guide duration of antibiotic therapy in intensive care patients: A randomized prospective controlled trial. *Crit Care* 2009; 13:R83
107. Schroeder S, Hochreiter M, Koehler T, et al: Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: Results of a prospective randomized study. *Langenbecks Arch Surg* 2009; 394:221–226
108. Bouadma L, Luyt CE, Tubach F, et al; PRORATA trial group: Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): A multicentre randomised controlled trial. *Lancet* 2010; 375:463–474
109. Shehabi Y, Sterba M, Garrett PM, et al; ProGUARD Study Investigators: Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. *Am J Respir Crit Care Med* 2014; 190:1102–1110
110. de Jong E, van Oers JA, Beishuizen A, et al: Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: A randomised, controlled, open-label trial. *Lancet Infect Dis* 2016; 16:819–827
111. Wirz Y, Meier MA, Bouadma L, et al: Effect of procalcitonin-guided antibiotic treatment on clinical outcomes in intensive care unit patients with infection and sepsis patients: A patient-level meta-analysis of randomized trials. *Crit Care* 2018; 22:191
112. Pepper DJ, Sun J, Rhee C, et al: Procalcitonin-guided antibiotic discontinuation and mortality in critically ill adults: A systematic review and meta-analysis. *Chest* 2019; 155:1109–1118