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D. C. Richter[1] · A. Heininger[2] · T. Brenner[1] · M. Hochreiter[1] · M. Bernhard[3] · J. Briegel[4] · S. Dubler[1] · B. Grabein[5] · A. Hecker[6] · W. A. Kruger[7] · K. Mayer[8] · M. W. Pletz[9] · D. Storzinger[8] · N. Pinder[8] · T. Hoppe-Tichy[2] · S. Weiterer[1] · S. Zimmermann[2] · A. Brinkmann[10] · M. A. Weigand[1] · C. Lichtenstern[1]

[1] Department of Anesthesiology, Heidelberg University Hospital, Heidelberg, Germany
[2] Zentrum für Infektiologie, Sektion für Krankenhaus- und Umwelthygiene, Universitätsklinikum Heidelberg, Heidelberg, Germany
[3] Zentrale Notaufnahme, Universitätsklinikum Leipzig, Leipzig, Germany
[4] Klinik für Anästhesiologie, Klinikum der Universität München, München, Germany
[5] Stabsstelle "Klinische Mikrobiologie und Krankenhaushygiene", Klinikum der Universität München, München, Germany
[6] Klinik für Allgemein-, Viszeral-, Thorax-, Transplantations- und Kinderchirurgie, Universitätsklinikum Gießen und Marburg, Standort Gießen, Gießen, Germany
[7] Klinik für Anästhesiologie und operative Intensivmedizin, Gesundheitsverbund Landkreis Konstanz, Klinikum Konstanz, Konstanz, Germany
[8] Apotheke, Universitätsklinikums Heidelberg, Heidelberg, Germany
[9] Zentrum für Infektionsmedizin und Krankenhaushygiene, Universitätsklinikum Jena, Jena, Germany
[10] Klinik für Anästhesie, operative Intensivmedizin und spezielle Schmerztherapie, Klinikum Heidenheim, Heidenheim, Germany

Bacterial sepsis

Diagnostics and calculated antibiotic therapy

Principles

Diagnostic criteria

Early diagnosis and rapid initiation of treatment are crucial factors in the treatment of sepsis and septic shock. Despite detailed criteria, establishment of diagnosis based on the classical systemic inflammatory response syndrome (SIRS) concept was associated with relevant problems and gray areas, which led to an underestimation of the disease [1]. For example, the retrospective analysis conducted by Kaukonen et al. [2], including a total of 109,663 patients, revealed that 12.5% of patients—despite severe infection and new-onset organ disfunction—did not fulfil the necessary SIRS criteria (according to SEPSIS-1 [3]) and the "sepsis" diagnosis was not established. Vice versa, an array of patients fulfilled the SIRS criteria at some point during their period of hospitalization, without ever developing a relevant infection or showing an associated increased mortality [4, 5]. Due to the poor validity of the SIRS concept (SEPSIS-1/2) and the demand for more sensitive diagnostic criteria, during The Third International Consensus Conference on the Definition of Sepsis and Septic Shock (SEPSIS-3), simplified and (presumably) more feasible diagnostic criteria were established. According to the SEPSIS-3 task force, high-risk patients can be identified (e. g., in an outpatient setting and the emergency department) by applying a simple modified quick SOFA score (qSOFA, SOFA: sequential organ failure assessment; [5]). The objective of qSOFA screening is identification of patients with probable sepsis, who then undergo further diagnostic tests and intensive monitoring. In patients fulfilling two of the three qSOFA criteria (respiratory rate >22/min, altered mentation, systolic blood pressure <100 mm Hg), intensive medical care and further diagnostic tests are indicated (including measurement of lactate levels). During the subsequent course, the classical SOFA score and new-onset organ dysfunction form the basis of a definitive "sepsis" diagnosis (SOFA score ≥2). Organ dysfunction is thus as of now the decisive diagnostic requirement.

Alongside hemodynamic, symptomatic treatment, the proclaimed goals of SEPSIS-3 are also rapid identification of the source of sepsis (and treatment of the infection) and earliest possible initiation of a calculated anti-infective therapy [5–7]. Whether or not SEPSIS-3 can fulfil all expectations remains questionable. On a critical note, the introduction of organ dysfunction as an obligatory diagnostic criterium may, under certain circumstances, delay definitive diagnosis until a later, possibly more severe disease stage [8]. A consequence of this would be, e. g., a delayed (and potentially less effective) initiation of treatment. Moreover, diagnosis of sepsis based on the SOFA score is not undisputed. For in-

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Table 1 Typical pathogens of selected intensive care medicine infections

CAP	HAP/VAP	Skin/soft tissue	Catheter-associated BSI	Intestine (secondary/tertiary peritonitis)
Streptococcus pneumoniae	*Enterobacteriaceae*	*Streptococcus pyogenes*	CoNS	*Enterobacteriaceae*
Mycoplasma pneumoniae	*Haemophilus influenzae*	*Staphylococcus aureus*	*S. aureus*	Anaerobes
H. influenzae	MSSA	Anaerobes	Gram-negative bacilli	Enterococci
S. aureus	*S. pneumoniae*	*Enterobacteriaceae* (+ *Clostridiaceae*)	*Corynebacterium jeikeium*	**Nosocomial/ postoperative**
Rarer CAP pathogens	**Common MDR pathogens**	*Pseudomoas aeruginosa*	Propionibacteria	
		Nosocomial/ pretreatment	*Candida* species	*Enterobacteriaceae* (ESBL)
Enterobacteriaceae	MRSA		**Nosocomial/ pretreatment**	Enterococci (VRE)
Chlamydophila species	*Enterobacteriaceae* (ESBL)	MRSA		MRSA
Legionella species	*Pseudomonas aeruginosa*	MRGN	MRSA	Anaerobes
–	*Acinetobacter baumannii*	–	MRGN	*Pseudomonas* species
	Stenotrophomonas maltophilia		Enterococci (VRE)	*Candida* species

BSI bloodstream infection (bacteremia), *CAP* community-acquired pneumonia, *ESBL* extended-spectrum β-lactamases, *HAP* hospital-acquired pneumonia (nosocomial pneumonia), *CoNS* coagulase-negative staphylococci, *MDR* multidrug-resistant pathogens, *MRSA* multiresistant/methicillin-resistant *Staphylococcus aureus*, *MRGN* multiresistant gram-negative pathogens, *MSSA* multisensitive *Staphylococcus aureus*, *VAP* ventilator-associated pneumonia, *VRE* vancomycin-resistant enterococci

stance, patients with chronic diseases affecting one or more axes (e. g., terminal renal failure; chronic obstructive pulmonary disease, COPD; hepatic insufficiency) already have a high SOFA score at baseline, which can hardly be increased by the presence of sepsis.

Conclusion. Sepsis is a life-threatening organ dysfunction caused by an infection. Diagnosis is established according to the SEPSIS-3 criteria. As of now, the newly introduced qSOFA score serves to identify high-risk patients outside of the intensive care unit (ICU); subsequently, definitive diagnosis is established using the SOFA score and the additional criterium of new-onset organ dysfunction. The objective is an increased sepsis detection rate.

Epidemiology

Pathophysiologically, sepsis is a dysregulated host response to infection [5, 9, 10]. Septic shock is a particularly serious course of sepsis with most severe cellular-metabolic and cardiocirculatory problems, as well as an associated very high rate of patient mortality (up to 50%; [9, 11]). Similar to the situation in stroke, myocardial infarction, and very severely injured patients (polytrauma), early diagnosis and treatment play a crucial role in sepsis. Increasing incidences during the past decade [12–14] have rendered sepsis a medical challenge in intensive care medicine [15]. Solid epidemiologic data on sepsis differ according to geography and due to the diversity of studies on the topic. For example, in retrospective works by Fleischmann et al. [12] between 2007 and 2013, an annual increase in sepsis incidence of 5.7% was observed. Patient mortality was very high, up to 55% (47% without and 62% with shock; [12, 13, 16]). The multicentric prospective Incidence of Severe Sepsis and Septic Shock in German Intensive Care Units (INSEP; [17]) trial published in 2016 delivered similar results: 12.6% of participants had severe sepsis or septic shock (1503 from 11,883 patients). The calculated incidence rate of severe sepsis and septic shock reached 11.64% per 1000 treatment days (95% confidence interval, 95%CI, 10.51–12.86) in INSEP [17]. Mortality in this collective was 34.3% during the stay in the ICU and 40.4% for the hospital stay. Data from international studies vary within a comparable range [14, 18–22]. Whereas sepsis is the third most common cause of death in non-surgical ICUs [23, 24], it is the primary cause of death in surgical ICUs [15]. However, in addition to the high mortality rates and still poor therapeutic outcomes, sepsis also generates relevant costs for the health care system every year [21].

Sepsis begins with an initial infectious stimulus and a dysregulated immune response to this infection. From an infectious diseases (ID) perspective, nosocomial infections play a special role. In INSEP [17], 57.2% of the detected infections were of nosocomial origin; in 25.7% of these nosocomial infections, infection occurred in the ICU. Upon considering the entire ICU population, the infection is in the region of the airways in about 60–63% of patients, is intraabdominal in 25–30%, and affects skin and soft tissues in up to 10% [24–26]. In surgical intensive medicine, intraabdominal and soft tissue infections are the primary starting points for sepsis. Important and frequently occurring "problem pathogens" causing selected diseases are presented in **Table 1**.

The spectrum of pathogens includes both gram-positive cocci such as *Staphylococcus aureus* and *Streptococcus pneumoniae*, as well as gram-negative bacilli, e. g., the *Enterobacteriaceae Escherichia coli* and *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [27–29]. Since the number of infections with multidrug-resistant (MDR) pathogens has increased significantly during recent years, these are now also more frequently the trigger

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Bacterial sepsis. Diagnostics and calculated antibiotic therapy

Abstract

The mortality of patients with sepsis and septic shock is still unacceptably high. An effective calculated antibiotic treatment within 1 h of recognition of sepsis is an important target of sepsis treatment. Delays lead to an increase in mortality; therefore, structured treatment concepts form a rational foundation, taking relevant diagnostic and treatment steps into consideration. In addition to the assumed infection and individual risks of each patient, local resistance patterns and specific problem pathogens must be taken into account during the selection of anti-infective treatment. Many pathophysiologic alterations influence the pharmacokinetics (PK) of antibiotics during sepsis. The principle of standard dosing should be abandoned and replaced by an individual treatment approach with stronger weighting of the pharmacokinetics/pharmacodynamics (PK/PD) index of the substance groups. Although this is not yet the clinical standard, prolonged (or continuous) infusion of β-lactam antibiotics and therapeutic drug monitoring (TDM) can help to achieve defined PK targets. Prolonged infusion is sufficient without TDM, but for continuous infusion, TDM is generally necessary. A further argument for individual PK/PD-oriented antibiotic approaches is the increasing number of infections due to multidrug-resistant (MDR) pathogens in the intensive care unit. For effective treatment, antibiotic stewardship teams (ABS teams) are becoming more established. Interdisciplinary cooperation of the ABS team with infectious disease (ID) specialists, microbiologists, and clinical pharmacists leads not only to rational administration of antibiotics, but also has a positive influence on treatment outcome. The gold standards for pathogen identification are still culture-based detection and microbiologic resistance testing for the various antibiotic groups. Despite the rapid investigation time, novel polymerase chain reaction(PCR)-based procedures for pathogen identification and resistance determination are currently only an adjunct to routine sepsis diagnostics, due to the limited number of studies, high costs, and limited availability. In complicated septic courses with multiple anti-infective therapies or recurrent sepsis, PCR-based procedures can be used in addition to treatment monitoring and diagnostics. Novel antibiotics represent potent alternatives in the treatment of MDR infections. Due to the often defined spectrum of pathogens and the practically (still) absent resistance, they are suitable for targeted treatment of severe MDR infections (therapy escalation). (Contribution available free of charge by "Free Access" [https://link.springer.com/article/10.1007/s00101-017-0396-z].)

Keywords

Drug resistance, multiple, bacterial · Lactams · Prolonged and continuous β-lactam infusion · Therapeutic drug monitoring · Patient care bundles

Bakterielle Sepsis. Diagnostik und kalkulierte Antibiotikatherapie

Zusammenfassung

Die Sterblichkeit von Patienten mit Sepsis und septischem Schock ist weiterhin inakzeptabel hoch. Eine effektive, kalkulierte Antibiotikatherapie binnen der ersten Stunde nach Erkennen der Sepsis ist ein wichtiges Ziel der effektiven Sepsistherapie. Verzögerungen führen zum deutlichen Anstieg der Sterblichkeit. Daher bilden strukturierte Behandlungskonzepte eine rationale Grundlage unter Beachtung relevanter Diagnose- und Behandlungsschritte. Neben dem vermuteten Focus und individuellen Risiken einzelner Patienten müssen lokale Resistenzmuster und spezifische Problemerreger bei der Wahl der antiinfektiven Therapie berücksichtigt werden. Vielfältige pathophysiologische Veränderungen beeinflussen im Rahmen der Sepsis die substanzspezifische Pharmakokinetik (PK) vieler Antibiotika. Daher sollte das Prinzip der „Standarddosierung" verlassen und durch einen individuelleren Therapieansatz mit stärkerer Gewichtung der Pharmakokinetik(PK)-/Pharmakodynamik(PD)-Indizes der Substanzgruppen ersetzt werden. Wenngleich dies noch nicht der klinische Standard ist, können Applikationsformen wie die prolongierte (oder kontinuierliche) Infusion von β-Lactamen und ein therapeutisches Drugmonitoring (TDM) helfen, definierte PK-Ziele zu erreichen. Während die prolongierte Infusion auch ohne TDM auskommt, ist TDM bei kontinuierlicher Infusion grundsätzlich notwendig. Ein weiteres Argument für den individuellen, PK/PD-orientierten Antibiotikaeinsatz ist die Zunahme komplizierter Infektionen durch multiresistente Erreger (MRE) auf Intensivstationen. Zur effektiveren Behandlung etablieren sich dort zunehmend „antibiotic stewardship teams" (ABS-Team). Die interprofessionelle Zusammenarbeit des Behandlungsteams mit Infektiologen/Mikrobiologen und klinischen Pharmazeuten führt nicht nur zum rationaleren Antibiotikaeinsatz, sondern beeinflusst das Behandlungsergebnis positiv. Den Goldstandard der Erregerdiagnostik stellen weiterhin der kulturbasierte Nachweis aus Probenmaterial und die mikrobiologische Resistenztestung auf die verschiedenen Antibiotikagruppen dar. Neue Polymerase-Kettenreaktion(PCR)-basierte Verfahren der Erregeridentifikation und Resistenzbestimmung ergänzen trotz hoher Untersuchungsgeschwindigkeit aufgrund der limitierten aktuellen Studienlage, der hohen Kosten und der eingeschränkten Verfügbarkeit derzeit die Sepsisroutinediagnostik lediglich. Bei komplizierten, septischen Krankheitsverläufen mit mehrfacher, antiinfektiver Vorbehandlung oder rekurrenter Sepsis können PCR-basierte Verfahren ergänzend zu Therapie-Monitoring und Diagnostik eingesetzt werden. Neue Antibiotika stellen potente Alternativen in der Behandlung von MRE-Infektionen dar. Aufgrund des oftmals definierten Erregerspektrums und der praktisch (noch) nicht vorhandenen Resistenzen sind diese zur gezielten Behandlung schwerer MRE-Infektionen geeignet (Therapieeskalation).

Schlüsselwörter

Medikamentenresistenz, multipel, bakteriell · Lactame · Prolongierte und kontinuierliche β-Lactam-Infusion · Therapeutisches Drugmonitoring · Patientenversorgungsbündel

for sepsis—particularly in the case of nosocomial infections [17]. The past few years have seen an increase in infections with MDR gram-negative (MDRGN) pathogens in Germany [30]. Even though this development has reached a considerably more serious extent in various other European countries [31–33], antibiotic-resistant pathogens are being increasingly isolated as the cause of severe, barely manageable (nosocomial) infections with high mortality in German ICUs. Classical MDRGN pathogens include *Enterobacteriaceae* (e. g., *E. coli* species, *Klebsiella* species) and nonfermenters (e. g., *Pseudomonas* species, *Acinetobacter*-species). These groups are frequently resistant to broad-spectrum antibiotics, in which enzymatic inactivation (e. g., β-lactamases) of antibiotics plays a particularly important role. MDR gram-positive pathogens, such as vancomycin-resistant enterococci (VRE) or methicillin-resistant staphylococci (MRSA), represent another problematic collective. Whereas the proportion of asymptomatic VRE carriers and VRE infections continues to rise [30, 34], the clinical relevance of MRSA as the trigger for sepsis has decreased in recent years [30].

The impact of global tourism and long-distance travel to areas with a high prevalence of MDR pathogens and MDR pathogen carriers on the distribution of MRD pathogens has only come into focus during the past few years [35]. A prospective study from 2017 [36] showed that up to 75% of the investigated travelers returning from, e. g., India, had acquired *Enterobacteriaceae*, which produce broad-spectrum β-lactamases. Although these tourists are primarily symptom-free carriers of MDR pathogens, these bacteria could become relevant in the case of an infection (e. g., abdominal infection). In light of the worrisome development of increasing MDR infection rates and the continued occurrence of new resistance phenotypes, the World Health Organization (WHO) published a global action plan for curtailing and preventing MDR pathogens and MDR infections in 2015 [37].

Conclusion. With increasing incidences, sepsis and septic shock represent the primary cause of patient mortality in surgical ICUs. Mortality remains high. Nosocomial infections and/or infections with difficult-to-manage MDR pathogens play an important role in the development and treatment of sepsis, and also contribute to the high mortality of this disease.

General therapeutic principles: sepsis bundles

For many years, the gold standard of sepsis treatment was "early goal-directed therapy" (EGDT), as postulated by Rivers et al. [38]. Intensive care medicine physicians of today are still versed in EGDT. By dictating a strict treatment algorithm and strictly adhering to this path, Rivers et al. were able to significantly reduce mortality in sepsis patients for the first time. However, subsequent studies on sepsis treatment optimization revealed that more flexible "sepsis bundles" were not inferior to strict EGDT [18, 19, 39, 40]. Consequently, treatment moved away from EGDT according to Rivers et al., and the sepsis bundles defined by the Surviving Sepsis Campaign (SSC) were implemented [7]. In addition to the definition of sepsis as a medical emergency, hemodynamic optimization (30 ml/kg fluid) of the patient, and the search for the source/pathogen-diagnostic tests, the sepsis bundles also include rapid initiation of a calculated antibiotic treatment within the first hour after recognition of sepsis [1, 7, 41–43]. That adherence to defined bundle measures reduces mortality among sepsis patients was demonstrated by Damiani et al. in a meta-analysis incorporating 50 studies (odds ratio, OR, 0.66; 95%CI 06–072; [44]). Prospective investigations, e. g., the International Multicentre Prevalence Study on Sepsis (IMPreSS) by Rhodes et al., achieved a reduction in in-hospital mortality of up to 36–40% by implementing bundle measures [45]. This has also been confirmed by other studies [18, 19, 40].

The fact that the measures in the sepsis bundles do not all have the same weight and the same priority was demonstrated by Seymour et al. [46] in a recent retrospective study. In this investigation, it was rapid completion of the 3-hour bundle and earliest possible commencement of antibiotic therapy that were the decisive factors for reducing mortality. Surprisingly, completion of the fluid bolus and thus hemodynamic stabilization in the acute phase seemed to be (at least in this study) less relevant for a sepsis patient's survival. Integration of ICU nurses into the treatment team is of high relevance, and studies have shown that this also reduces mortality [47, 48].

Conclusion. The SSC bundle measures are the new therapeutic standard in sepsis treatment. Adherence to these recommendations leads to a reduction in in-hospital mortality. In addition to hemodynamic optimization of the patients, earliest possible (≤1 h) initiation of a calculated antibiotic therapy and rapid treatment of the infection are the central elements.

Biomarkers and pathogen diagnostics

According to SEPSIS-3 [5], diverse biomarkers continue to be used for diagnosis, treatment management, and prognostic estimation. The relevance of the different sepsis markers remains, however, unclear. Many new biomarkers have been investigated over the years, of which none had the power to accurately recognize or definitively exclude sepsis with sufficient specificity and sensitivity [49, 50]. In the following sections, several important infection markers that are frequently assessed in clinical routine are discussed in terms of their value and prognostic advantages in the context of sepsis. Moreover, experimental biomarkers that have not yet found entry into clinical routine are also presented.

Biomarkers

Lactate

As a product of anaerobic glycolysis, lactate (the anion resulting from dissociation of lactic acid) serves as a biomarker for tissue hypoxia. The accelerated glycolysis and reduced mitochondrial metabolism occurring during shock

lead to increased lactate production. Lactate levels are further increased in this situation by decreased elimination and enzyme induction. In the context of sepsis, lactate can be used for prognosis as well as for treatment monitoring (stagnation or diminishment of plasma concentrations; [51–55]). After years of controversial discussion, the new definition of septic shock [5] states the criterium of hyperlactatemia >2 mmol/l (≈18 mg/dl) as obligatory for diagnosis [10]. In an analysis of data from more than 280,000 patients of the SSC collective, Casserly et al. [53] showed that hyperlactatemia >4 mmol/l and low lactate clearance during the first 6 h were associated with a significant increase in in-hospital mortality.

Procalcitonin

Over the past years, procalcitonin (PCT) has become established in clinical routine as a sensitive and rapid parameter of bacterial infection. Due to its kinetics (response half-time, response-HT, up to 4–6 h), PCT is viewed as the diagnostic gold standard for bacterial infections [56, 57]. In spite of these advantages, particularly locally limited infections, e. g., ventilator-associated pneumonia (VAP) or abscesses, can occurred without an increase in PCT [58, 59]. Interpretation of the PCT value in critically ill patients with relevant liver diseases or after liver surgery is sometimes equally difficult: a PCT increase may be measured in these patients in the absence of a bacterial infection. Whether PCT can be considered a sufficiently reliable marker for differentiating between different grades of sepsis severity and noninfectious SIRS is controversially discussed [58, 60, 61]. The specificity and sensitivity of PCT for sepsis diagnosis are under 90%, irrespective of the cutoff value used by the measuring laboratory [62, 63]. Therefore, the PCT value should always be interpreted under consideration of the patient's clinical condition and the limitations of this marker [58]. With an induction time of approximately 4 h, it is, in principle, possible for fulminant septic shock to develop without a relevant increase in PCT levels.

Interleukin 6

A biomarker that is particularly frequently measured in pediatric IDs is interleukin 6 (IL-6). IL-6 is released at an early stage of the immune reaction and reaches its peak in plasma within 2 h (induction time approximately 20 min). The peak level correlates positively with the severity and course of the infection [64, 65]. A limitation to the value of IL-6 as a biomarker is the fact that an array of other diseases are also associated with in an increase in IL-6 levels ([59]; e. g., autoimmune diseases, surgery, and trauma). In patients with severe sepsis or septic shock, a reduction in IL-6 levels can be used as a prognostic factor [66]. The kinetics of the IL-6 level can be used to monitor the effectiveness of an anti-infective therapy [66]. Despite these advantages and the increasing trend toward chemical laboratory measurement of IL-6 in emergency departments and ICUs, IL-6 is not a routine parameter for diagnosis of sepsis in adult patients.

C-reactive protein

C-reactive protein (CRP) is one of the hepatically synthesized acute-phase proteins, and has been measured as a routine parameter for diagnosis and treatment monitoring for many years. The specificity of CRP for diagnosis of an infection is low [56]. Increases in CRP are not only observed during infection, but also after surgery, trauma, and burns, or in patients with acute (aseptic) pancreatitis. Particularly for diagnosis of sepsis must CRP be viewed very critically. In fulminant disease courses, the CRP induction time (response-HT after stimulus 6–10 h, relative increase 10–100-fold) means that septic shock can already be present before laboratory analysis detects an increase in the CRP value. CRP is, however, of value for evaluation of disease course and monitoring of treatment efficiency [59, 67]. Persistent increases in CRP level or a secondary increase in plasma concentration in patients on anti-infective therapy may indicate inadequate control of the infection (e. g., infectious complications, secondary infections, polymicrobial infections, MDR pathogens, ineffective antibiotic, inadequate antibiotic dosage; [59]). In this situation, the CRP concentration course can lead to re-evaluation of the overall clinical situation, the assumed source, and the treatment regimen [50, 68].

Proadrenomedullin and soluble subtype of the CD14 cell surface receptor

New experimental biomarkers for sepsis include the anti-inflammatory and antimicrobial peptide proadrenomedullin (proADM) and the soluble subtype of the CD14 cell surface receptor (sCD14-ST, presepsin; [59]).

In clinical studies, proADM was of higher prognostic value for sepsis patients with nosocomial pneumonia (hospital-acquired pneumonia, HAP) than the classical biomarkers CRP and PCT [69, 70]. However, since raised plasma levels of ADM are seen in diverse diseases, e. g., cardiovascular and autoimmune diseases [71], ADM is unsuitable for initial detection of sepsis. In clinical studies, the ADM plasma level correlated very well with disease course/disease severity and the mortality of the patient collective [69]. Therefore, ADM may become a suitable marker for prognostic estimations in sepsis patients in the future. Furthermore, in one clinical investigation, ADM had a significantly higher prognostic significance for in-hospital mortality than the classical markers CRP and PCT [70].

The sCD14-ST (presepsin) concentrations in plasma increase within 6 h after bacterial infection [72]. Due to the relatively strong correlation with bacterial infection [73], presepsin may become a specific marker for detection of sepsis and its discrimination from noninfectious SIRS in the future [74, 75]. Since the height of the measured plasma levels correlates poorly with the grade of sepsis severity, presepsin appears to be unsuitable as prognostic marker [75].

Other chemical laboratory tests

The complete battery of chemical laboratory tests used in clinical routine obviously includes leucocyte count (leukocytosis and leucopenia) and the classical differential blood count. These can deliver additional information in sepsis

patients but should not be used for diagnosis.

Conclusion. No sufficiently sensitive and specific sepsis biomarkers are currently available. The PCT, IL-6, and lactate markers can substantiate the diagnosis and may be drawn upon for monitoring treatment efficiency and/or estimating prognosis (lactate). It is important to be aware of the fact that during fulminant disease courses, the initial values may be within the normal range and only increase in subsequence stages. Therefore, diagnosis or exclusion of sepsis should never be based solely on these parameters.

Blood cultures

An implication of the earliest-possible initiation of a calculated antibiotic therapy [7, 76] is immediate evaluation of the possible infection and expected causal pathogen. Whereas the search for the infection is based primarily on clinical examination and imaging, isolation of the causal pathogen requires that a considerable number of samples be taken. In addition to other samples (e. g., deep tracheal secretions/bronchoalveolar lavage, BAL; abscess punctures; cerebrospinal fluid collection; tissue samples), blood cultures play an important role. Two to three paired blood culture samples [77, 78] should be collected aseptically from different areas prior to commencement of antibiotic therapy. A fresh puncture site should be used at least once, and if a catheter-associated infection is suspected, a blood sample should also be taken from the corresponding catheter (e. g., central venous catheter, CVC; Shaldon catheter; arterial catheter) and sent for microbiologic testing. Collection of three paired blood culture samples is possible within minutes [79], and is sufficient to identify the pathogen in 90% of cases of bacteremia [80, 81]. Even one application/the initial application of antibiotic can render identification of the pathogen impossible in blood culture medium [82, 83]. Although pathogen identification is of elementary importance in sepsis management (reduction of health care costs, possibility of de-escalation or pathogen-specific treatment, reduction of selective pressure on pathogens, reduction of mortality; [84, 85]) and the likelihood of isolating the pathogen in the presence of bacteremia is very high, the rate of sample taking in Germany—approximately 55 blood cultures per 1000 patient days in German ICUs—is considerably below the international average (100–200/1000 patient days; [86]). An increase in this rate to around 100/1000 patient days must thus be promoted as a matter of urgency [87].

When handling blood cultures, the preanalytical phase is of great importance. Not only sterile sample collection but also the inoculation volume (8–10 ml/tube) and immediate (with as little delay as possible) delivery to the microbiologic laboratory are critical factors. The once-propagated collection of blood samples for in vitro pathogen diagnosis during the fever onset phase does not increase detection rates, nor does inoculation of the blood culture medium with large volumes [88, 89]. It is important to note that coagulase-negative staphylococci (CoNS) are classical blood culture contaminants. It these are detected, it must be critically considered whether this result is relevant to infection or due to non-sterile handling.

The decisive disadvantage of blood cultures in the context sepsis is the latency period between sample collection and culture results (18–24 h to pathogen identification, up to 72 h for resistance testing).

Conclusion. Immediate initiation of the search for the infection and the pathogen—before starting the calculated antibiotic therapy—forms the foundation of successful sepsis treatment. Identification of the infection delivers important information concerning the spectrum of pathogens, and thus influences the calculated antibiotic therapy. Blood cultures remain the gold standard for detection of bacteremia, and collection of samples is thus essential for sepsis management.

New techniques

Molecular genetic and culture-independent methods for pathogen detection have been commercially available for many years now. These techniques appear rational, since the phase of empirical antibiotic therapy without differentiated microbiologic finding should be kept as short as possible—not only in the interests of the individual patient, but also in the interests of specific and economical use of antibiotics [90]. Furthermore, in addition to identifying the pathogen, it is also important to know its resistance to various antibiotics, particularly in intensive care medicine. Whereas detection of MRSA (*mecA* or *mecC* gene) poses no technical difficulties, adequate determination of β-lactam resistance in gram-negative bacteria is a challenge, due to the hundreds of different types of β-lactamases [91]. Most multiplex polymerase chain reaction (PCR) approaches are thus limited to a few frequently occurring resistance determinants. However, molecular genetic techniques have only been able to identify a few resistance mechanisms to date [92]. Whether the shorter latency period between sample collection and results [93] propagated by the manufacturers of these products is realizable in clinical routine appears questionable. Since a eubacterial PCR with subsequent sequencing of the amplification product takes many hours, a clear time advantage of PCR-based pathogen diagnostics is primarily achievable when searching for defined pathogens or within a limited pathogen spectrum, e. g., when looking for *Neisseria meningitidis* and *Listeria monocytogenes* in patients with meningoencephalitis, or for viral infection diagnostics. An undeniable advantage of PCR-based techniques is that pathogens (DNA fragments) are still detectable when the blood culture is compromised, e. g., due to prior anti-infective treatment.

To what extent PCR-based diagnostic testing has an influence on treatment decisions which consecutively improve patent outcome has hardly been investigated. In an observational study investigating implementation of multiplex PCR in the clinical routine of an ICU, an influence on treatment course was only observed when a pathogen was detected that was not susceptible to the

initial calculated therapy—specifically, MDR (VRE and MRSA) bacteria and *Candida* species [94]. Only two randomized studies have been published on this topic so far: In one study comparing *Aspergillus* PCR to standard diagnostic testing in patients with fever and neutropenia, mortality could be significantly reduced by the PCR-directed treatment [95]. In another investigation conducted in an neonatal ICU in India, a significant survival advantage was conferred by multiplex PCR-based diagnostics compared to blood cultures [96]. However, concerning the latter study, it must be critically noted that in an environment with a very high rate of extended-spectrum β-lactamases (ESBL), an initial calculated therapy with cephalosporins is standard.

In the following sections, three new types of pathogen diagnostic test are presented.

Combination of PCR and mass spectrometry

The IRIDICA® system (Abbott, Chicago, IL, USA) is based on a combination of PCR and mass spectrometry (PCR/electrospray ionization mass spectrometry, PCR/ESI-MS). By using distinct primers in a target-oriented analysis, 800 bacterial, fungal, and viral pathogens can be identified in about 6 h. In a second step, the amplification products yielded in PCR undergo a fully automated database comparison and can be assigned to a specific pathogen on the basis of their molecular weight. Possible sample materials include blood but also, e. g., sputum or tissue particles. The prospective Rapid Diagnosis of Infections in the Critically Ill (RADICAL; [97]) study compared results of conventional blood cultures with those of the IRIDICA® system in 616 patient samples. Use of the PCR/ESI-MS technique achieved a sensitivity of 81% and a specificity of 69%. The negative predictive value of the test was 97% in this investigation. IRIDICA® is also able to detect the presence of some resistance genes (*mecA*, *vanA/B*, *KPC*). In addition to the potential time advantage, pathogen diagnosis can also be successfully accomplished with this method even after initiation of antibiotic therapy, when conventional/culture-based techniques are no longer possible. Further prospective data on this technique are currently lacking.

Next-generation sequencing

Another technique is next-generation sequencing (NGS). In this method, cell-free DNA (cfDNA) is extracted from plasma samples, and all pathogens are detected and sequenced. Discrimination between infection and colonization is made possible by calculating the Sepsis Indicating Quantifier (SIQ) score [98]. Analogous to PCR-based techniques, a further advantage of NGS is the prediction of particular resistance phenotypes [98]. NGS will become increasingly interesting in the future, since with this method—analogous to blood cultures—there exists the possibility of a widescale search for the pathogen which is independent of the pathogen growth rate.

Pathogen identification and determination of the specific minimum inhibitory concentration

A method for pathogen identification and determination of the specific minimum inhibitory concentration (MIC) is the Accelerate PhenoTest™ BC Kit (Accelerate Diagnostics™ Inc., Tucson, AZ, USA). Using fully automated testing of pathogen-positive blood samples, a large number of gram-positive and gram-negative pathogens (as well as *Candida* species) can be identified, and the MCI of classical broad-spectrum antibiotics can be tested. According to the manufacturer, the identification of the pathogen in positive blood samples succeeds within 90 min; the results of susceptibility testing are available within 7 h. This technique therefore appears suitable for significantly reducing the time interval between empirical and targeted pathogen-specific (MIC-adapted) treatment, and thus also for reducing the increased mortality of patients who receive inadequate initial treatment of bacteremia (bloodstream infection, BSI; [99, 100]). The possibility of early adaptation of the anti-infective therapy is drawing nearer.

Future perspectives

The abovementioned PCR- and NGS-based techniques provide interesting options for accelerating pathogen identification and resistance phenotyping, in order to positively influence sepsis treatment. However, these methods are currently not routinely implemented [93]. The costs of these investigations are presently very high [101, 102], which limits their use primarily to studies. In addition to pathogen identification, applications such as the Accelerate PhenoTest™ BC Kit may also rapidly deliver MIC data in the future, thus enabling early individualization of treatment.

Conclusion. The PCR-based techniques for pathogen diagnosis have been established for many years now. New methods based on molecular genetics presently only detect defined pathogens and specific resistance types. They are currently not applied in clinical routine. Due to the possibility of covering a very broad spectrum of pathogens (analogous to blood cultures), NGS is a highly promising technique for the future.

Calculated antibiotic therapy

Principles of treatment

Surgical intensive care patients with sepsis and septic shock are nowadays managed by an interdisciplinary, interprofessional treatment team comprising intensive care physicians, surgeons, clinical pharmacists/pharmacologists, microbiologists/hygienists, and consultant physicians from other disciplines (e. g., neurology, cardiology).

The central maxim of a successful anti-infective therapy was formulated in 1913 by Paul Ehrlich at the 17th International Congress of Medicine by the statement [103] "Frapper fort et frapper vite" ("hit hard and fast")—a principle which still applies today.

Ehrlich's principle of fast antibiotic therapy was taken up at the end of the 1990s by Kollef et al. They showed [104] that delayed application of antibiotics was associated with a significant increase in the mortality of sepsis patients. The fact that in addition to the time factor

the effectiveness of the antibiotic therapy is also critical was summed up by Kumar and Kethireddy 100 years after Paul Ehrlich, in an editorial of the year 2013 [105]: "Speed is life but a hammer helps too." This principle is underlined by an analysis of the first (approximately 1000) patients of the Medical Education for Sepsis Source Control and Antibiotics (MEDUSA; [6]) study. In MEDUSA, sepsis patients with an inadequate initial therapy had a significantly increased 28-day mortality. On one hand, delaying (>6 h) surgical treatment of the infection and source control increased mortality by 16.2% (42.9 vs. 26.7%, $p < 0.001$); on the other, an inadequate antibiotic therapy (irrespective of the time point of the first application) was also associated with a significant increase in mortality (30.3 vs. 40.9%, $p < 0.001$). After completion of the study, Bloos et al. [106] evaluated the entire MEDUSA dataset with a total of 4000 patients, investigating, among other things, the effect of the timepoint of the first application on patient mortality. These authors found that with every hour the antibiotic therapy was delayed, mortality increased by 2%. Delayed treatment of the source infection was also associated with an increase in mortality of 1% per hour [106]. Diverse other studies were also able to prove the association of a delayed first application with increased mortality [6, 107–111] and worsening of secondary endpoints (e. g., acute kidney damage; development of acute respiratory distress syndrome, ARDS; increase of the SOFA score; [112–114]) among the investigated patient collective. It is therefore not surprising that rash initiation of a calculated antibiotic therapy is one of the most important cornerstones of sepsis treatment [1, 7, 76, 115–119] and a central element of current guidelines [7]. In 2006, Kumar et al. [115] demonstrated in a retrospective analysis that the factor "time" is an independent predictor for survival in septic shock patients. Referring to the recommended timeframe for treatment initiation in very seriously injured patients, these authors paraphrased their results as the "golden hour of sepsis." Subsequent studies showed similar results [76, 107, 120]. Although the time factor and the mortality increase resulting from delayed administration of antibiotics appear to be very well proven, the "golden hour of sepsis" concept and the implied necessity of a calculated antibiotic therapy within the first hour is subject to justified criticism [7, 115]. In a very recent editorial, Singer [121] summarizes these criticisms and relativizes the "golden hour of sepsis" dogma with respect to the problem of overuse of antibiotics in critically ill ICU patients and the phenomenon of "incestuous amplification."

Modern sepsis treatment is nowadays an interprofessional challenge. The constant reevaluation of all therapeutic aspects is too complex for the individual specialists or indeed a single discipline. Therefore, treatment today is generally managed by an antimicrobial stewardship (ABS) team [122]. This team comprises ID specialists/microbiologists and clinical pharmacists. A current meta-analysis of the effectiveness of ABS teams (based on 145 studies addressing 14 ABS measures) was able to show that improved adherence to guidelines was associated with reduced mortality (mortality reduced by 35%; relative risk, RR, 0.65; 95%CI 054–080; $p < 0.0001$) and stringent de-escalation (mortality reduced by 65%; RR 0.44; 95%CI 0.30–0.66; $p < 0.0001$; [123]). The ABS measures are now an integral component of ICUs and are included in the Deutsche Gesellschaft für Infektiologie e. V. (DGI; "German Society of Infectious Diseases") S3 guideline [124].

Conclusion. Calculated antibiotic therapy of sepsis should be initiated as soon as possible (ideally within the first hour after recognition of sepsis); the interprofessional ABS team takes over further treatment management.

Tarragona strategy

A concrete treatment concept is represented by the Tarragona strategy [125]. Originally established for VAP, this strategy can also be applied to the initial calculated antibiotic therapy in sepsis patients, and incorporates the most important diagnostic and therapeutic considerations. The key elements of the Tarragona strategy are presented in **Table 2**.

The central aspect here is once again an early, high-dose, sufficiently broad-spectrum antibiotic therapy. Again, the assumed infection, the individual patient's risk profile, the possibility of an MDR pathogen, and local antibiotic resistance rates are incorporated into the concept. Particularly in ICU and/or invasive ventilation patients, nosocomial infections caused by MDR pathogens are highly relevant [21, 30] and must be considered during the antibiotic selection process. A frequent consequence of deviating from established treatment concepts is treatment failure [126]. It should be noted that the Tarragona strategy incorporates the possibility of constant reevaluation and treatment monitoring. Regular checking of the concept's key questions at fixed time intervals and in the event of the patient's condition changing is obligatory.

Treatment duration and treatment management

The persistent high mortality of patients with sepsis and septic shock [116], as well as the association with delayed and/or ineffective antibiotic therapy, led to the recommendation for earliest possible (<1 h) calculated first application of a broad-spectrum antibiotic [7]. Since pathogen identification and, perhaps even more importantly, resistance phenotyping can take many hours to days, extreme vigilance and caution must be taken with the antibiotic therapy. The selection of substance class and the decision for calculated mono- or combination therapy are based on the (assumed) source and the clinical condition of the patient (presence of septic shock, immune suppression, etc.). Therefore, despite the critical time-dependent nature of a "sepsis" emergency, the following basic questions must be clarified:

- Which infection is the source of sepsis, and how can this infection be treated (surgically or interventionally, e. g., using CT-guided drainage)? Which pathogens can be expected?
- Does the patient exhibit septic shock?

Table 2 Tarragona strategy. (Modified from Sandiumenge et al. [125])

Core element		Explanation
1	Look at your patient	Infection? → search for the infection/pathogen diagnostics
		Preexisting disease?
		Immune status?
		Risk of an MDR pathogen? (Antibiotic pretreatment, frequent hospitalization, known MDR colonization, travel in MDR pathogen endemic regions)
2	Listen to your hospital	Surveillance: Knowledge of local pathogens/resistance phenotypes, ABS measures
3	Hit hard and early	High-dose application of a broad-spectrum antibiotic (≤1 h), combination therapy as appropriate
4	Get to the point	Assumed infection → PK/PD profile and tissue penetration of the antibiotic
5	Focus	Reevaluation of treatment at regular intervals
		De-escalate if possible
		Escalate if clinically and/or microbiologically necessary

With a total of five relevant points, the Tarragona strategy represents a structured diagnostic and therapeutic pathway for the management of infections. Although originally developed as a guideline for treatment of ventilation-associated pneumonia, the concept is also suitable for treatment of sepsis

ABS antibiotic stewardship program, *MDR* multidrug-resistant gram-negative pathogens, *PK/PD profile* substance-specific pharmacokinetic and pharmacodynamic profile of an antibiotic

- How likely is the patient to have an infection with an MDR pathogen? Existing risk factors: previous anti-infective treatment, frequent hospitalization, known colonization with MDR bacteria, or frequent travel in endemic regions?

Based on these considerations, the necessity of primary combination versus monotherapy can be derived. During the course of continued therapeutic reevaluation and after microbiologic identification of the pathogen, treatment is adapted in terms of de-escalation or escalation [102].

In this way, it is possible to preserve the patient's chance of survival [7]. A general combination therapy comprising two (or more) broad-spectrum antibiotics cannot be recommended due to the inconsistency of current data. Some studies have demonstrated reduced mortality achieved by combination therapy [127–132], whereas the randomized multicentric comparison of two antibiotic regimens (meropenem vs. meropenem + moxifloxacin) in the treatment of severe sepsis and septic shock by Brunkhorst et al. (Max-Sep study; [133]) found no superiority of combination treatment (meropenem + moxifloxacin) over monotherapy (meropenem) for severe sepsis. In this study, mortality 28 days after randomization was 23.9% (95%CI 19–29.4%) in the combination group and 21.9% (95%CI 17.1–27.4%) in the monotherapy group. Treatment outcomes at day 90 did not differ significantly [133]. To summarize, it must be stated that primary combination therapy of sepsis was never superior when the antibiotic used as monotherapy was a carbapenem. Moreover, in retrospective analyses it could be shown that in only about 30% of patients did the initial calculated antibiotic therapy actually encompass the pathogen, and de-escalation of therapy was only undertaken in a third of patients [127–133]. Combining broad-spectrum antibiotics simultaneously potentiates the selective pressure on pathogens and leads to increased development of resistance [134].

On the basis of contradictory evidence, according to the SSC [7], mono- or combination therapy can be used as the primary treatment for septic shock (recommendation grade: high; evidence: moderate). Whereas primary monotherapy is to be preferred for sepsis without signs of septic shock (exception: catheter-associated BSI), a primary combination therapy to broaden the spectrum may be urgently required in, e. g., septic shock patients and/or upon suspicion of infection with an MDR pathogen. Carbapenems such as meropenem and imipenem/cilastatin are often useful combination partners for treatment escalation or combination therapy in the presence of septic shock, since they are also effective against gram-negative, broad-spectrum β-lactamase (ESBL)-producing pathogens. Gram-positive "problem" pathogens such as MRSA have shown stable resistance types for some time now (as well as a constant incidence of infections), and are generally susceptible to vancomycin, teicoplanin, tigecycline, and linezolid. While the incidence of VRE is clearly increasing [34], an increase in linezolid-resistant enterococci has also been registered [135]. Increasing VRE incidences are thus likely to represent a problem in the future.

When the source of sepsis is known, it is often possible to limit the spectrum of possible pathogens. However, sepsis resulting from an unknown infection represents a challenge.

Principally, as part of a structured treatment, therapy must be reevaluated after 48–72 h of treatment at the latest; adaptation of the anti-infective therapy should be initiated as appropriate (escalation if necessary, de-escalation if possible). Similarly, in patients with an insufficient response to treatment, the infection should be reexamined. As a surrogate parameter for assessing the effectiveness of therapy, as well as for treatment management and monitoring of disease course, the course of plasma PCT levels can be used. Many studies on the topic have shown that a decrease in plasma PCT correlates with an effective antibiotic therapy (a bacterial infection is very unlikely with PCT < 0.5 µg/l), and that this is a useful parameter for treatment management [79, 136–140]. In the Multicenter Procalcitonin Monitoring Sepsis Study (MOSES; [141]), Schuetz et al. additionally showed that a decrease in PCT level of less than 80% of the initial level within 4 days of therapy was an independent predictor for death of the patient. In their study on PCT-guided de-escalation of anti-infective therapy, Jong et al.

[138] observed—in addition to shortened antibiotic exposure—significantly reduced patient mortality among the patient collective; however, this survival advantage could not be confirmed by a current Cochrane analysis [142] including 10 studies and over 100 patients. In summary, PCT-guided treatment monitoring should take precedence over other biomarkers [79, 140, 143, 144]. Even if a survival advantage has not yet been proven beyond all doubt, this approach can shorten the exposure to antibiotics and thus reduce side effects and resistance development. In patients exhibiting clinical and chemical indications of an insufficient therapy, not only must the antibiotic regimen be reevaluated, but imaging must be performed anew and low-threshold second-look surgery should be considered. Furthermore, in the absence of a response, the presence of an MDR infection or invasive mycosis must be considered. Vice versa, in patients with a response to treatment, with plausible microbiologic pathogen findings and resistance testing results, de-escalation should be strived for [145]: the "never change a winning team" principle is not valid here.

Although investigations assessing questions related to treatment duration and prompt de-escalation did not yield consistent results, Leone et al. [146] showed in their study published in 2014, e.g., that antibiogram-directed adaptation of the calculated antibiotic therapy did not have a negative influence on mortality compared to continuation of the empirical therapy. Similar results on de-escalation strategies were delivered by the studies of Turza and Havey et al. [147, 148]. Neither clinical and microbiologic recovery, nor survival were negatively influenced by a shorter treatment duration compared to groups with longer therapy. This was the conclusion also reached by Sawyer et al. in the treatment of complicated intraabdominal infections (cIAI): After successful surgical treatment of the infection and 4 days of antibiotic therapy, there was no difference to an 8-day therapy in terms of therapeutic success [149]. Chastre et al. [150] were also unable to show an advantage of long (15 days) over short therapy duration (8 days) in the treatment of VAP. The principle of pathogen-specific adaptation and de-escalation of therapy after identification and resistance testing is thus supported by current data [151, 152] and incorporated into current SSC guidelines [7]. Treatment duration should only exceed 7–10 days in exceptional cases (e. g., endocarditis). Modern treatment of severe infections in ICUs should always be multidisciplinary. Strategies such as ABS teams have become established and found entry into specialist society guidelines [124].

Conclusion. The decision on whether to initiate mono- or combination therapy is made based on individual patient-specific risk factors, the (assumed) infection, and the likelihood that sepsis was triggered by an MDR pathogen. De-escalation of therapy following clinical improvement or pathogen identification is essential and does not negatively influence therapeutic outcomes. For treatment management and monitoring, PCT measurements can be used. Only in exceptional cases should treatment duration exceed 7–10 days.

Examples

Sepsis of unknown source without pretreatment

Sepsis of unknown source without pretreatment initially permits monotherapy ([7, 153]; exceptions: catheter-associated BSI in particular). Primarily broad-spectrum β-lactam with β-lactamase inhibitors (BLI; e. g., piperacillin/tazobactam) should be administered. Alternatively, carbapenems (e. g., meropenem, imipenem/cilastatin) can be used, particularly if ESBLs are likely. Combination with group 2/3 fluoroquinolones is possible. In addition to considering the patient's characteristics and risk factors, when the source of sepsis is unclear, it is vital to have knowledge of local pathogens, as well as of the resistance epidemiology of "problem pathogens." ESBL-synthesizing pathogens can inactivate almost all cephalosporins and in some cases also piperacillin/tazobactam. If ESBL producers are to be expected, carbapenems should generally be preferred, even though several clinically relevant ESBL variants (temoneira β-lactamase, TEM; sulfhydryl variable type β-lactamase, SHV; cefotaxime-Munich β-lactamase, CTX-M) may retain susceptibility to piperacillin/tazobactam [154]. If the antibiogram reveals an ESBL pathogen to be susceptible to piperacillin/tazobactam, treatment of urinary tract infections is usually unproblematic; however, for bacteremia, no consensus has been reached regarding the adequacy of therapy due to the inoculum effect [155] and the serious implications of altered β-lactam pharmacokinetics in sepsis patients [156, 157]. Whether antibiogram-directed treatment against ESBL-synthesizing pathogens should be conducted with piperacillin/tazobactam thus remains a decision that must be made on the basis of an individual risk–benefit assessment. High-risk groups (major surgery, long-term intensive care, anti-infective pretreatment, ventilation) and frequent complications due to MRSA infections at the particular site, or colonization of the patient with MRSA, justify combination with a glycopeptide (vancomycin, teicoplanin). Alternatively, in some constellations, combination with a lipopeptide (daptomycin) may be appropriate (caveat: not in MRSA pneumonia). In septic shock of unknown origin, combination therapy should be administered primarily [7]. In addition to a carbapenem, recommendable combination partners included vancomycin (broadening of the spectrum against MRSA, CoNS, and vancomycin-sensitive enterococci) or a fluoroquinolone. An exemplary algorithm for calculated therapy of sepsis and septic shock of unknown source is presented in **Fig. 1**. The therapeutic objective in the initial phase is rapid, calculated antibiotic therapy (>1 h). The decision on mono- versus combination therapy should be based on the clinical status of the patient (presence of septic shock), a possible anti-infective pretreatment, and the risk of infection with an MRD pathogen. As with every algorithm, this is not binding and can of course be adapted or abandoned at any time in light of the clinical situation or local problem pathogens.

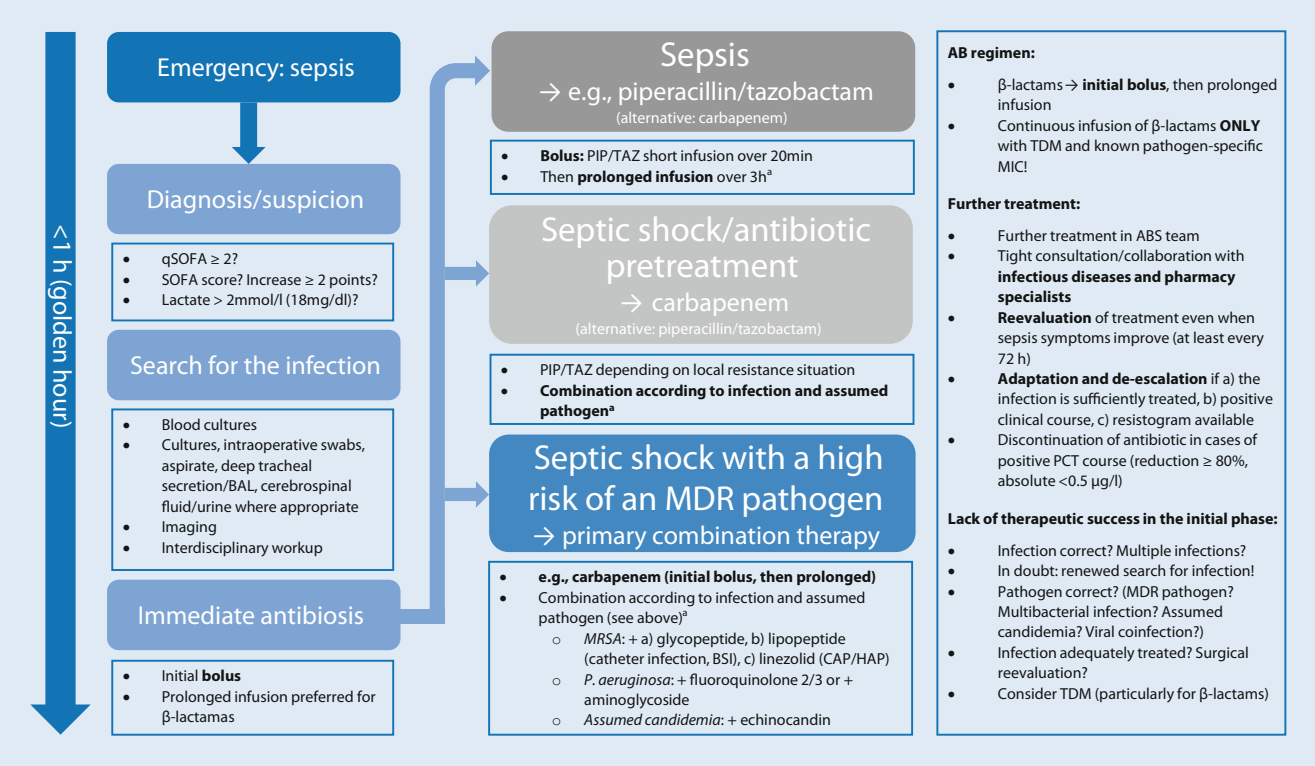

Fig. 1 ▲ Example algorithm for initial calculated therapy of sepsis of unclear origin. *AB* antibiotics, *ABS* antibiotic stewardship program, *BAL* bronchoalveolar lavage, *BSI* bloodstream infection (bacteremia), *CAP* community-acquired pneumonia, *HAP* hospital-acquired pneumonia, *MIC* minimum inhibitory concentration, *MDR* multidrug resistant gram-negative pathogen, *MRSA* multiresistant/methicillin-resistant *S. aureus*, *PIP/TAZ* piperacillin/tazobactam, *qSOFA* Quick Sequential Organ Failure Assessment Score, *PCT* procalcitonin, *TDM* therapeutic drug monitoring. [a]Catheter-associated sepsis/BSI: combination therapy with vancomycin or daptomycin

Catheter-associated infection

If patients with a catheter-associated infection develop bacteremia (catheter-associated BSI) and sepsis, immediate treatment of the source, i. e., change of the catheter, is indicated. In the widest sense, not only classical catheters, but also port systems, pacemaker probes, or dialysis catheters are possible causal infection loci. Removed catheters must be subjected to microbiologic investigation. Of paramount importance for identification of a catheter-associated BSI pathogen is inoculation of multiple multilocular paired blood cultures [80, 81]. Since CoNS comprise the majority of catheter infection pathogens, and because these are generally resistant to penicillin and cephalosporin, glycopeptides are the most important elements of the initial treatment of catheter-associated BSI. In order to also target the significantly rarer gram-negative pathogens, combination with a β-lactam antibiotic (piperacillin/tazobactam or carbapenem) is necessary. Since intermittent administration of a vancomycin bolus is often associated with nephrotoxic side effects, regular measurement of vancomycin concentrations are a necessary part of treatment monitoring (target: with intermittent infusion, trough level: 15 µg/ml; [158, 159]). Nephrotoxicity appears to be reduced with continuous vancomycin infusion [158]. Alternatively, instead of vancomycin, teicoplanin or the lipopeptide daptomycin can also be used (6–12 mg/kg/day; [153]). According to current data, daptomycin appears to be safe up to a maximal daily dose of 12 mg/kg [160]. This variant therapy also seems to be effective when VRE (*E. faecium*) are likely. If infection with a resistant gram-negative pathogen is probable, the primary combination partner should be a carbapenem.

In patients without a septic disease course and without antibiotic pretreatment, if regression of symptoms is observed following catheter change, a watchful waiting strategy may be indicated or therapy commenced after identification of the pathogen. In cases of bacteremia caused by methicillin-sensitive *S. aureus* (MSSA) species, the rationality of de-escalation to flucloxacillin or the cephalosporin cefazoline has been demonstrated [161]. Other cephalosporins or β-lactam/BLI combinations cannot be recommended on the basis of current evidence [162]. If vancomycin treatment of a catheter-associated MRSA, CoNS, or enterococci BSI is unsuccessful, a combination of high-dose daptomycin (10–12 mg/kg/day) with gentamicin or rifampicin can be administered [136]. Case studies have described effective use of ceftaroline as a treatment option for daptomycin-refractory persistent MRSA bacteremia in patients with infectious endocarditis or osteomyelitis [164, 165]. In several studies on catheter-associated BSI with gram-positive pathogens, the new lipoglycopeptide dalbavancin showed signif-

icantly better outcomes than vancomycin in terms of clinical and microbiologic response rates [166, 167]. The duration of therapy depends on the course of infection. An uncomplicated *S. aureus* infection is represented by bacteremia without evidence of endocarditis, the absence of septic foci/metastatic infections, the absence of intravascular foreign bodies (vascular catheters, heart valve prostheses, vascular prostheses, pacemaker, etc.), a sterile follow-up blood culture collected 2–4 days after the initial positive blood culture, and defervescence within 72 h. Uncomplicated infections should be treated for at least 2 weeks. In patients with a complicated infection, treatment for 4–6 weeks is indicated [163]. Management of *Staphylococcus* bacteremia includes not only treatment of the infection and control blood cultures during therapy, but also transesophageal echocardiography (TEE) to exclude valve vegetation/endocarditis [163, 168, 169].

Nosocomial and ventilator-associated pneumonia

HAP and VAP are frequent causes of sepsis in intensive care medicine. According to their definitions, HAP is diagnosed when the symptoms of pneumonia arise >48 h after hospitalization. The terms established by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS; [110]) for the US American region in 2005, i. e., healthcare-associated pneumonia (HCAP) and nursing home-acquired pneumonia (NHAP), have not become established in Germany due to their lack of predictive value for infection with MDR pathogens. The term NHAP has now also been revised in the IDSA guideline. According to the definition, one speaks of VAP when the symptoms of pneumonia arise after at least 48 h of ventilation. The symptoms of VAP in ventilated patients are not very specific (purulent tracheal secretion, fever, newly appearing opacity on the chest x-ray, and compromised gas exchange), and it is not always possible to definitively differentiate VAP from other entities. The risk of VAP increases continuously during the first 7 days of ventilation, but declines again thereafter. HAP and VAP constitute up to 22% of all nosocomial infections [171]. With mortality rates of about 13% [172] and numerous other negative effects [173, 174] for patients, VAP is considered to be a more complex infection than HAP; however, with complication rates of 50% ([175]; e. g., empyema formation, renal failure, and sepsis), HAP is anything but a trivial challenge for ID specialists, and is also associated with mortality rates comparable to those of VAP [175, 176].

Calculated therapy of nosocomial pneumonia in sepsis patients without septic shock or anti-infective pretreatment, and who are also at a low risk of having an MRD pathogen, can initially comprise monotherapy with piperacillin/tazobactam [177]. Group 1 carbapenems (imipenem/cilastatin, meropenem) cover a similar pathogen spectrum as piperacillin/tazobactam, but are superior to piperacillin/tazobactam in the presence of ESBL-producing pathogens. Due to their activity against many *P. aeruginosa* isolates, cefepime or ceftazidime preparations represent an important element in the treatment of pneumonia. However, monotherapy of nosocomial pneumonia is not recommended in the German S3 guidelines because of limited effectiveness against gram-positive pneumonia pathogens [187]. In contrast, the IDSA mentions cefepime (not ceftazidime) as a substance suitable for monotherapy [170]. Initial treatment with fluoroquinolones (moxifloxacin or levofloxacin) is possible in principle, but must be critically evaluated. Monotherapy with an aminoglycoside is to be avoided [170]. Primary combination therapy of HAP/VAP with two substances potentially active against *P. aeruginosa* (and possibly extended by a preparation with action against MRSA) should be considered when the risk of infection with an MRD pathogen is high and/or the patient has reached the stage of septic shock. In this situation, German and American standards [170, 177] dictate therapy comprising a β-lactam (e. g., piperacillin/tazobactam, ceftazidime/cefepime, or a group 1 carbapenem) in combination with a fluoroquinolone active against *Pseudomonas* species (ciprofloxacin, levofloxacin), an aminoglycoside, or aztreonam [178]. These combinations sufficiently cover the most important and frequently highly resistant problem pathogens such as *P. aeruginosa*, as well as ESBL-producing gram-negative bacteria (*E. coli*, *K. pneumoniae*, *Acinetobacter baumannii*). Particularly the combination of carbapenem/fluoroquinolone generally achieves good effectiveness against resistant pathogens such as ESBL-producing *E. coli* or *K. pneumoniae*, as well as *P. aeruginosa*. For patients with anti-infective pretreatment, a change of substance class is also recommended in order to prevent and avoid possible resistance [178]. The IDSA recommendations consider the combination of two β-lactams to be of little use [170]. In cases where the MRSA risk is high (e. g., known colonization of the patient), an substance with activity against MRSA is required—at least in patients with nosocomial pneumonia with septic shock [177, 179]. Linezolid or vancomycin (not daptomycin; see below) can be administered for this indication. Individual patient characteristics and pathogen identification then lead to specific monotherapy (MRSA, *P. aeruginosa*, ESBL-producing *Enterobacteriaceae*, etc.). Therefore, for successful, rational treatment of VAP/HAP, knowledge of the pathogen and its specific resistance phenotype is highly important. Particularly in VAP/HAP caused by gram-negative MDR pathogens that are, e. g., susceptible to polymyxins (colistin, polymyxin B) or aminoglycosides, the combination of an intravenous (i. v.) and an inhalation therapy can be considered [170]. Although the evidence for an inhalation therapy is low, it does lead to a high local concentration of antibiotic at the site of infection (i. e., the lungs). If carbapenemases are detected in the isolated pathogen, treatment must be oriented towards the antibiogram and may necessitate administration of polymyxins (i. v. and inhaled; [170]). The fixed combination of ceftazidime/avibactam has also recently been approved for treatment of HAP. This combination has good in vitro efficacy against ESBL producers and carbapenemase synthesizers (*Klebsiella pneumoniae* carbapen-

emase, KPC; and oxacillinase, OXA-48), as well as against *P. aeruginosa*; it is therefore very interesting for targeted treatment of HAP caused by MPD pathogens with these resistance phenotypes. The combination of ceftolozane/tazobactam may receive approval for treatment of VAP and HAP in the near future. Results of recent studies are still awaited (NCT01853982, NCT02387372, NCT02070757). *Stenotrophomonas maltophilia* is normally resistant to carbapenems but generally susceptible to cotrimoxazole, which thus represents the typical therapeutic option—provided the pathogens are considered to be the cause of HAP/VAP. If this approach is not possible, other preparations must be evaluated (e. g., ceftazidime, moxifloxacin, levofloxacin). Carbapenems are generally effective against *Acinetobacter* species and are indicated in instances of high intrinsic resistance to other β-lactams. Panresistance to β-lactams, which is frequently accompanied by resistance to fluoroquinolones, renders combination of colistin with another substance dictated by resistance testing the only possible option. MRSA pneumonia can in principle be treated by vancomycin (alternatively teicoplanin) or linezolid [170, 178]. As a modern alternative for treatment of MRSA pneumonia, tedizolid can also be employed successfully: In the Linezolid in the Treatment of Subjects with Nosocomial Pneumonia Proven to be Due to Methicillin-Resistant *Staphylococcus aureus* (ZEPHyR; [179]) study, tedizolid was shown to be more effective than vancomycin. Since daptomycin is inactivated by surfactants, its administration in MRSA pneumonia is not rational [178]. A further option has been available since 2014, namely ceftobiprole (only HAP; [180]), which is also effective against MRSA. The duration of VAP and HAP treatment should only exceed 7 days in isolated cases. Clinical studies and meta-analyses of VAP/HAP treatment duration found no differences in terms of mortality, pneumonia recurrence, treatment failure, or duration of invasive ventilation when comparing short (7–8 days) and longer (up to 15 days) treatment durations [150, 170, 181, 182]. In a subgroup analysis of the study by Chastre et al. [150] on VAP, it was shown that in pneumonias caused by non-fermenters such as *P. aeruginosa* and *A. baumannii*, for equal mortality rates, the group with shorter treatment (8 days) had more recurrent infections (40.6 vs. 25.5%). However, this aspect is now judged by the IDSA to be so weak (at least for *P. aeruginosa*), that it is recommended against generalized prolongation of treatment [170]. The duration of antibiotic therapy of VAP and HAP is always based on clinical and radiologic criteria.

Identification of *Candida* species, enterococci, or CoNS in tracheal secretion from a non-neutropenic patient does not represent an indication for treatment. In the vast majority of cases, this is not an invasive infection but rather represents the resident local flora or sample contamination.

Intraabdominal infections

Intraabdominal infections (IAI) are the cause of severe sepsis or septic shock in about 30% of patients, and are one of the most frequent diagnoses in surgical ICUs [26]. In 90% of cases, the IAI requires primary surgical treatment and antibiotic therapy. Close collaboration with surgical colleagues is vital from the outset. The calculated antibiotic therapy should always cover aerobic and anaerobic gram-negative pathogens, as well as gram-positive pathogens of the gastrointestinal tract [183]. Although one still differentiates between ambulant and nosocomial IAI, it must be kept in mind that patients these days are frequently colonized with MDR pathogens due to long-distance travel, antibiotic pretreatment, or immunosuppression. Sepsis of intraabdominal origin without septic shock or pretreatment can initially undergo anti-infective treatment with piperacillin/tazobactam or carbapenem monotherapy. Based on knowledge of the local pathogen spectrum, combination of, e. g., a cephalosporin or a fluoroquinolone with metronidazole is also possible. In particularly severe disease courses, tigecycline can serve as the combination partner, which has activity against *Enterobacteriaceae* and VRE. In refractory IAI, an invasive *Candida* infection and antimycotic treatment must be considered; echinocandins are a possible treatment option [153]. If the response to treatment is inadequate, surgical intervention must be discussed. Postoperative IAIs (e. g., anastomotic insufficiency after anterior rectal reconstruction) are associated with a high risk of MDR infection. In these cases, a selected pathogen spectrum encompassing enterococci (including VRE), gram-negative problem pathogens (carbapenemase synthesizers), fungi, and rarer KPC producers must be expected. In this situation, administration of second substance additional to a carbapenem must therefore be considered—at least in patients with septic shock—in order to broaden the empirically addressed spectrum. Alongside carbapenems (such as meropenem, imipenem/cilastatin, ertapenem), e. g., tigecycline and fosfomycin (never as monotherapy) can be used. A treatment with activity against MRSA is indicated when a patient with a nosocomial cIAI is colonized with MRSA or has a high risk of an MRSA infection [183]. MRSA-cIAI is then additionally treated with vancomycin, tigecycline, or linezolid [183]. New escalation variations include ceftolozane/tazobactam or ceftazidime/avibactam [184, 185] in combination with metronidazole for cIAI with resistant gram-negative pathogens [186]. Provided effective surgical control of the infection is achieved and the patient's clinical condition improves, a treatment duration of 4–7 days is sufficient [149, 153, 183].

Particularly in esophageal surgery is mediastinitis due to the anastomotic situation a possible infection focus. Frequent pathogens after esophageal surgery are mainly gram-positive cocci, anaerobes, and *Candida* species. Primary treatment of mediastinitis should comprise a group 1/2 carbapenem (imipenem/cilastatin, ertapenem, meropenem). Alternatively, an acyl-aminopenicillin/BLI or group 3/4 cephalosporin with metronidazole can be administered. If there is a risk of MRSA, linezolid, tigecycline, or daptomycin is indicated [153]. With respect to the possibility of invasive mycosis, an antimycotic may be indicated. In patients with septic shock or

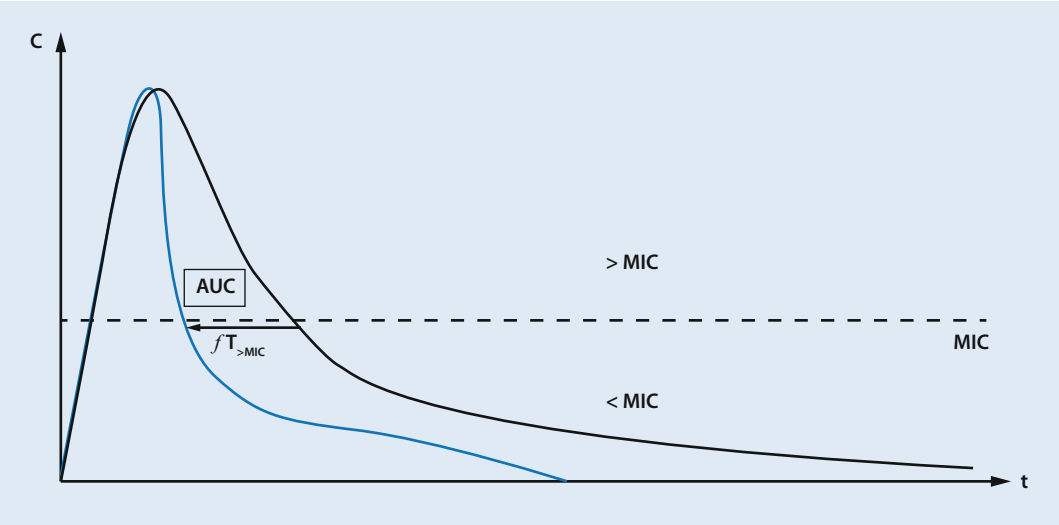

Fig. 2 ◀ Influence of augmented renal clearance of a β-lactam on the course of serum levels (*blue curve*) in comparison to the course of serum levels with physiologic elimination (*black curve*), with an *arrow* indicating the reduction in the interval during which serum levels above are above MIC. *MIC* minimum inhibitory concentration, *AUC* area under the curve, *C* serum concentration, $fT_{>MIC}$ time interval during which the serum concentration of antibiotic is above the pathogen-specific MIC, *t* time

a complicated disease course, surgical intervention must also be considered. In addition to endoscopic exploration, modern concepts include insertion of a vacuum suction system (e. g., Endo-SPONGE®, B. Braun, Melsungen, Germany) or an interventional drainage catheter. As a last resort, surgical revision of the area/anastomosis must be performed.

Necrotizing fasciitis/Fournier gangrene is a potentially life-threatening soft tissue infection that frequently exhibits a fulminant disease course. Alongside classical streptococcal infections, predominantly polymicrobial infections with gram-negative pathogens and *S. aureus* also exist in necrotizing fasciitis. In light of the pathogen spectrum and frequently polymicrobial infection, primary treatment must comprise a sufficiently broad combination therapy. Generally, acyl-aminopenicillins/BLI or a carbapenem (e. g., meropenem), penicillin G, and clindamycin (or linezolid) are combined. Clindamycin is a sufficiently tissue-penetrating lincosamide with activity against anaerobes and *S. aureus*; in combination with a β-lactam, it also inhibits protein biosynthesis in gram-positive pathogens. The latter effect can reduce the rate of complications due to microbial exotoxins [187]. In patients with clindamycin intolerance, linezolid (or tedizolid) represents an alternative (caveat: hemotoxicity, optic neuritis; [187]). Penicillin G has the greatest effectivity against streptococci. If infection with MRSA is likely, in the context of a soft tissue infection, linezolid should be preferred to vancomycin [153]. For some time now, therapeutic alternatives have been available in the form of tedizolid, or more recently, oxazolidinone. Due to the fulminant disease course and frequently fatal symptoms upon inadequate control of the infection, the necessity of surgical reevaluation and the indication for revision surgery must be checked regularly.

Other causes

Other causes of sepsis include endocarditis, community-acquired pneumonia, complicated urinary tract infections, osteomyelitis, erysipelas, and meningitis. For treatment recommendations, the authors refer to the guidelines of the respective specialist societies (www.awmf.org).

Pharmacokinetic concepts

Calculated antibiotic therapy of sepsis aims to achieve a sufficiently high drug concentration. Wherever possible, this objective should be reached with the first dose of antibiotic, i. e., with the loading dose (LD). This is particularly important for the time-dependent β-lactams [188]. Independent of organ dysfunction, augmented renal clearance (ARC), or organ support therapy, sufficient plasma levels must be maintained during the course of therapy in order to maximize the anti-infective potency of β-lactams. Whereas the necessary plasma concentration of an antibiotic is determined primarily by the pathogen-specific MIC, estimation of drug elimination rates and the volume of distribution is very difficult in critically ill patients. Particularly in patients with sepsis and septic shock, almost all anti-infective substances lead to considerable changes in substance-specific pharmacokinetics. The example in ◘ **Fig. 2** shows the effect of ARC on the kinetics of plasma concentrations of a β-lactam antibiotic. ARC of β-lactam results in premature decline of the serum level to below the pathogen-specific MIC, therefore reducing the time for which the concentration remains above the MIC ($fT_{>MIC}$)—a factor which is crucial for the bactericidal effect of the preparation.

In order for the calculated antibiotic therapy to cover the widest possible spectrum of potential pathogens when the identity of the pathogen is unknown, broad-spectrum antibiotics in the highest possible concentrations are required at the site of infection. Dosage recommendations and microbiologic determination of the susceptibility of a bacterial strain to particular antibiotics are based on the assumption that the pharmacokinetics of the drug correspond to those of a "normal patient." However, the distribution and elimination capacity of various antibiotic groups is highly variable in sepsis patents, and difficult to predict [189–196]. Although specialist societies such as the Paul Ehrlich Gesellschaft (PEG) or IDSA allow for this in their

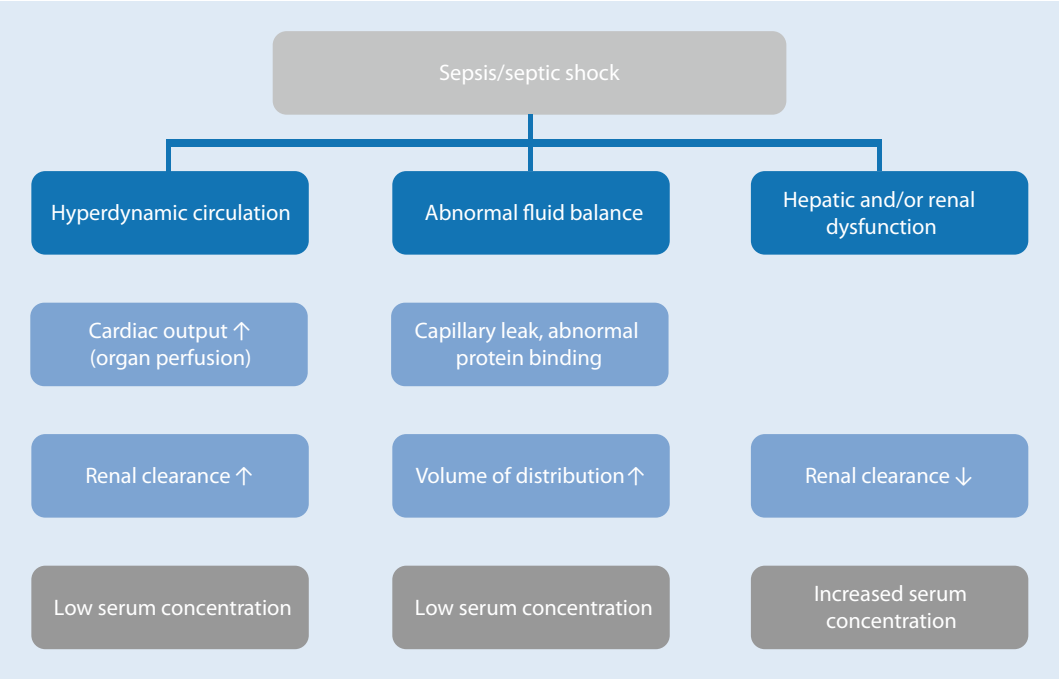

Fig. 3 ◄ Pathophysiologic influences of sepsis on the serum concentration of antibiotics

recommendations [153, 178, 183], these facts are still paid too little attention in clinical routine—with the effect of increased mortality in seriously ill patients [104, 197–200]. Numerous organ dysfunctions are at the center of substance-specific changes in pharmacokinetics. The resultant changes in antibiotic concentrations in various compartments can lead to treatment failure on one hand, and development of resistance on the other; moreover, these changes may predispose the patient to potential toxic effects [159]. The time-dependent β-lactam antibiotics are particularly problematic in this context. A summary of the effects of various important pathophysiologic changes occurring during sepsis on the serum concentrations of antibiotics is presented in **Fig. 3**.

Whereas a considerably shorter time above the MIC is sufficient for bacteriostasis, maximal bactericide with penicillins and cephalosporins requires an unbound-drug concentration exceeding the MIC for at least 50–70% of the dosing interval ($fT_{>MIC}$). Carbapenems require an $fT_{>MIC}$ of about 40% [153, 198]. The $fT_{>MIC}$ is lower for carbapenems because a more pronounced post-antibiotic effect is assumed for this substance class than for other substances [198]. These recommendations are derived from animal experiments; clinical investigations underscore the fact that in sepsis patients, an $fT_{>MIC}$ of 100% elicits a more effective anti-infective effect, and is thus relevant for outcome [190, 201–203]. Especially on the basis of striving to achieve adequate tissue concentrations even in deep-lying compartments (pneumonia; bone infections; infections of the central nervous system, CNS)—frequently in the context of disturbed microcirculation in sepsis patients [204–206] and also wishing to avoid development of resistance [207, 208]—many experts recommend aiming for a concentration of β-lactam antibiotics in the primary compartment (serum/plasma) that exceeds the MIC by 4-times (up to 6-times) for 60–100% of the dosing interval [209]. In addition to individual dosing of antibiotics, the current DGI guideline [124] names therapeutic drug monitoring (TDM) as a possibility for treatment management and reduction of undesirable side effects of antibiotics.

How difficult it can be to reach effective serum/plasma concentrations in sepsis patients was illustrated by Roberts et al. [202] in a prospective study from 2014: Of 248 patients with a severe infection, 16% did not even achieve the minimum pharmacokinetics/pharmacodynamics (PK/PD) goal of 50% of the dosing interval above the MIC (50% $fT_{>MIC}$). This result was associated with a significantly reduced probability of a good clinical outcome. That insufficient plasma concentrations represent a frequent problem in sepsis patients was demonstrated by Taccone et al. [209] and Udy et al. [210], but also in the prospective study by Roberts et al. (Defining Antibiotic Levels in Intensive Care Unit Patients, DALI; [202]) using the example of β-lactams. In the latter study, the dose of β-lactam antibiotic had to be adjusted in 175 of 236 patients (75%); in 119 cases (50.4%) this adjustment comprised a dosage increase [211]. The results of the study by Taccone et al. showed that following the initial administration of the standard dose in critically ill patients, only meropenem achieved a sufficient pharmacokinetic profile in 75% of patients (12/16). In contrast, ceftazidime (28%), cefepime (16%), and piperacillin/tazobactam (44%) only achieved an unsatisfactory PK profile, with correspondingly insufficient effects [209]. These data illustrate not only the problems associated with antibiotic therapy, but also show how important precise knowledge of the pharmacodynamic and pharmacokinetic characteristics of the employed antibiotic is.

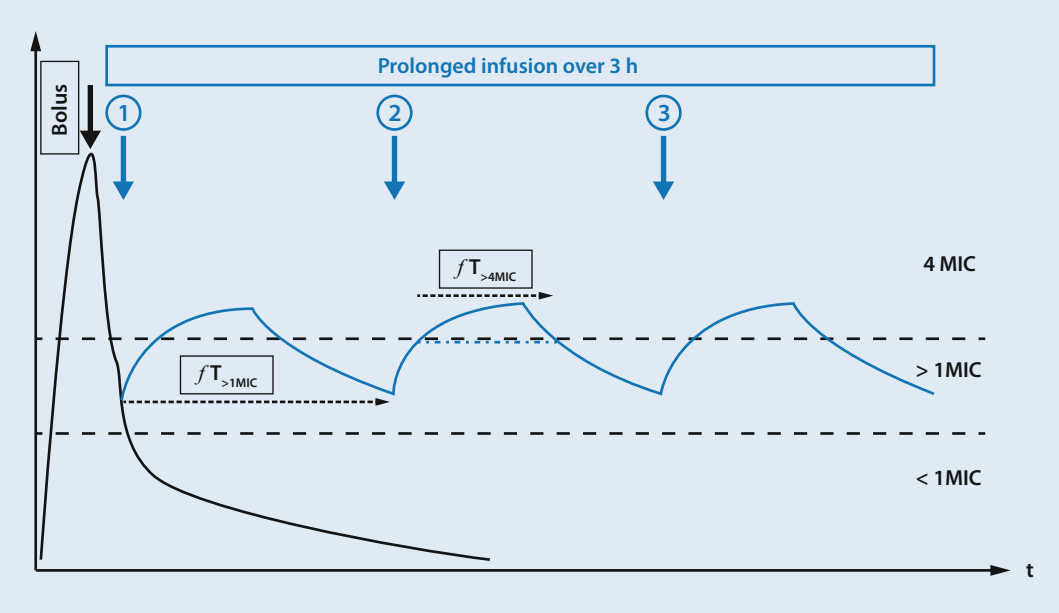

Fig. 4 ◀ Effect of prolonged infusion of β-lactams in sepsis. $fT_{>xMIC}$ time interval during which the serum concentration of antibiotic is 1- or x-times above the pathogen-specific minimum inhibitory concentration (*MIC*)

For a more effective treatment of critically ill sepsis patients, the authors of the current article recommend an infusion regimen that it is on one hand feasible, while on the other hand capable of at least partially counteracting the aforementioned pharmacokinetic problems: prolonged infusion of β-lactam antibiotics. In this scenario, an initial high-dose bolus application over 20–30 min first generates a peak plasma level, which should ensure a sufficient concentration of antibiotic in the target compartment. Thereafter, subsequent doses are administered as a prolonged infusion over 3 h via an infusion pump. In this manner, $fT_{>MIC}$ can be maximized and the effectiveness of β-lactams increased via optimal exposure of the antibiotic to the pathogen (**Fig. 4**). After reaching a peak plasma level, intermittent bolus applications (**Fig. 4** *black curve*) are characterized by a rapid decline of the plasma concentrations to below the MIC. This results in relatively short time spans during which the effective concentrations (for sepsis and septic shock) are maintained ($fT_{>1-4MIC}$). After an initial bolus (**Fig. 4** *blue curve*), prolonged infusion over 3 h (up to 4 h) achieves a significant extension of the time interval during which the effective concentration is maintained ($fT_{>MIC}$ and $fT_{>4MIC}$).

A beneficial effect of prolonged piperacillin/tazobactam infusion in patients with *P. aeruginosa* infections was shown in 2007 by Lodise et al. [212]. One year later, Lee et al. demonstrated using pharmacokinetic models that prolonged application of meropenem and imipenem/cilastatin increased the cumulative probability of a $fT_{>MIC}$ sufficient for clinically relevant pathogens [213]. After the DALI study was able to show regular insufficient β-lactam concentrations in critically ill patients [202], a subgroup analysis of these data by Abdul-Aziz et al. demonstrated that prolonged/continuous infusion of piperacillin/tazobactam and meropenem led to significant improvement of 30-day survival ($p < 0.05$) in patients with pneumonia and/or SOFA score >9, and the cure rate of patients with SOFA >9 was also significantly higher with prolonged infusion [214].

Linezolid also showed a high variability of plasma levels in patients with severe infections, with insufficient blood concentrations using standard dosing concepts. Current data from Taubert et al. [215] show that in this case—similar to vancomycin [158]—continuous infusion can help to attain effective PK/PD targets and reduce toxicity.

In summary, for the treatment of sepsis, prolonged infusion of β-lactam antibiotics after an initial bolus application should be preferred to intermittent bolus therapy. For improved treatment management as well as in order to avoid over- and under-dosing, therapeutic concentration monitoring may be a rational complementary module. Particularly in the context of sepsis, clinicians lack a parameter in the highly acute phase (24–48 h) by which they can judge the success or lack of success of the calculated antibiotic therapy. Here, TDM of β-lactams can at least demonstrate that effective therapeutic plasma concentrations have been reached. For this reason, TDM is now mentioned in the DGI recommendations as a rational complementary and treatment optimizing module [124, 153]. Despite the fact that a positive influence of TDM on patient mortality remains unproven as yet, there are a variety of pathophysiologic conditions under which TDM would appear essential, i. e., high variability of drug distribution, changes in metabolism and elimination, organ dysfunction, organ support therapy/extracorporeal support systems, interactions of diverse drug groups, or dangerous over-/under-dosing of the antibiotic, and this is clearly preferred in the corresponding studies [159, 216–223]. TARGET was the first German prospective multicenter study to investigate the influence of TDM of piperacillin/tazobactam in sepsis patients (https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-000136-17/DE). Prolonged

infusion of β-lactams is, however, not approved for any of the commercially available preparations, and should only be performed if the substance is at least sufficiently stable at room temperature over the application interval of 3–4 h. This holds true for piperacillin/tazobactam, meropenem, ceftazidime, and cefepime.

Conclusions

Rapid diagnosis and treatment of sepsis is of critical importance for the patients. For this reason, a new and not uncontroversial definition of sepsis was established in 2016, which is based primarily on the presence of infection-associated organ dysfunction. The presence of organ dysfunction should be established in the first instance using a modified SOFA score (qSOFA).

Blood cultures remain the gold standard of ID diagnostics. The time point of sampling, sample site, and correct sampling technique can eliminate a number of potential sources of error. Molecular genetic techniques for pathogen diagnosis represent highly promising approaches; however, these cannot currently replace blood cultures and are not yet established in clinical routine. These methods may gain importance in the future.

Antimicrobial therapy is one of the cornerstones of successful sepsis treatment. High sepsis mortality rates and the often unknown causal pathogen render initial application of a high-dose broad-spectrum mono- or combination therapy essential. Commencement of treatment within 1 h of recognition of sepsis must be strived for, since every delay leads to a significant increase in mortality. Regular reevaluation of the infection and the antibiotic therapy should be dictated by practical guidelines and coordinated within a multidisciplinary team (ABS team).

The grave pathophysiologic changes accompanying sepsis (changes in the volume of distribution, ARC, organ support therapies) continue to frequently receive inadequate consideration, although these can have a profound influence on the pharmacokinetics of antibiotics. In light of these changes and in order to avoid incorrect dosing and suboptimal drug concentrations in sepsis patients, treatment is increasingly diverging from standard dosing concepts and being oriented toward the PK/PD index of the particular antibiotic. For β-lactams this means that, e. g., a prolonged (or continuous) infusion should be preferred in sepsis patients, such that the optimal drug concentration ($fT_{>MIC}$) can be achieved in the "blood" compartment throughout the dosing interval. For treatment management in sepsis, TDM is available. Studies assessing the benefit of TDM have demonstrated positive results in terms of more effective treatment, improved stability of plasma levels of the antibiotic, and reductions in treatment duration.

New antibiotics cover a defined spectrum of pathogens and are characterized predominantly by their highly potent activity against MDR pathogens. In order to delay development of resistance, application of these new preparations should be limited to specific escalation therapy of MDR infections. The administration of new antibiotics should be discussed within and decided upon by an ABS team. Only in this way can the rational use of new antibiotics be ensured.

Practical conclusion

- **In-depth knowledge of the pathophysiologic changes associated with sepsis and their influence on the pharmacokinetics of antibiotics (particularly β-lactams) has led to revision of the use of β-lactams in particular.**
- **With respect to PK/PD targets, prolonged infusion of β-lactams (after an initial bolus) should be preferred to intermittent application in sepsis.**
- **Studies now exist which prove the advantages of prolonged infusion over intermittent bolus application. Irrespective of the dosing strategy, an initial LD (high-dose bolus application) is required.**
- **TDM can be useful for sepsis treatment management.**

Corresponding address

Dr. D. C. Richter
Department of Anesthesiology, Heidelberg University Hospital
Im Neuenheimer Feld 110, 69120 Heidelberg, Germany
daniel1.richter@med.uni-heidelberg.de

Compliance with ethical guidelines

Conflict of interest. D. C. Richter, A. Heininger, T. Brenner, M. Hochreiter, M. Bernhard, J. Briegel, S. Dubler, B. Grabein, A. Hecker, W. A. Kruger, K. Mayer, M. W. Pletz, D. Storzinger, N. Pinder, T. Hoppe-Tichy, S. Weiterer, S. Zimmermann, A. Brinkmann, M. A. Weigand, and C. Lichtenstern declare that they have no competing interests.

This article does not contain any studies with human participants or animals performed by any of the authors. Local ethical guidelines applied to all studies included in the current review.

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