


NARRATIVE REVIEW



Antibiotic therapy for severe bacterial infections

Jean-François Timsit^{1,2,3*} , Lowell Ling⁴, Etienne de Montmollin^{1,2,3}, Hendrik Bracht⁵, Andrew Conway-Morris^{6,7}, Liesbet De Bus^{8,9}, Marco Falcone^{10,11}, Patrick N. A. Harris^{12,13,14,15}, Flavia R. Machado¹⁶, José-Artur Paiva^{17,18,19}, David L. Paterson^{12,20}, Garyphallia Poulakou²¹, Jason A. Roberts^{12,14,22,23}, Claire Roger²³, Andrew F. Shorr²⁴, Alexis Tabah^{12,25,26} and Jeffrey Lipman^{12,14,23,26,27}

© 2025 Springer-Verlag GmbH Germany, part of Springer Nature

Abstract

Background: Early antibiotic therapy for patients with severe infections is essential to improve outcomes. Conversely, use of overly broad antibiotic therapy for susceptible pathogens or unnecessary antibiotics in patients without bacterial infections is associated with adverse life-threatening events and superinfections. Antibiotics-induced changes in the human microbiota alter both immune and metabolic systems. Uncontrolled antibiotic use encourages emergence of antibiotic-resistant organisms. Around 50% of ICU patients receiving antibiotic therapy do not have confirmed infections, whilst de-escalation and shortened treatment duration are infrequently performed. Mortality from serious infections remains high, highlighting the need for treatment optimisation.

Methods: Narrative review.

Objectives: To summarise the available evidence, emerging options, and unresolved controversies in optimising antibiotic therapy in severe infections.

Results: Local epidemiology, underlying illnesses, accessibility to health care systems, and diagnostic and therapeutic resources are important factors to consider. Rapid diagnostic tests combined with individualised decision-making improve the selection of antibiotic therapy. Rapid de-escalation to narrow-spectrum monotherapy and shortening of the duration of therapy should be the rule. Uncertainty still persists regarding the personalisation of therapy for difficult-to-treat resistant bacteria. Pharmacokinetic (PK) optimisation and prolonged or continuous beta-lactam use is safe and may improve outcomes. Therapeutic drug monitoring (TDM) should be used, especially when altered volume of distribution and/or drug clearance is suspected or where toxicity is likely. The impact of TDM combined with prompt dose adjustment is encouraged. Emerging technologies including rapid broad diagnostic tests and electronic antibiotic optimisation tools will further support collaboration between pharmacists, microbiologists, infectious diseases specialists, and intensivists for optimising antibiotic therapy and stewarding these precious resources.

Keywords: Sepsis, Antibiotics, Rapid diagnostic tests, Antibiotic stewardship, Pharmacokinetics, Critically ill

Introduction

Each year, 48.9 million individuals are affected by sepsis, resulting in 11 million related deaths globally [1]. Hospital mortality from severe infections remains high, with community-acquired pneumonia (CAP) exhibiting mortality rates of 20–30%. Hospital-acquired infections, such as hospital-acquired pneumonia (HAP),

*Correspondence: Jean-francois.timsit@aphp.fr

² APHP, Bichat Hospital, Medical and Infectious Diseases ICU, Paris, France
Full author information is available at the end of the article

ventilator-associated pneumonia (VAP), or hospital-acquired bloodstream infection (HABSI), have mortality ranging between 20 and 50% [2–4]. Since bacterial pathogens account for over 70% of serious infections and sepsis, optimising antibiotic therapy is essential for improving outcomes [5, 6]. However, the need for early antibiotic administration must be carefully balanced against the risks of overuse, which contributes to the growing threat of antimicrobial resistance (AMR) [7]. Rapid pathogen detection can guide the initiation, selection, and duration of antibiotics, and multidisciplinary collaboration involving clinicians, microbiologists, and pharmacists is beneficial. In this narrative review, we provide a comprehensive overview of the epidemiology of severe infections, clinical contexts, diagnostics, therapeutic strategies, and approaches to optimise antibiotic use in critically ill patients.

Epidemiology of severe infections

Community vs hospital-acquired

Classifying infections based on acquisition site—community-acquired (CAI), hospital-acquired (HAI), or

ICU-acquired (ICU-AI)—is crucial for assessing the risk of AMR and selecting appropriate antimicrobial therapy. These groups also differ in infection source, microbial epidemiology [1]. Studies consistently report increasing duration of hospital stay and mortality from CAI to ICU-AI [8–10], with ICU-AI frequently occurring in debilitated patients with multiple comorbidities, prior antibiotic exposure, and resistant pathogens [10].

CAIs typically involve respiratory, intra-abdominal, or urinary infections. In contrast, HAIs and ICU-AIs are often linked to medical interventions, including surgical site infections ventilatory-acquired pneumonia, intravascular catheter-related infections, and intra-abdominal infections [2, 10, 11] with pathogens varying according to acquisition location, and source (Fig. 1).

Bacterial resistance is associated with 4.9 million deaths globally, with sub-Saharan Africa, South Asia, and Eastern Europe carrying the highest burden. AMR—including multidrug resistance (MDRO)—increases progressively from CAI to ICU-AI, although patterns vary by region [4, 11]. AMR may delay the initiation of appropriate therapy which worsening

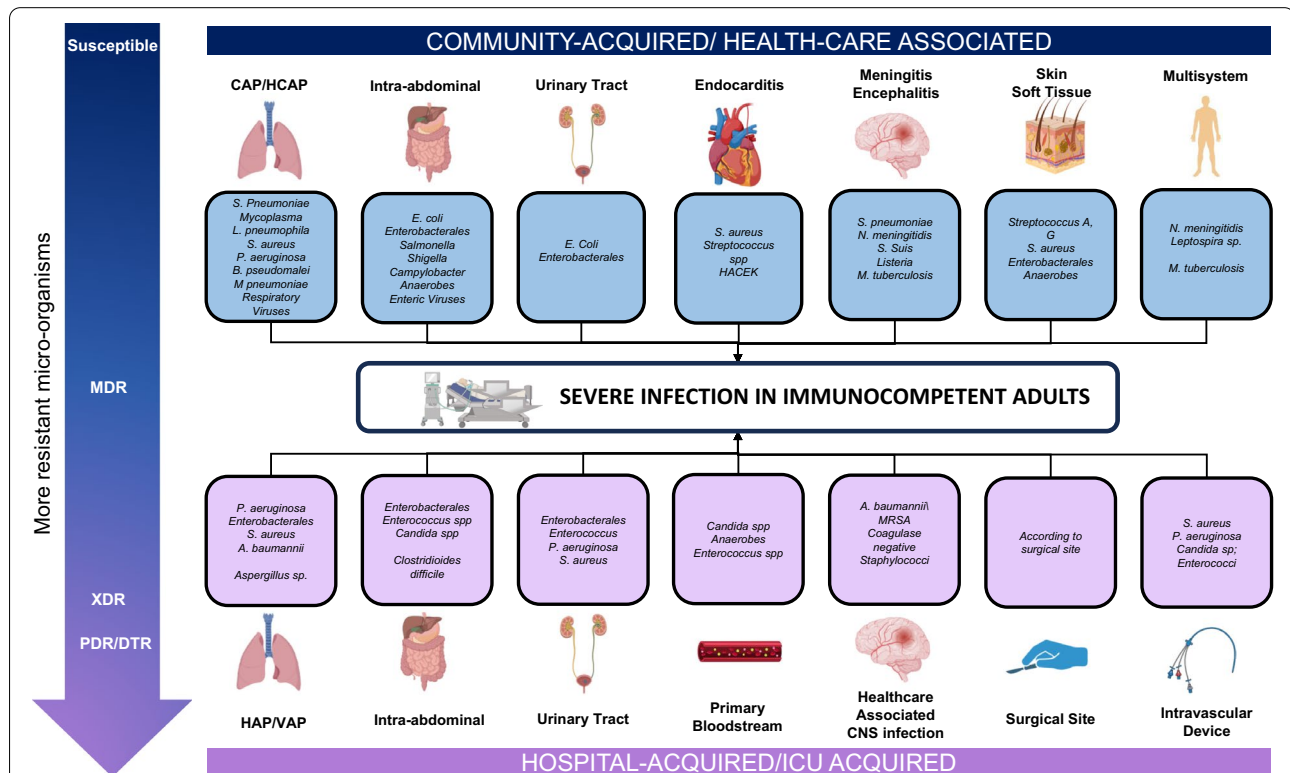


Fig. 1 Severe infection in immunocompetent individuals. *UTI* urinary tract infection; *CAP* community-acquired pneumonia; *HCAP* healthcare-associated pneumonia; *HAP* hospital-acquired pneumonia; *VAP* ventilatory-associated pneumonia; *MDR* multidrug-resistant bacteria; *XDR* extensively drug-resistant bacteria; *PDR* pan-drug-resistant bacteria; *DTR* difficult-to-treat bacteria. NB: for community/healthcare-associated meningo-encephalitis consider also viruses such as HSV/VZV. For multisystem, community-acquired infections consider the risk of non-bacterial diseases such as Malaria or Dengue

outcomes [2]. Whilst current AMR data do not always distinguish CAI and HAI, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) appears to have plateaued [12] (see <https://data.who.int/indicators> for details). Meanwhile, extended-spectrum beta-lactamase-producing *E. coli* is increasing currently representing 42% of the BSIs recorded by WHO, and exceeding two-thirds of cases in the Middle East, Africa and Asia. For HAIs, carbapenem-resistance Enterobacteriales (CRE) and *A. baumannii* (CRAB) are on the rise [13, 14], particularly metallo-beta-lactamases, (NDM) and OXA-48 producing strains some of which have spread into community settings.

Indeed, infections with AMR organisms in the community are more common in the case of recent and frequent use of antibiotics, especially within the past 90 days, exposure to healthcare settings (recent hospitalisation, residence in nursing homes, or long-term-care facilities). Comorbidities, such as COPD, chronic renal failure, and diabetes, are other factors to consider. Finally, high-risk social environments, overcrowding or poor sanitation, and IV drug abuse are other notable factors of infections due to AMR organisms in the community.

Low- and-middle-income nations

Resource-poor settings bear a disproportionate sepsis burden, accounting for 85% of cases and deaths. Most sepsis cases in these regions are CAI, especially diarrheal illnesses in children under five years of age [1]. HCAs are also prevalent, often secondary to non-communicable diseases [1] and maternal disorders [1, 15]. A microbiological diagnosis is often lacking due to limited resources and access to microbiological tests. The incidence and mortality of sepsis are inversely related to socioeconomic indicators like income and education [16]. Similar to high-resource settings, pyogenic bacterial pathogens dominate; however, leptospirosis, melioidosis, typhus, and tuberculosis are also prevalent. Additionally, severe forms of malaria, dengue, and other viral haemorrhagic fevers are common [17], as are coinfections with HIV [18] and tuberculosis [19].

Delays in seeking and accessing care—due to low health literacy, cultural beliefs, geography, financial barriers, and insufficient infrastructure—contribute to poor outcomes [20–22].

Clinical management is further hampered by limited personnel, diagnostics, ICU capacity [18], and overcrowded emergency departments (ED) [23] or general wards [24, 25]. Restricted access to microbiological testing impairs diagnosis and hinders antimicrobial stewardship (AMS), fostering antimicrobial inadequacy and resistance [26–28].

When to start and not to start antibiotics?

Antibiotics and source control are key pillars of the treatment of severe bacterial infections [29, 30]. Ideally, antibiotics should target confirmed bacterial infections guided by objective criteria (Fig. 2). However, diagnosing infections, sepsis, and septic shock remains complex, despite diagnostic advancements [31], and uncertainty often leads to antibiotic overuse.

Current guidelines emphasise two decision-making factors: likelihood of infection and illness severity [29]. In patients with shock or high suspicion of bacterial infection, antibiotics should be administered immediately—within the hour. In suspected sepsis without shock, a 3-h diagnostic window is preferred to reduce overtreatment.

Currently, there is no single biomarker that reliably distinguishes infection-related shock from other causes of shock and inflammation. Commonly used biomarkers, e.g., C-reactive protein (CRP) and procalcitonin (PCT), lack sufficient specificity and sensitivity to reliably guide antibiotic initiation [32]. A multifaceted approach, including patient history, clinical examination, laboratory findings, and utilising imaging studies should therefore be adopted in the diagnosis of infection [33, 34]. Microbiological tests can confirm the presence of bacterial pathogens, but must be appropriately interpreted to differentiate colonisation from true infection. Rapid molecular and microbiological techniques are transforming diagnostics (see later).

First, antibiotics should only be used for true bacterial infections. In cases where source control (e.g., catheter removal in the absence of positive blood culture) is complete, antibiotics may not always be necessary [35, 36]. A watchful-waiting approach is appropriate when patients are stable and closely monitored allowing for precise diagnosis and more targeted therapy [37]. Meanwhile, close monitoring is needed to detect clinical deterioration and start empirical therapy if microbiological documentation is pending. The results of before-after studies suggested that this conservative strategy may be beneficially applied for nosocomial infections including VAP [38, 39]. Antibiotic initiation must consider not only whether to treat, but also the appropriate agent and spectrum of treatment, factoring in illness severity and AMR risk [40, 41].

Ultimately, the decision to start or withhold antibiotics requires careful balancing of risks and benefits, ensuring that treatment is both timely and appropriate whilst avoiding unnecessary antimicrobial use.

Specific issues

Migrants/travellers, emerging infectious diseases

The globalisation of travel and migration increases the risk of emerging infectious diseases (EIDs). Table 1 lists

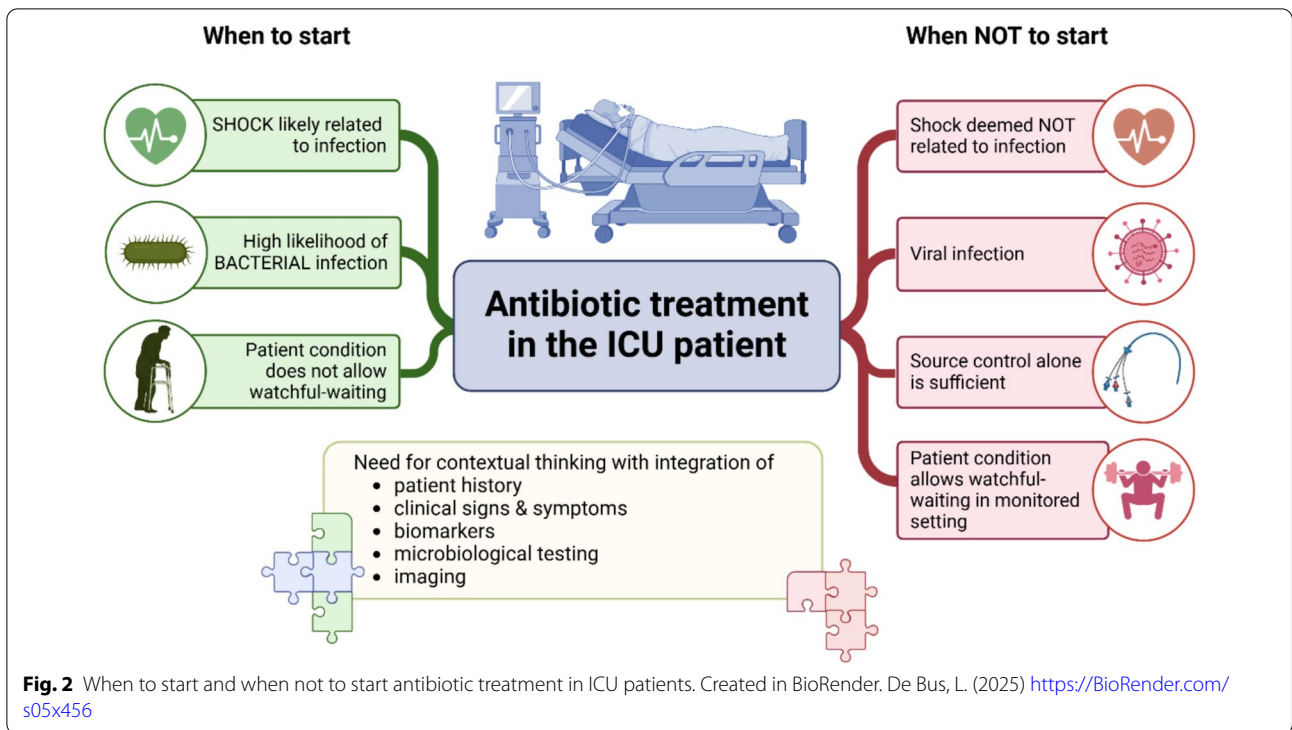


Table 1 Emerging and re re-emerging Infectious Diseases leading to ICU admission in Travelers and Migrants [45, 48, 49]

Disease	Area of acquisition	Transmission	Clinical picture	Potential for ICU admission
Malaria (<i>Plasmodium falciparum</i> more likely)	Sub-Saharan Africa, Asia	Mosquito bite Anopheles	Fever, chills, anaemia, organ failure	High
Enteric fever	India and South-east Asia	Consumption of contaminated food or water containing <i>Salmonella typhi</i> or <i>S. paratyphi</i> species	Fever, chills, bradycardia, rash. Shock and sepsis. Encephalopathy, intestinal perforation	Moderate to high
Rickettsial diseases	South Africa, Mediterranean, India, South America, Korea, Russia	Different vectors (lice, mites, or ticks)	The classical clinical triad of fever, rash, and eschar ("tache noire") should raise suspicion. Myalgia, headache, cough	Moderate to high
Tuberculosis (including multidrug-resistant-TB)	Global	Airborne	Cough, fever, weight loss, respiratory failure, central nervous system disease	Moderate
Leptospirosis	Endemic in tropical/subtropical regions: South & Southeast Asia, Central/South America, Caribbean, parts of Africa	Skin/mucosal contact with water or soil contaminated by urine of infected animals (especially rodents)	Sepsis like shock, intra-alveolar haemorrhage, tubulointerstitial nephritis. Myocarditis, Jaundice also common	Moderate to high
Dengue fever	South and Central America, including the Caribbean, Southeast Asia, Kenya, and Tanzania	Mosquito bite	Vary from mild fever, haemorrhagic fever to dengue shock syndrome	Moderate to high

NB: according to symptoms many other diseases should be considered but are rare. Ebola, Lassa, Crimean-Congo HF, Yellow Fever: may present with haemorrhagic shock. Bacterial meningitis is common. Japanese Encephalitis, West Nile virus, Oropouche virus are common causes of severe neurologic disease seen in travelers

common EIDs. Travellers and migrants may be exposed to pathogens uncommon in their destination countries. A retrospective study of 14,554 ICU admissions in France

showed that undocumented migrants were younger, and more likely to have infections, shock, or respiratory failure, though with similar mortality to general ICU

patients [42]. Another study showed increased rates of ICU admission and ARDS in migrants [43], both studies showing that delayed access to primary care is a major driver of ICU admission.

Overcrowding, malnutrition, and limited healthcare access exposes migrant populations to gastrointestinal and respiratory infections. Returning travellers with acute febrile illness are most commonly diagnosed with malaria, dengue, or rickettsial infections and may carry MDROs even years later [44, 45]. Notably, 2–4% of febrile travellers require ICU admission, primarily due to *Plasmodium falciparum* infections [45, 46].

A comprehensive travel and exposure history, awareness of incubation periods and regional prevalence, and referencing global maps of outbreaks (e.g., CDC (<https://www.cdc.gov/outbreaks/index.html> accessed 01/04/2025)) are essential for diagnosis. Empiric protocols include antimalarials (e.g., artesunate) and one or more antibacterial drugs (ceftriaxone + doxycycline/azithromycin) [47]. Rapid pathogen testing and early infectious disease consultation are key, along with appropriate infection control precautions [48].

Immunocompromised patients

Immunosuppression encompasses solid organ cancers, haematological malignancies, autoimmune diseases,

organ transplantation, and HIV/AIDS. In recent decades, the survival of immunocompromised patients has improved, leading to increased prevalence in the population (2.7%–2013, 6.6% in 2021 in the U.S.) [50]. In the EPIC III cohort, 24% of the 15,202 ICU patients included were immunocompromised, 41% of whom were admitted for an infection [51]. Sepsis outcomes in immunosuppressed patients vary according to underlying condition: cancer patients face higher mortality due to intrinsic vulnerabilities [51], whereas solid organ transplant recipients tend to have lower mortality than non-transplant patients [52].

Immunocompromised individuals are vulnerable to a wide range of pathogens, including opportunistic organisms. T-cell dysfunction and steroids predispose to fungal/mycobacterial infections [53], whilst other deficits influence bacterial susceptibility (Fig. 3). Nevertheless, empirical antibiotic therapy must always cover classical bacteria in these patients. In CAP, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Haemophilus* spp. are the most common [54], whilst non-classical CAP pathogens such as *Pseudomonas aeruginosa* should be considered only in those with risk factors such as COPD or prior colonisation.

Risk of MDROs is more closely tied to repeated hospitalisations or antibiotic exposure than immune status [54,

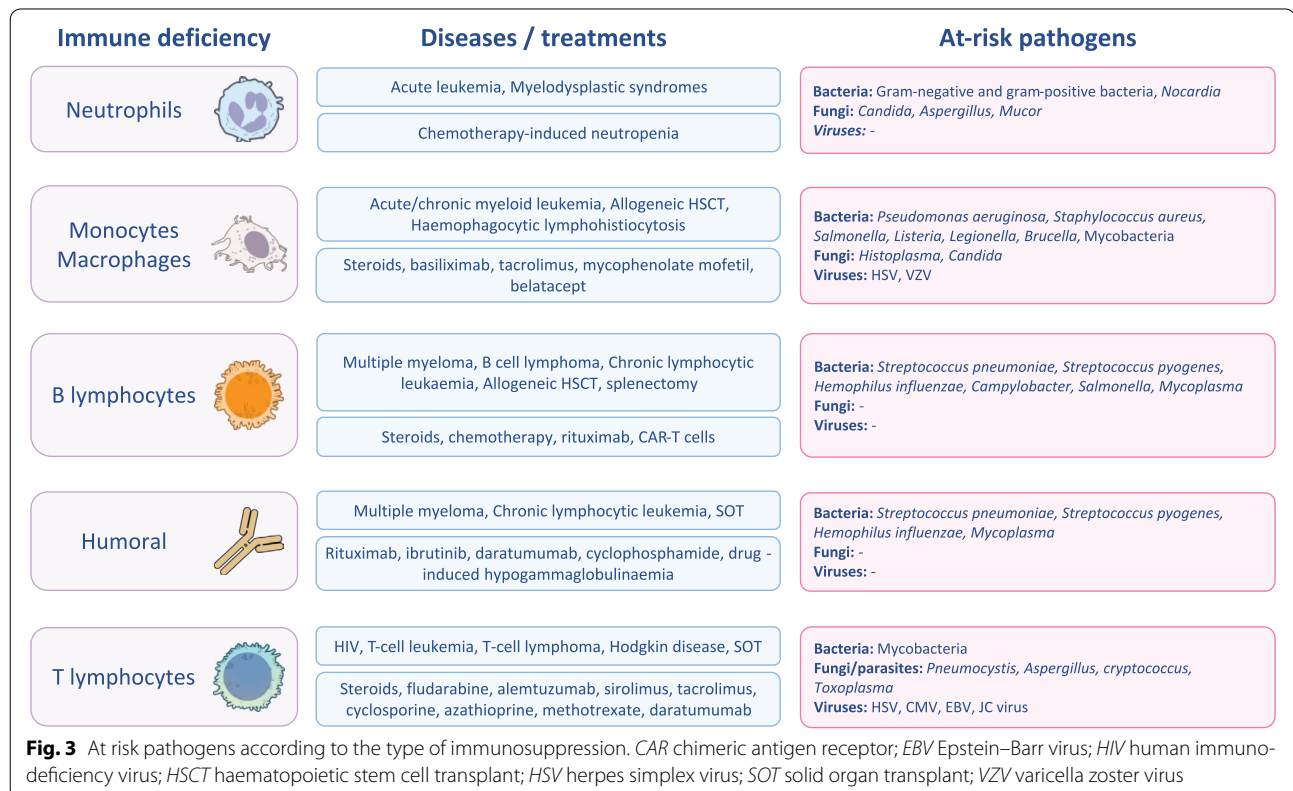


Fig. 3 At risk pathogens according to the type of immunosuppression. CAR chimeric antigen receptor; EBV Epstein–Barr virus; HIV human immunodeficiency virus; HSCT haematopoietic stem cell transplant; HSV herpes simplex virus; SOT solid organ transplant; VZV varicella zoster virus

55]. Empirical antibiotics selection should focus on illness severity and MDRO risk. Combination therapy may benefit neutropenic patients and cases involving pathogens with reduced susceptibility [56]. Guidelines recommend an anti-pseudomonal beta-lactam with aminoglycosides for neutropenia and septic shock [51]. Immunocompromised patients are often excluded from trials on antibiotic duration. Retrospective data suggest short and long treatments for *P. aeruginosa* BSI may be equally effective [57], but more evidence is needed.

Role of the microbiology laboratory and rapid diagnostic tests

The microbiology lab remains central in management of serious bacterial infections. Traditional culture methods are slow and labour-intensive. MALDI-TOF has revolutionised workflows with faster and more accurate pathogen identification (see Fig. 4) [58].

Automated multiplex PCR platforms detect multiple pathogens and AMR genes [59]. Their clinical benefit—especially mortality reduction—is best demonstrated when paired with AMS interventions. Banerjee et al. showed improved treatment modification with multiplex PCR, particularly when integrated with AMS [60]. They found that rapid testing had advantages in modifying treatment, but was most effective when paired with AMS, a finding that has been replicated elsewhere [61]. Demonstrating clear mortality benefit has proved more elusive, with few studies powered only to detect modest effects. In high-prevalence settings, early carbapenemase detection improved outcomes in CRE BSI patients [62].

A meta-analysis of 25,682 bloodstream infection cases found rapid testing with AMS reduced mortality (OR 0.72) and time to optimal therapy by 29 h [63]. Yet, studies like MULTICAP or INHALE WP3 on rapid PCR in CAP/HAP/VAP failed to show benefits in clinical cure benefits, despite faster appropriate therapy [64, 65]. Furthermore, it underscores that the appropriateness of the initial empiric treatment is of unparalleled importance. The impact of this in countries where bacterial resistance is high remains unexplored [66].

More generally, whilst these tests offer greater sensitivity and specificity than traditional cultures, limitations persist, including predefined pathogen panels, detection of non-viable organisms, and high costs [67].

Platforms, such as BioFire and T2MR, are FDA-approved, whilst others like clinical metagenomics are still under development. An additional key consideration for any diagnostic is pre-test probability, especially for uncommon pathogens that may be included in multiplexed testing panels, where corroborating evidence may be required to secure the diagnosis. Equally, rapid testing may need to be specifically directed towards the likely

infectious agents (or resistance pattern) relevant to the clinical setting. For instance, the BioFire FilmArray Meningitis/Encephalitis Panel is very useful for community-acquired central nervous system infections, but is much less appropriate for post-neurosurgical infections, where an entirely different array of organisms and resistance patterns predominate.

Initial antimicrobial selection

Whilst the emphasis often lies on timeliness of empirical antibiotic administration, initial appropriate antibiotic therapy (IAAT) is equally critical in determining patient outcomes. A study found that for every four patients with septic shock receiving IAAT, one life was saved—especially in infections caused by MDR Gram-negative organisms [68]. In addition to reducing mortality, IAAT shortens hospital length of stay (LOS) by approximately 2.5 days, contributing to substantial cost savings [69].

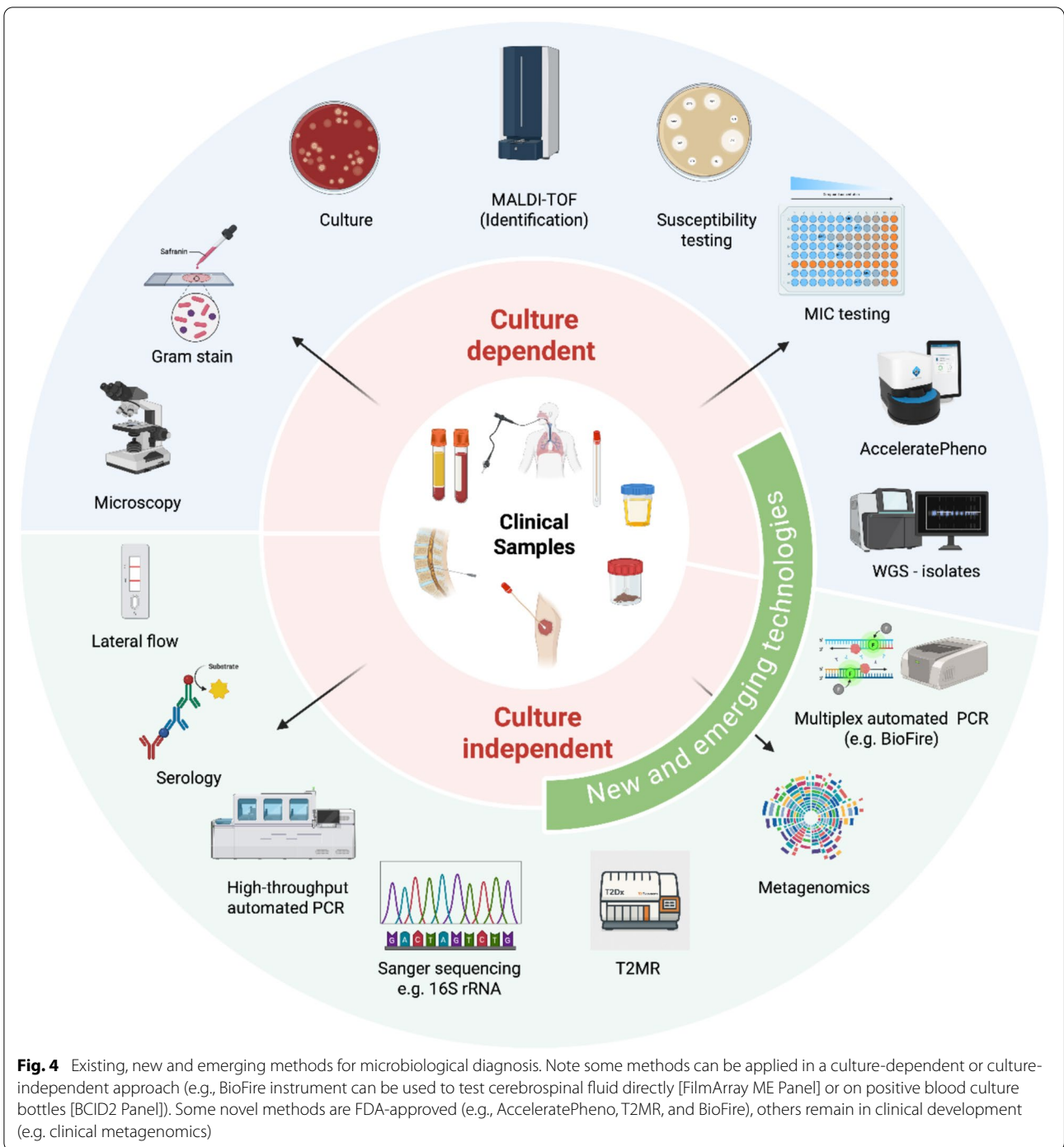
Despite the limitations of retrospective data, the consistent association between IAAT and improved outcomes underscores the need for structured strategies to ensure its delivery in severe bacterial infections [70]. This requires consideration of infection source, patient risk factors, and available antimicrobial options (Fig. 5).

Excessively broad-spectrum antibiotic use can be detrimental. In CAP, one-third of cases receive overly broad empiric therapy, which is linked to increased mortality, LOS, superinfections, and disruption of microbiota leading to AMR [71, 72]. Similarly, in ED presentations of sepsis with bloodstream infections, one-third of patients received unnecessarily broad MDRO coverage, resulting in worse outcomes, including higher mortality and increased *C. difficile* and acute kidney injury rates [73].

Given the empirical nature of initial therapy in severe infections, clinicians must balance early, adequate coverage against the risks of overuse. Rapid pathogen diagnostics enable early de-escalation and careful stewardship of newer agents active against MDR organisms are crucial. Proposed empiric regimens tailored to resistance risks are summarised in Table E1.

Monotherapy vs combination therapy

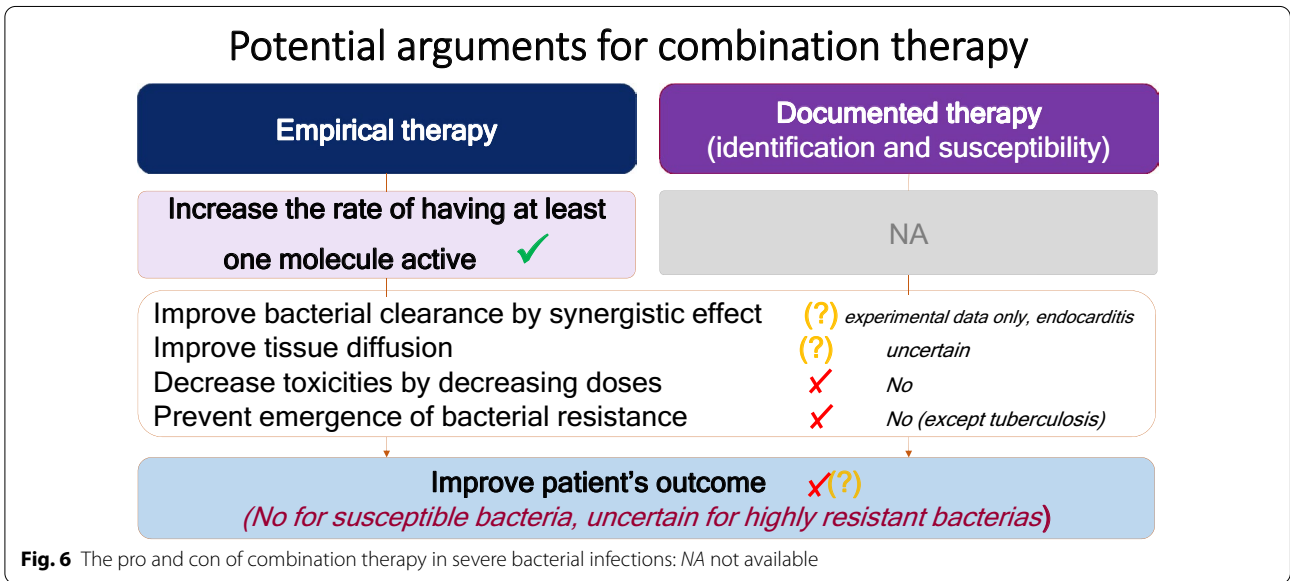
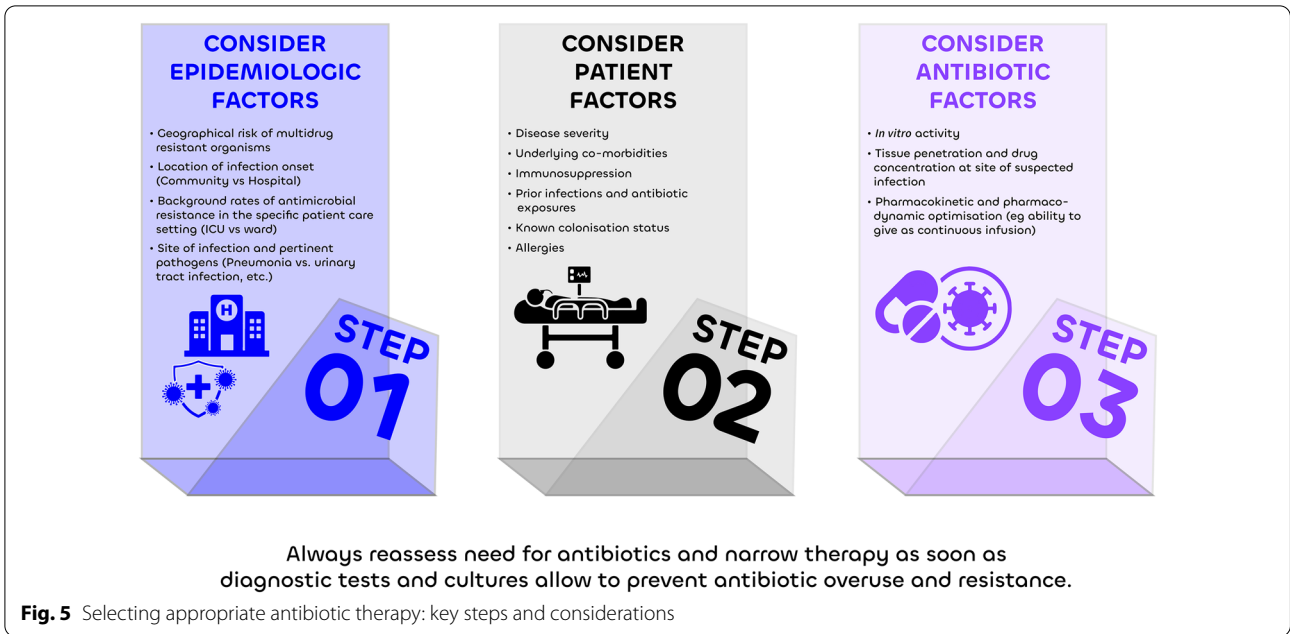
Combination therapy is commonly used in severe infections to enhance coverage and leverage potential synergy between agents. Guidelines often recommend empiric combination regimens with subsequent de-escalation once susceptibilities are known (Fig. 6). Evidence on de-escalation is mixed. In a small RCT by Leone et al., patients randomised to de-escalation had higher rates of superinfections and longer antibiotic courses, though mortality was unchanged [74]. In contrast, Lopez-Cortes et al. found that de-escalation from broad-spectrum beta-lactams to narrower agents in *Enterobacterales* BSI



resulted in non-inferior outcomes compared to continued broad-spectrum therapy [75].

The most recent guidance from the Infectious Diseases Society of America [76] advocates combination therapy for definitive therapy of serious infections due to *Acinetobacter baumannii* or *Stenotrophomonas*

maltophilia, but not CRE or *Pseudomonas aeruginosa*. Two randomised-controlled trials have explicitly addressed this issue by comparing colistin monotherapy with colistin combined with a carbapenem for patients with infection due to CRE. Neither showed a significant reduction in mortality using combination therapy [77, 78].



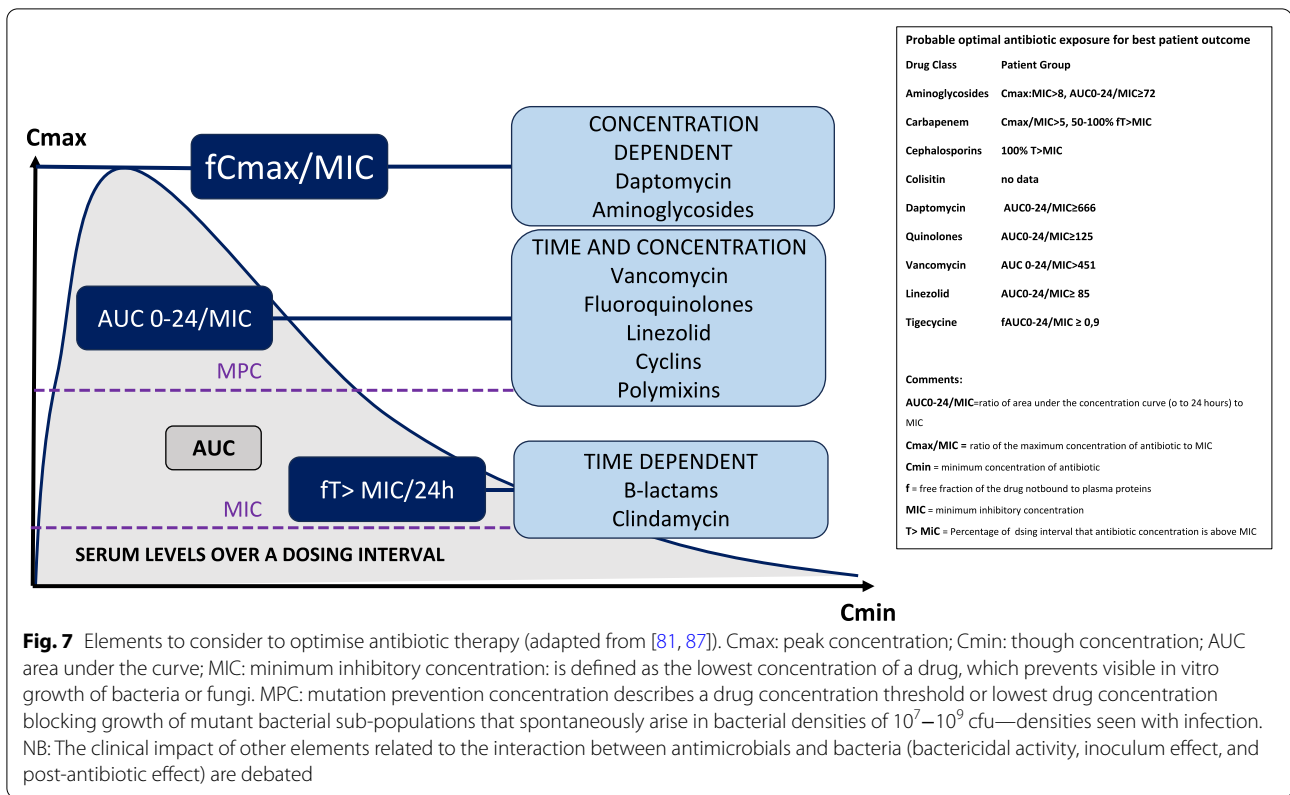
Role of the clinical pharmacist

PK/PD principles

Beyond selecting appropriate antimicrobials, achieving optimal and timely pharmacokinetic/pharmacodynamic (PK/PD) target attainment significantly improves clinical and microbiological outcomes in critically ill patients [79].

PK describes the effect that the body has on the drug—through absorption, distribution, metabolism, and elimination. Important PK parameters are shown in Fig. 7.

PD describes the effect that the drug has on the body. For antibiotics, PD relates the antibiotic concentration to its ability to kill or inhibit the growth of a pathogen. This is often expressed in terms of concentration relative to the minimum inhibitory concentration (MIC). Unbound drug concentrations (i.e., free concentrations) are most relevant for efficacy, and protein binding can limit drug action [80]. Numerous studies have demonstrated that different antibiotics have different PD properties and can be categorised into three categories that, by and large reflect their modes of bacterial killing [79, 81]; the



duration of time that free drug concentration remains above the MIC during a dosing interval ($fT > MIC$; time dependency), the ratio of AUC_{0-24} to MIC (total exposure/time), and the ratio of C_{max} to MIC (concentration dependency) (Fig. 7). Achieving the appropriate target for each antibiotic class is key to maximising efficacy whilst minimising toxicity.

Figure 7 suggests proposed optimal antibiotic exposures in an attempt to improve outcomes. Clearance of the drug and the volume of distribution are the most dynamic parameters and their surrogates in terms of organ function (kidney, liver) must be closely monitored and interpreted.

Underdosing may occur when clearance of a drug is higher than expected. When renal function is not impaired in the hyperdynamic circulation of sepsis, renal clearance of drugs is often higher than “normal”. This phenomenon called ‘augmented renal clearance’ (ARC) [82] can be expected in populations at risk including (neuro)-trauma, burns, pancreatitis, pregnancy, and younger patients. Care is required in these patients to provide adequate dosing [82].

In view of their “time-dependent” kill characteristics, the pharmacokinetic properties of β -lactams, the most frequently prescribed antibiotics in ICU, can be optimised by modifying their application to a bolus followed

immediately by a continuous infusion. A recent large RCT and meta-analysis together strongly identify clinical outcome benefits [83, 84]. Whilst there are no large RCT’s on extended infusion of β -lactams vs bolus dosing, such infusions are pharmacologically sound [85, 86].

Drug–drug interactions

Severe infections often require complex, multidrug regimens that heighten the risk of toxicity and interactions. Clinical pharmacists play a key role in reviewing all medications to minimise these risks. Nephrotoxicity is a major concern with aminoglycosides, vancomycin, and polymyxins, especially when combined with diuretics or other nephrotoxins. Macrolides and triazoles can cause significant drug-concentration fluctuations due to metabolic interactions.

It follows that a full review of all medications is required as part of pharmacological management of severe infections. For both acute therapies related to critical illness (e.g., sedatives and anticonvulsants) but also long-term medications (e.g. antiretroviral treatment, antipsychotics, and antidepressants), careful review of ongoing dosing needs is required.

Pharmacists also manage interactions with long-term medications (e.g., antipsychotics, anticonvulsants, and antiretrovirals) and support dose adjustments during

acute illness. Regular medication reviews by pharmacists reduce hospital stay [88] and may improve outcome [89].

Therapeutic drug monitoring: when and how

TDM is essential in optimising antibiotic therapy ensuring efficacy whilst minimising toxicity. It is particularly important in high-risk scenarios such as: (1) severe infections, e.g., sepsis or septic shock, (2) use of narrow therapeutic index drugs (vancomycin, aminoglycosides, or antifungals like voriconazole), (3) altered PK such as ARC, impaired renal/hepatic function, or extracorporeal therapies (e.g., renal replacement therapy or extracorporeal membrane oxygenation-ECMO), (4) situations with high interpatient PK variability risks, such as burn, obese patients, or those with fluctuating organ function, and (5) infections at complex sites (endocarditis, central nervous system, pulmonary, or bone joint infections) where drug penetration is critical.

Recent reviews have examined the role of β -lactam TDM in critically ill patients [90–92]. β -lactam TDM improved target attainment, and microbiological and clinical cure but failed to improve mortality and AMR [91, 92]. However, challenges, including robustness of TDM recommendations, intervention deviations, and confounding factors, may have influenced these results.

A recent multicentre RCT by Hagel et al. ($n=249$) found no significant difference in SOFA scores between TDM and control groups ($p=0.39$), though TDM reduced underdosing and improved target concentration attainment [93].

Another crucial issue is the high PK variability of antimicrobials even within the same patient throughout the ICU stay, particularly related to altering renal function, emphasising the need for individualised dosing strategies and dynamic reassessments.

High intra-patient PK variability—especially from changing renal function—supports the need for individualised, dynamic dosing. Improving turnaround time and interpretation of TDM results that is crucial and improving result interpretation support are key priorities in enhancing their practical clinical application. Strategies to support more accurate and effective TDM include use of nomograms and model-informed precision dosing (MIPD) [92, 94].

When antimicrobials are harmful

Antimicrobial-associated harm (Fig. 8) includes adverse drug events and microbiotoxicity [95]. Broader spectrum [38, 96, 97], longer duration [98–100], combination therapy [101], and repeated courses increase the likelihood of side effects and superinfections. Each day of antimicrobial use raises the odds of adverse and severe adverse events by 4% and 9%, respectively [102].

Adverse drug events may be immune-mediated idiosyncratic reactions, potentially involving interactions with viral pathogens, or dose-dependent events [103]. Dose-dependent reactions result from PD interactions between antimicrobials and mammalian cells. Beta-lactams are often used at higher-than-conventional dosing regimens in critically ill patients and when used in patients without ARC, renal dysfunction increases the risk of neurotoxicity. This can present as confusion, hallucinations, myoclonus, convulsions, and non-convulsive status epilepticus, in up to 10–15%, especially in the event of underlying brain abnormalities. Cefazolin, cefepime, and imipenem are more commonly implicated [104]. Cefepime neurotoxicity has been reported in 48% of overdosed and 26% of appropriately dosed patients [105]. Whilst rare, beta-lactam-induced nephrotoxicity may increase when combined with agents like vancomycin, particularly piperacillin–tazobactam [106].

Antimicrobials disrupt commensal microbiota [107]. Following a course of antimicrobials, there is rapid reduction in the total numbers and diversity of health-associated bacteria like *Bifidobacterium*, *Lactobacillus*, and *Bacteroides* species [108] and a bloom of potential pathogens, including *Enterobacterales*, *Enterococcus*, *Clostridium*, and *Candida* [109] and of the total burden of resistance genes (“resistome”) in the host’s gut [95, 110–113]. This microbiotoxicity is especially marked during pregnancy, early life, elderly age, immunosuppression, and severe illness [95, 114] and with anti-anaerobic and biliary-excreted antibiotics [72, 115]. Dysbiosis may lead to localised disease at the colonisation site, such as *Clostridioides difficile* colitis [107], but it may also facilitate translocation of microorganisms to cause disease in a different site, namely BSIs [116–118]. Usually intestinal microbiota recover within 2–8 weeks following antibiotics [109, 111]; however, multiple species may remain undetectable even after 6 months [109]. Antibiotic-associated dysbiosis of the upper respiratory tract may cause increased colonisation by various *Enterobacterales* and *Streptococcus pyogenes*, eventually causing respiratory infections [107].

Exposure to bactericidal antimicrobials results in mitochondrial toxicity that may contribute to development and perpetuation of organ dysfunction [103, 119] and to immunoparalysis in sepsis [120].

When to stop antibiotics/optimal duration of therapy

The ideal duration of antibiotic therapy remains debated. In-vitro antimicrobial exposure leads to eradication of bacteria within hours [121], whilst in clinical settings, pathogens are often eliminated only within 3 days of therapy. Effective antibiotics led to rapid

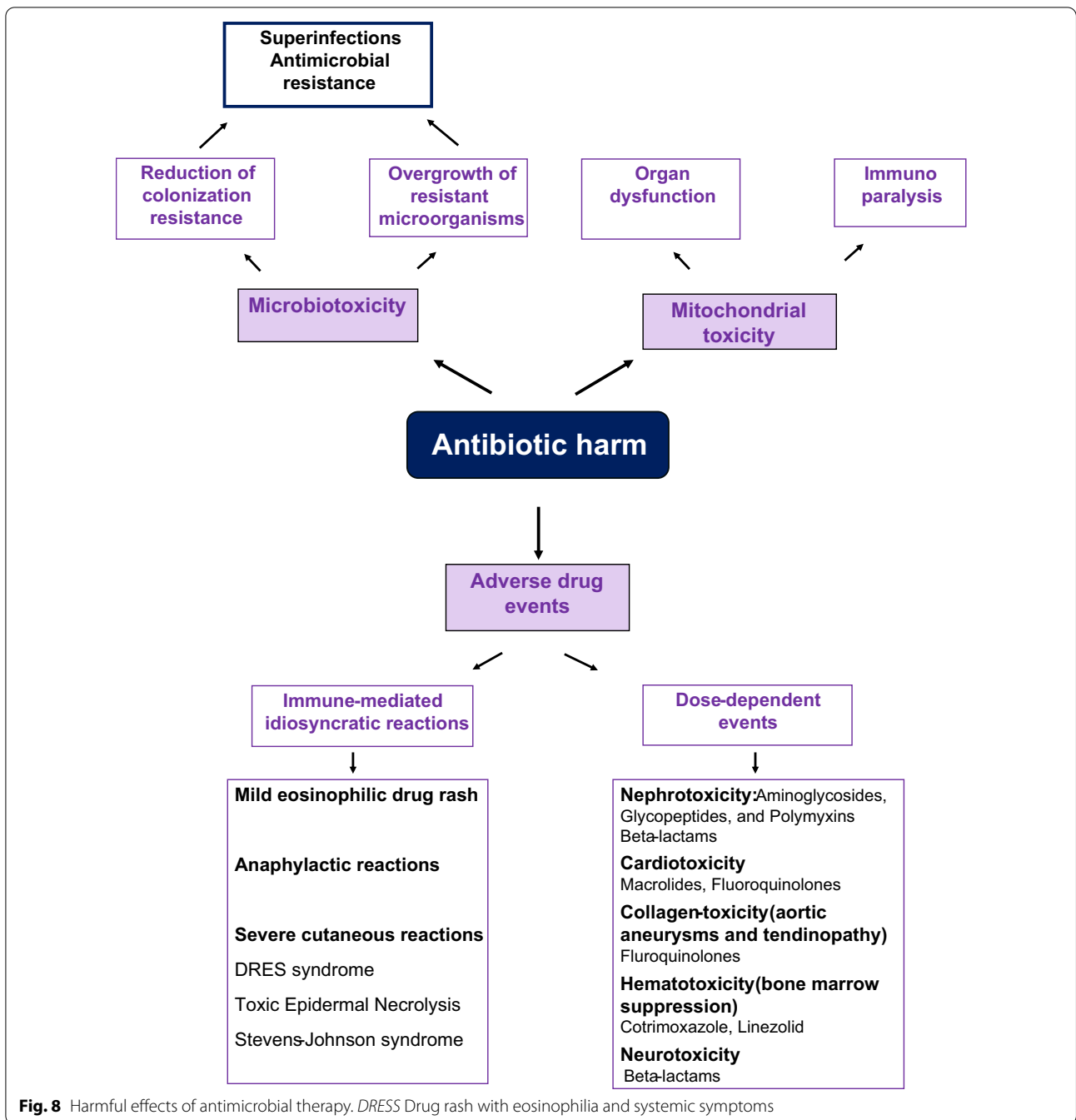


Fig. 8 Harmful effects of antimicrobial therapy. *DRESS* Drug rash with eosinophilia and systemic symptoms

reductions in organism detection by PCR in *Acinetobacter baumannii* bacteraemia [122]. Notably, patients with immunocompromising conditions, but not those with more severe illness, cleared *A. baumannii* slower, with an associated increase in mortality [122]. However, inflammation and organ failure may persist for some time after pathogen clearance [123], where continuing antibiotics risks harm with no benefit [103].

Three strategies guide therapy duration: fixed duration, clinical assessment, and biomarker-guided approaches [124]. Traditional fixed durations often follow 7- or 14-day schedules, perhaps influenced by historical or cultural norms [125, 126], although a preference for prime numbers (3, 5, 7) is also noted [127]. The common feature of almost all these trials is the non-inferiority, and frequent superiority, of short-duration antimicrobials

[127]. A note of caution however, many of these studies required clinical stability and source control as entry criteria and thus may not be directly applicable to patients with severe infection. However, a shorter duration appears safe in hospital-acquired BSIs [128], VAP [129], and intra-abdominal infections [130, 131].

Whilst clinicians often rely on inflammatory markers and clinical stability, features of inflammation/infection can persist despite microbiological cure [132]. However, as noted, features of inflammation may persist beyond pathogen eradication and shorter fixed duration courses appear non-inferior to those guided by clinical features [131, 133].

The most widely tested biomarker is procalcitonin (PCT), whilst several studies have examined C-reactive protein (CRP). A large trial comparing PCT and CRP-guided strategies found that PCT shortened therapy by 1 day (from 8 to 7 days), whilst CRP guidance did not reduce duration and showed a potential mortality signal [134]. The reduction in antimicrobial duration in the PCT arm is consistent with the previous studies [135], although this systematic review only noted mortality reduction with PCT-guided therapy when liberal protocols (PCT falling by > 80% from peak or < 0.5 ng/ml) were used.

Whilst the principle that antimicrobial duration should be “as short as possible” there remains a lack of consensus regarding “how short is possible” and how to individualise durations to given patients, microorganisms and sites of infection. The best approach we can advocate is daily multidisciplinary review [136], with intensivists, microbiologist, and pharmacist asking every day (1) has the correct antimicrobial been given and (2) can we now stop it?

Area for future research

Despite progress in understanding antibiotic–patient–pathogen interactions, significant gaps remain. Achieving rapid etiological diagnoses and administering the narrowest adequate antibiotic promptly should be the goal. Current multiplex PCR tools fall short of this objective. Sophisticated genomics-based diagnostics in the form of “pan-pathogen” detection using shotgun metagenomics (i.e., sequencing all nucleic acids in a sample) or more targeted approaches (e.g., amplicon or hybrid-capture enrichment prior to sequencing) [137, 138] may help revolutionise pathogen detection. This will require a major re-orientation of how clinicians use and interpret genomics-based tests, careful validation, and assessment of diagnostic accuracy and cost–benefit [139].

Studies linking antibiotic exposure–response relationships show reduced mortality when dosing is optimised [83, 84, 140]. Current evidence is for continuous infusion beta-lactam dosing [84], whilst extended infusions which

be more convenient have yet to be proven as good as or better than continuous infusion. However, even when the established PK/PD target is attained, a proportion of patients do not respond to therapy or develop resistance during treatment. Further research is therefore needed in optimising dosing, especially in special populations such as critically ill patients. Multi-omics approaches—integrating transcriptomics, proteomics, and metabolomics—could enhance understanding of resistance mechanisms and guide synergistic antibiotic combinations [141]. This multi-omics approach has already been successfully used to optimise synergistic antibiotic combinations in the clinical setting [142].

Another area of investigation is related to the complex interactions between bacteria and our immune system in response to specific bacterial strains. Furthermore, research into host–pathogen interactions may enable personalised sepsis therapies. Stratifying patients based on immune transcriptomic profiles could identify those most likely to benefit from immunomodulatory treatments and predict mortality risk [143]. Several studies have used blood leukocyte transcriptome data to stratify patients with septic shock according to their immune responses [144].

Finally, ongoing research is active in identifying non-traditional therapies, such as bacteriophages, anti-virulence drugs, or microbiome-modulating treatments [145]. Realising their potential will require collaborative research platforms involving diverse stakeholders and global settings. Key areas for investigation are summarised in the Table 2. We would like to complete this section with the statement that we have all seen some patients with the best therapy available just do not thrive, and this may be due to sepsis subtypes for which there is a dire need to investigate further [146].

Conclusion

Poor outcomes associated with severe infections and rising multidrug resistance underscore the urgent need to optimise antibiotic therapy. Evidence shows that appropriate antibiotic use can improve outcomes and that misuse causes harm.

Even with considerable advancements in rapid diagnostic tools, early administration of appropriately chosen and adequately dosed antibiotics remains challenging. Empiric therapy should be started immediately only in patients with septic shock. Otherwise, the decision of treatment may be safely deferred until careful clinical evaluation and investigation of the patient, and review of microbiological results. With the help of multidisciplinary rounds, early cessation should be considered in culture-negative and improving cases.

Table 2 Suggested areas of future research

Topics for future investigations	Comments and questions
Burden of sepsis	<p>Measuring the burden of untreated sepsis within communities is critical for identifying gaps in healthcare delivery and improving outcomes</p> <p>Understanding the pathways of care, including how patients navigate the healthcare system, and identifying specific barriers unique to different settings will be essential steps</p> <p>Gathering data on the prevention, recognition, management, and rehabilitation of sepsis in resource limited settings is key to develop targeted interventions</p>
Rapid diagnostic tests	<p>Rapid diagnostics to inform antibiotic choice more rapidly should be undertaken. There are several expensive state of the art systems which should also be tested for health system cost-effectiveness</p> <p>Accurate interpretation of RDT requires expertise, and further research is necessary to evaluate their impact on AMS and patient outcomes</p> <p>The impact of syndromic mPCR including not only suspected but also very uncommon pathogens should be refined</p> <p>Rapid pan pathogen genomic-based diagnostics should be developed and tested in severe infections</p>
TDM: use of rapid TDM and dosing softwares	<p>Interventional dose optimization studies using rapidly applied TDM and dosing software to see if patient outcomes and healthcare costs can be improved</p> <p>To overcome the barriers related to antimicrobial TDM-guided dose optimization, innovative approaches using real-time health record data and artificial intelligence (AI) embedded into dosing software deserve further investigation</p> <p>Further to this, the effect of dose optimization on emergence of AMR is important</p>
Refine the knowledge about host pathogen interactions and virulence factors	To evaluate in a wide range of clinical isolates the bacterial genomic, transcriptomic, and metabolomic fingerprints that are predictive of efficacious antimicrobial therapy
Improve knowledge about possible adverse effects of antibiotics	<p>Exposure to bactericidal antimicrobials results in mitochondrial toxicity that may contribute to development and perpetuation of organ dysfunction and to immunoparalysis in sepsis</p> <p>To evaluate the respective impact of broad spectrum antibiotics on the gut microbiota through novel metagenomic approaches</p>
The use of mono active vs dual active antibiotic therapy	The comparison of monoactive antimicrobial therapy vs dual active antibiotic therapy should be tested in a large RCT focusing on highly resistant Gram-negative bacteria (<i>A baumannii</i> , <i>S maltophilia</i> and other difficult-to-treat gram negative bacteria)
Duration of antibiotic therapy	<p>When short duration of antibiotic therapy is too short? A comparison of a fixed short duration of therapy to an individualized assessment of the duration of therapy in patients with severe infections</p> <p>Early cessation vs antibiotic continuation in case of culture negative sepsis</p>
To identify new targets for severe infections	Role of bacteriophages, antivirulence drugs or microbiome modulating treatments

Narrow-spectrum agents at correct doses should be prioritised. Dose optimisation, aided by nomograms and therapeutic drug monitoring (TDM), minimises toxicity. The duration of therapy should be as short as possible. However, in severe infection, when source control cannot be achieved or when recovery is incomplete, the optimal duration should be personalised according to the microorganisms, the host, and the clinical status, again informed by multidisciplinary rounds. Artificial

intelligence may support future antibiotic management, but robust validation is required.

Out of the scope of this review, but of considerable importance, is the control of diffusion of resistant bacteria in the community by limiting antimicrobial use in animals, avoiding spread of antibiotics in the environment, improving global hygiene in a one-health approach. Finally, we should keep in mind that the most appropriate way to save antibiotics for future use is to prevent

infections and to combine antibiotic stewardship programmes with good infection control system [147].

Louis Pasteur: « *au lieu de s'ingénier à tuer microbes dans la plaie, ne serait-il pas plus raisonnable de ne pas en introduire ?* » "Instead of trying to kill microbes in the wound, wouldn't it be more reasonable not to introduce any?"

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s00134-025-08063-0>.

Author details

¹ Université Paris-Cité, INSERM, IAME, U1137, Team MOCLID, Paris, France. ² APHP, Bichat Hospital, Medical and Infectious Diseases ICU, Paris, France. ³ OUTCOME REA Research Network, Drancy, France. ⁴ Department of Anaesthesia and Intensive Care, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China. ⁵ Department of Anesthesiology, Intensive Care, Emergency Medicine, Transfusion Medicine, and Pain Therapy, University Hospital OWL, Campus Bielefeld-Bethel, Bielefeld, Germany. ⁶ Perioperative, Acute, Critical Care and Emergency Medicine Section, Department of Medicine, University of Cambridge, Cambridge, UK. ⁷ JVF Intensive Care Unit, Addenbrooke's Hospital, Cambridge, UK. ⁸ Department of Intensive Care Medicine, Ghent University Hospital, Ghent, Belgium. ⁹ Department of Internal Medicine and Pediatrics, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium. ¹⁰ Infectious Diseases Unit, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy. ¹¹ Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy. ¹² The University of Queensland, UQ Centre for Clinical Research, Brisbane, Australia. ¹³ Department of Infectious Disease, Royal Brisbane & Women's Hospital, Herston, Australia. ¹⁴ Herston Infectious Disease Institute, Metro North Hospitals and Health Service, Brisbane, Australia. ¹⁵ Pathology Queensland, Central Microbiology, Royal Brisbane & Women's Hospital, Herston, Australia. ¹⁶ Intensive Care Department, Hospital São Paulo, Escola Paulista de Medicina Universidade Federal de São Paulo, São Paulo, Brazil. ¹⁷ Intensive Care Medicine Department, ULS São João, Porto, Portugal. ¹⁸ Faculty of Medicine, University of Porto, Porto, Portugal. ¹⁹ Infection and Sepsis I&D Group, Porto, Portugal. ²⁰ ADVANCE-ID, Saw Swee Hock School of Public Health, National University of Singapore, Singapore. ²¹ Third Department of Internal Medicine and Laboratory, Medical School, "SOTIRIA" General Hospital, National and Kapodistrian University of Athens, Athens, Greece. ²² Departments of Pharmacy and Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia. ²³ Division of Anesthesia Critical Care and Emergency and Pain Medicine, UR UM 103, University of Montpellier, Nîmes University Hospital, Nîmes, France. ²⁴ Medstar Washington Hospital Center, Washington, DC, USA. ²⁵ Intensive Care Unit, Redcliffe Hospital, Metro North Hospital and Health Services, Redcliffe, Australia. ²⁶ Queensland University of Technology (QUT), Brisbane, Australia. ²⁷ Jamieson Trauma Institute, Royal Brisbane and Women's Hospital, Herston, Australia.

Declarations

Conflicts of interest

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests. J-FT; received research grants from Pfizer, Merck, was speaker in conferences for Pfizer, Advanz, Biomerieux, Shionogi, Mundipharma, Qiagen, and participates to advisory boards organised by Menarini, Biomerieux, Merck, Advanz pharma all out of the submitted article. LL Non-financial research support from Biomerieux; received funding from Health and Medical Research Fund of the Health Bureau of Hong Kong SAR Government (No. 18190381) to support this work. EdM none; HB none; ACM speaking fees Biomerieux, Thermo-Fisher, Fischer and Paykel and Boston Scientific (paid to institution); ACM is supported by a Clinician Scientist Fellowship from the UK Medical Research Council (MR/V006118/1); LdB none; MF received research grants from Gilead and Viiv, and was speaker for conferences or advisory boards organised by Pfizer, Menarini, Infectiopharm, Thermo-Fisher; PNAH received research grants from Tamrisa, Microbio and Gilead, honoraria for speaking events from Pfizer, Biomerieux

and Gilead and has served on advisory boards for Sandoz and OpGen and received travel support from Shionogi; FRM none; J-AP Talks or advisory boards for Pfizer, Merck-Sharp-Dohme, Gilead, AOP Orphan Pharmaceuticals, Cepheid; DLP received research funding from Shionogi, Merck, bioMérieux, BioVersys, Gilead and Pfizer, consulting fees from the AMR Action Fund, CARB-X, GARDP, Aurobac, Pfizer, Merck, Cepheid, bioMérieux, and Spero.; GP Grants/Research Support: Pfizer, MSD, Gilead, Menarini, PharmaMar, Fabentech, Bausch, Astra-Zeneca, Hellenic Institute for the Study of Sepsis, University College London/University of Minnesota; Scientific Advisory board: Pfizer, Astra-Zeneca, Gilead, MSD, Menarini, SOBI; CR received speaker's fees from Shionogi, bioMérieux, AOP Orphan, Advanz Pharma, Fresenius, Pfizer and MSD. attended Scientific Advisory Board from bioMérieux, Advanz Pharma and Viatris; JAR Consultancies/Advisory Boards—Sandoz (2024); Wolters Kluwer (2024); Qpex (2022); Gilead (2022); Advanz Pharma (2022); Speaking Fees—Sandoz (2024); Pfizer (2023); MSD (2022); Gilead (2022); Industry Grants—Biomerieux (2024); Pfizer (2023); AFS Consultant to Merck, Pfizer and Eagle Pharmaceuticals; AT none; JL none.

Ethical approval

Not needed.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

Received: 28 May 2025 Accepted: 24 July 2025

Published online: 01 September 2025

References

1. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievian DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C, Machado FR, Reinhart KK, Rowan K, Seymour CW, Watson RS, West TE, Marinho F, Hay SI, Lozano R, Lopez AD, Angus DC, Murray CJL, Naghavi M (2020) Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet* 395:200–211
2. Tabah A, Buetti N, Staiquily Q, Ruckly S, Akova M, Aslan AT, Leone M, Conway Morris A, Bassetti M, Arvaniti K, Lipman J, Ferrer R, Qiu H, Paiva JA, Povoas P, De Bus L, De Waele J, Zand F, Gurjar M, Alsisi A, Abidi K, Bracht H, Hayashi Y, Jeon K, Elhadi M, Barbier F, Timsit JF, Eurobact-2 Study Group EEE, the ON (2023) Epidemiology and outcomes of hospital-acquired bloodstream infections in intensive care unit patients: the EUROBACT-2 international cohort study. *Intensive Care Med* 49:178–190
3. Barbier F, Buetti N, Dupuis C, Schwebel C, Azoulay E, Argaud L, Cohen Y, Hong Tuan Ha V, Gannier M, Siami S, Forel JM, Adrie C, de Montmollin E, Reigner J, Ruckly S, Zahar JR, Timsit JF, OutcomeRea Study G (2025) Prognostic impact of early appropriate antimicrobial therapy in critically ill patients with nosocomial pneumonia due to gram-negative pathogens: a multicenter cohort study. *Crit Care Med* 53:e1066–e1079
4. Vincent JL, Sakr Y, Singer M, Martin-Loeches I, Machado FR, Marshall JC, Finfer S, Pelosi P, Brazzi L, Aditiansih D, Timsit JF, Du B, Wittebole X, Maca J, Kannan S, Gorordo-Delsol LA, De Waele JJ, Mehta Y, Bonten MJM, Khanna AK, Kollef M, Human M, Angus DC, Investigators EI (2020) Prevalence and outcomes of infection among patients in intensive care units in 2017. *JAMA* 323:1478–1487
5. Li A, Ling L, Qin H, Arabi YM, Myatra SN, Egi M, Kim JH, Mat Nor MB, Son DN, Fang WF, Wahyuprajitno B, Hashmi M, Faruq MO, Patjanasoonontorn B, Al Bahrani MJ, Shrestha BR, Shrestha U, Nafees KMK, Sann KK, Palo JEM, Mendsaikhan N, Konkayev A, Detleuxay K, Chan YH, Du B, Divatia JV, Koh Y, Gomersall CD, Phua J (2022) Epidemiology, management,

- and outcomes of sepsis in ICUs among countries of differing national wealth across Asia. *Am J Respir Crit Care Med* 206:1107–1116
6. Umemura Y, Ogura H, Takuma K, Fujishima S, Abe T, Kushimoto S, Hifumi T, Hagiwara A, Shiraishi A, Otomo Y, Saitoh D, Mayumi T, Yamakawa K, Shiino Y, Nakada TA, Tarui T, Okamoto K, Kotani J, Sakamoto Y, Sasaki J, Shiraishi S, Tsuruta R, Masuno T, Takeyama N, Yamashita N, Ikeda H, Ueyama M, Gando S, Japanese Association for Acute Medicine Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome S, Trauma Study G (2021) Current spectrum of causative pathogens in sepsis: a prospective nationwide cohort study in Japan. *Int J Infect Dis* 103:343–351
 7. Browne AJ, Chipeta MG, Haines-Woodhouse G, Kumaran EPA, Hamadani BHK, Zarea S, Henry NJ, Deshpande A, Reiner RC Jr, Day NPJ, Lopez AD, Dunachie S, Moore CE, Stergachis A, Hay SI, Dolecek C (2021) Global antibiotic consumption and usage in humans, 2000–18: a spatial modelling study. *Lancet Planet Health* 5:e893–e904
 8. Blot S, Antonelli M, Arvaniti K, Blot K, Creagh-Brown B, de Lange D, De Waele J, Deschepper M, Dikmen Y, Dimopoulos G, Eckmann C, Francois G, Girardis M, Kouletti D, Labeau S, Lipman J, Lipovestky F, Maseda E, Montravers P, Mikstacki A, Paiva JA, Pereyra C, Rello J, Timsit JF, Vogelaers D, Abdominal Sepsis Study group on behalf of the Trials Group of the European Society of Intensive Care M (2019) Epidemiology of intra-abdominal infection and sepsis in critically ill patients: “AbSeS”, a multinational observational cohort study and ESICM Trials Group Project. *Intensive Care Med* 45:1703–1717
 9. Gouel-Cheron A, Swihart BJ, Warner S, Mathew L, Strich JR, Mancera A, Follmann D, Kadri SS (2022) Epidemiology of ICU-onset bloodstream infection: prevalence, pathogens, and risk factors among 150,948 ICU patients at 85 U.S. Hospitals. *Crit Care Med* 50:1725–1736
 10. Perez-Crespo PMM, Lanz-Garcia JF, Bravo-Ferrer J, Canton-Bulnes ML, Sousa Dominguez A, Goikoetxea Aguirre J, Reguera-Iglesias JM, Leon Jimenez E, Arminanzas Castillo C, Mantecon Vallejo MA, Marrodan Giordina T, Fernandez Suarez J, Boix-Palop L, Cuquet Pedragosa J, Jover Saenz A, Sevilla Blanco J, Galan-Sanchez F, Natera Kindelan C, Del Arco Jimenez A, Bahamonde-Carrasco A, Smithson Amat A, Vinuesa Garcia D, Herrero Rodriguez C, Reche Molina IM, Perez Camacho I, Sanchez-Porto A, Guzman Garcia M, Becerril Carral B, Merino de Lucas E, Lopez-Hernandez I, Rodriguez-Bano J, Lopez-Cortes LE (2021) Revisiting the epidemiology of bloodstream infections and healthcare-associated episodes: results from a multicentre prospective cohort in Spain (PRO-BAC Study). *Int J Antimicrob Agents* 58:106352
 11. Valles J, Alvarez-Lerma F, Palomar M, Blanco A, Escobresca A, Armestar F, Sirvent JM, Balasini C, Zaragoza R, Marin M, Study Group of Infectious Diseases of the Spanish Society of Critical Care M (2011) Health-care-associated bloodstream infections at admission to the ICU. *Chest* 139:810–815
 12. See I, Mu Y, Albrecht V, Karlsson M, Dumyati G, Hardy DJ, Koeck M, Lynfield R, Nadle J, Ray SM, Schaffner W, Kallen AJ (2020) Trends in incidence of methicillin-resistant *Staphylococcus aureus* bloodstream infections differ by strain type and healthcare exposure, United States, 2005–2013. *Clin Infect Dis* 70:19–25
 13. Sati H, Carrara E, Savoldi A, Hansen P, Garlasco J, Campagnaro E, Bocchia S, Castillo-Polo JA, Magrini E, Garcia-Vello P, Wool E, Gigante V, Duffy E, Cassini A, Huttner B, Pardo PR, Naghavi M, Mirzayev F, Zignol M, Cameron A, Tacconelli E, Group WHOBPPPLA, (2025) The WHO Bacterial Priority Pathogens List 2024: a prioritisation study to guide research, development, and public health strategies against antimicrobial resistance. *Lancet Infect Dis*. [https://doi.org/10.1016/S1473-3099\(25\)00118-5](https://doi.org/10.1016/S1473-3099(25)00118-5).
 14. Rahbe E, Watier L, Guillemot D, Glaser P, Opatowski L (2023) Determinants of worldwide antibiotic resistance dynamics across drug-bacterium pairs: a multivariable spatial-temporal analysis using ATLAS. *Lancet Planet Health* 7:e547–e557
 15. Baguiya A, Bonet M, Brizuela V, Cuesta C, Knight M, Lumbiganon P, Abalos E, Kouanda S, Group WHOGMSSR (2024) Infection-related severe maternal outcomes and case fatality rates in 43 low and middle-income countries across the WHO regions: results from the Global Maternal Sepsis Study (GLOSS). *PLOS Glob Public Health* 4:e0003109
 16. Dong R, Liu W, Weng L, Yin P, Peng J, Chen Y, Li S, Wang C, Jiang W, Hu X, Du B, Zhou M, China Critical Care Clinical Trials G (2023) Temporal trends of sepsis-related mortality in China, 2006–2020: a population-based study. *Ann Intensive Care* 13:71
 17. Dondorp AM, Hoang MNT, Mer M, Sepsis in Resource-Limited Settings-Expert Consensus Recommendations Group of the European Society of Intensive Care M, the Mahidol-Oxford Research Unit in Bangkok T (2017) Recommendations for the management of severe malaria and severe dengue in resource-limited settings. *Intensive Care Med* 43:1683–1685
 18. Ma X, Vervoort D (2020) Critical care capacity during the COVID-19 pandemic: global availability of intensive care beds. *J Crit Care* 58:96–97
 19. Jacob ST, Pavlinac PB, Nakiyingi L, Banura P, Baeten JM, Morgan K, Magaret A, Manabe Y, Reynolds SJ, Liles WC, Wald A, Joba ML, Mayanja-Kizza H, Scheld WM (2013) Mycobacterium tuberculosis bacteremia in a cohort of HIV-infected patients hospitalized with severe sepsis in Uganda-high frequency, low clinical suspicion [corrected] and derivation of a clinical prediction score. *PLoS ONE* 8:e70305
 20. Ouma PO, Maina J, Thurania PN, Macharia PM, Alegana VA, English M, Okiro EA, Snow RW (2018) Access to emergency hospital care provided by the public sector in sub-Saharan Africa in 2015: a geocoded inventory and spatial analysis. *Lancet Glob Health* 6:e342–e350
 21. Hossain I, Hill P, Bottomley C, Jasseh M, Bojang K, Kaira M, Sankareh A, Sarwar G, Greenwood B, Howie S, Mackenzie G (2021) Healthcare seeking and access to care for pneumonia, sepsis, meningitis, and malaria in rural Gambia. *Am J Trop Med Hyg* 106:446–453
 22. Herdman MT, Maude RJ, Chowdhury MS, Kingston HW, Jeeyapant A, Samad R, Karim R, Dondorp AM, Hossain MA (2016) The relationship between poverty and healthcare seeking among patients hospitalized with acute febrile illnesses in Chittagong. *Bangladesh PLoS One* 11:e0152965
 23. Machado FR, Cavalcanti AB, Braga MA, Tallo FS, Bossa A, Souza JL, Ferreira JF, Pizzol FD, Monteiro MB, Angus DC, Lisboa T, Azevedo LCP, Spread Ed Investigators tLAdSN (2023) Sepsis in Brazilian emergency departments: a prospective multicenter observational study. *Intern Emerg Med* 18:409–421
 24. African Critical Illness Outcomes Study I (2025) The African Critical Illness Outcomes Study (ACIOS): a point prevalence study of critical illness in 22 nations in Africa. *Lancet* 405:715–724
 25. da Silva Ramos FJ, Freitas FGR, Machado FR (2024) Boarding in the emergency department: challenges and mitigation strategies. *Curr Opin Crit Care* 30:239–245
 26. Thwaites CL, Lundeg G, Dondorp AM, Sepsis in resource-limited settings-expert consensus recommendations group of the European Society of Intensive Care M, the Mahidol-Oxford Research Unit in Bangkok T (2016) Recommendations for infection management in patients with sepsis and septic shock in resource-limited settings. *Intensive Care Med* 42:2040–2042
 27. Cornistein C, Nucetelli Y, Rodriguez VM, Cudmani N, Roca MV, Sadino G, Brizuela M, Fernandez A, Gonzalez S, Aguila D, Macchi A, Staneloni MI, Estenssoro E, Prevar Study G (2025) Prevalence and mortality associated with multidrug-resistant infections in adult intensive care units in Argentina (PREV-AR). *Antimicrob Agents Chemother* 69:e0142624
 28. Allel K, Stone J, Undurraga EA, Day L, Moore CE, Lin L, Furuya-Kanamori L, Yakob L (2023) The impact of inpatient bloodstream infections caused by antibiotic-resistant bacteria in low- and middle-income countries: a systematic review and meta-analysis. *PLoS Med* 20:e1004199
 29. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, McIntyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Bellamy-Cote E, Berry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Moller MH, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McLaughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papanthanasoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M (2021) Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med* 47:1181–1247
 30. De Waele JJ, Boelens J, Leroux-Roels I (2020) Multidrug-resistant bacteria in ICU: fact or myth. *Curr Opin Anaesthesiol* 33:156–161
 31. Rhee C, Kadri SS, Danner RL, Suffredini AF, Massaro AF, Kitch BT, Lee G, Klompas M (2016) Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes. *Crit Care* 20:89

32. Povoia P, Coelho L, Dal-Pizzolo F, Ferrer R, Huttner A, Conway Morris A, Nobre V, Ramirez P, Rouze A, Salluh J, Singer M, Sweeney DA, Torres A, Waterer G, Kalil AC (2023) How to use biomarkers of infection or sepsis at the bedside: guide to clinicians. *Intensive Care Med* 49:142–153
33. Timsit JF, Bassetti M, Cremer O, Daikos G, de Waele J, Kallil A, Kipnis E, Kollef M, Laupland K, Paiva JA, Rodriguez-Bano J, Ruppe E, Salluh J, Taccone FS, Weiss E, Barbier F (2019) Rationalizing antimicrobial therapy in the ICU: a narrative review. *Intensive Care Med* 45:172–189
34. De Bus L, Arvaniti K, Sjøvall F (2024) Empirical antimicrobials in the intensive care unit. *Intensive Care Med* 50:1338–1341
35. Timsit JF, Baleine J, Bernard L, Calvino-Gunther S, Darmon M, Dellamonica J, Desruennes E, Leone M, Lepape A, Leroy O, Lucet JC, Merchaoui Z, Mimoz O, Misset B, Parienti JJ, Quenot JP, Roch A, Schmidt M, Slama M, Souweine B, Zahar JR, Zingg W, Bodet-Contentin L, Maxime V (2020) Expert consensus-based clinical practice guidelines management of intravascular catheters in the intensive care unit. *Ann Intensive Care* 10:118
36. Buetti N, Zahar JR, Adda M, Ruckly S, Bruel C, Schwebel C, Darmon M, Adrie C, Cohen Y, Siami S, Laurent V, Souweine B, Timsit JF, Network O (2024) Treatment of positive catheter tip culture without bloodstream infections in critically ill patients. A case-cohort study from the OUT-COMEREA network. *Intensive Care Med* 50:1108–1118
37. Denny KJ, De Waele J, Laupland KB, Harris PNA, Lipman J (2020) When not to start antibiotics: avoiding antibiotic overuse in the intensive care unit. *Clin Microbiol Infect* 26:35–40
38. Hranjec T, Rosenberger LH, Swenson B, Metzger R, Flohr TR, Politano AD, Riccio LM, Popovsky KA, Sawyer RG (2012) Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study. *Lancet Infect Dis* 12:774–780
39. Martin M, Forveille S, Lascarrrou JB, Seguin A, Canet E, Lemarie J, Agbakou M, Desmedt L, Blonz G, Zambon O, Corvec S, Le Thuaud A, Reignier J (2024) Immediate vs culture-initiated antibiotic therapy in suspected non-severe ventilator-associated pneumonia: a before-after study (DELAVAP). *Ann Intensive Care* 14:33
40. Zhou H, Buetti N, Perez-Galera S, Bravo-Ferrer J, Gutierrez-Gutierrez B, Paniagua-Garcia M, Feifel J, Sauser J, Kostyanov T, Canton R, Tan LK, Basoulis D, Pintado V, Roilides E, Dragovac G, Torre-Cisneros J, Medic D, Akova M, Goossens H, Bonten M, Harbarth S, Rodriguez-Bano J, De Kraker MEA, team C-Ep (2024) Risk factors for bloodstream infections due to carbapenem-resistant Enterobacterales: a nested case-control study. *J Antimicrob Chemother* 79:2132–2141
41. Falcone M, Tiseo G, Galfo V, Giordano C, Leonildi A, Marciano E, De Simone P, Biancofiore G, Boggi U, Barnini S, Menichetti F, Italian Group of Antimicrobial S (2022) Bloodstream infections in patients with rectal colonization by *Klebsiella pneumoniae* producing different type of carbapenemases: a prospective, cohort study (CHIMERA study). *Clin Microbiol Infect* 28:298 e291–298 e297
42. Hraiech S, Pauly V, Orleans V, Auquier P, Boyer L, Papazian L, Azoulay E (2022) Undocumented migrants in French intensive care units in 2011–2018: retrospective nationwide study. *Intensive Care Med* 48:290–299
43. Hraiech S, Pauly V, Orleans V, Auquier P, Azoulay E, Roch A, Boyer L, Papazian L (2023) COVID-19 among undocumented migrants admitted to French intensive care units during the 2020–2021 period: a retrospective nationwide study. *Ann Intensive Care* 13:99
44. Zanotti P, Odolini S, Tomasoni LR, Grecchi C, Caligaris S, Gulletta M, Matteelli A, Cappa V, Castelli F (2018) Imported malaria in northern Italy: epidemiology and clinical features observed over 18 years in the Teaching Hospital of Brescia. *J Travel Med*. <https://doi.org/10.1093/jtm/tax081>
45. Grobusch MP, Weld L, Goorhuis A, Hamer DH, Schunk M, Jordan S, Mockenhaupt FP, Chappuis F, Asgerirsson H, Caumes E, Jensenius M, van Genderen PJJ, Castelli F, Lopez-Velez R, Field V, Bottieau E, Molina I, Rapp C, Menendez MD, Gkrania-Klotsas E, Larsen CS, Malvy D, Lalloo D, Gobbi F, Florescu SA, Gautret P, Schlagenhauf P (2021) Travel-related infections presenting in Europe: a 20-year analysis of EuroTravNet surveillance data. *Lancet Reg Health Eur* 1:100001
46. Bottieau E, Clerinx J, Schrooten W, Van den Enden E, Wouters R, Van Esbroeck M, Vervoort T, Demey H, Colebunders R, Van Gompel A, Van den Ende J (2006) Etiology and outcome of fever after a stay in the tropics. *Arch Intern Med* 166:1642–1648
47. Karnad DR, Richards GA, Silva GS, Amin P, Council of the World Federation of Societies of I, Critical Care M (2018) Tropical diseases in the ICU: a syndromic approach to diagnosis and treatment. *J Crit Care* 46:119–126
48. Herten PJ, Vlieghe E, Bottieau E, Florence E, Jorens PG (2022) The emergence of travel-related infections in critical care units. *J Transl Int Med* 10:328–339
49. Rajapakse S, Fernando N, Dreyfus A, Smith C, Rodrigo C (2025) Leptospirosis. *Nat Rev Dis Primers* 11:32
50. Martinson ML, Lapham J (2024) Prevalence of immunosuppression among US adults. *JAMA* 331:880–882
51. Nates JL, Pene F, Darmon M, Mokart D, Castro P, David S, Povoia P, Russell L, Nielsen ND, Gorecki GP, Gradel KO, Azoulay E, Bauer PR, Nine II (2024) Septic shock in the immunocompromised cancer patient: a narrative review. *Crit Care* 28:285
52. Donnelly JP, Locke JE, MacLennan PA, McGwin G Jr, Mannon RB, Safford MM, Baddley JW, Muntner P, Wang HE (2016) Inpatient mortality among solid organ transplant recipients hospitalized for sepsis and severe sepsis. *Clin Infect Dis* 63:186–194
53. Azoulay E, Russell L, Van de Louw A, Metaxa V, Bauer P, Povoia P, Montero JG, Loeches IM, Mehta S, Puxty K, Schellongowski P, Rello J, Mokart D, Lemiale V, Mirouse A, Nine-i I (2020) Diagnosis of severe respiratory infections in immunocompromised patients. *Intensive Care Med* 46:298–314
54. Di Pasquale MF, Sotgiu G, Gramegna A, Radovanovic D, Terraneo S, Reyes LF, Rupp J, Gonzalez Del Castillo J, Blasi F, Aliberti S, Restrepo MI, Investigators G (2019) Prevalence and etiology of community-acquired pneumonia in immunocompromised patients. *Clin Infect Dis* 68:1482–1493
55. Kreitmann L, Helms J, Martin-Loeches I, Salluh J, Poulakou G, Pene F, Nseir S (2024) ICU-acquired infections in immunocompromised patients. *Intensive Care Med* 50:332–349
56. Ripa M, Rodriguez-Nunez O, Cardozo C, Naharro-Abellan A, Almela M, Marco F, Morata L, De La Calle C, Del Rio A, Garcia-Vidal C, Ortega MDM, Guerrero-Leon MLA, Feher C, Torres B, Puerta-Alcalde P, Mensa J, Soriano A, Martinez JA (2017) Influence of empirical double-active combination antimicrobial therapy compared with active monotherapy on mortality in patients with septic shock: a propensity score-adjusted and matched analysis. *J Antimicrob Chemother* 72:3443–3452
57. Fabre V, Amoah J, Cosgrove SE, Tamma PD (2019) Antibiotic therapy for *Pseudomonas aeruginosa* bloodstream infections: how long is long enough? *Clin Infect Dis* 69:2011–2014
58. Rodriguez-Sanchez B, Cercenado E, Coste AT, Greub G (2019) Review of the impact of MALDI-TOF MS in public health and hospital hygiene, 2018. *Euro Surveill* 24:1800193
59. Peri AM, Stewart A, Hume A, Irwin A, Harris PNA (2021) New microbiological techniques for the diagnosis of bacterial infections and sepsis in ICU including point of care. *Curr Infect Dis Rep* 23:12
60. Banerjee R, Teng CB, Cunningham SA, Ihde SM, Steckelberg JM, Moriarty JP, Shah ND, Mandrekar JN, Patel R (2015) Randomized trial of rapid multiplex polymerase chain reaction-based blood culture identification and susceptibility testing. *Clin Infect Dis* 61:1071–1080
61. Timbrook TT, Morton JB, McConeghy KW, Caffrey AR, Mylonakis E, LaPlante KL (2017) The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: a systematic review and meta-analysis. *Clin Infect Dis* 64:15–23
62. Satlin MJ, Chen L, Gomez-Simmonds A, Marino J, Weston G, Bhowmick T, Seo SK, Sperber SJ, Kim AC, Eilertson B, Derti S, Jenkins SG, Levi MH, Weinstein MP, Tang YW, Hong T, Juretschko S, Hoffman KL, Walsh TJ, Westblade LF, Uhlemann AC, Kreiswirth BN (2022) Impact of a rapid molecular test for *klebsiella pneumoniae* carbapenemase and ceftazidime-avibactam use on outcomes after bacteremia caused by carbapenem-resistant enterobacterales. *Clin Infect Dis* 75:2066–2075
63. Peri AM, Chatfield MD, Ling W, Furuya-Kanamori L, Harris PNA, Paterson DL (2024) Rapid diagnostic tests and antimicrobial stewardship programs for the management of bloodstream infection: what is their relative contribution to improving clinical outcomes? A systematic review and network meta-analysis. *Clin Infect Dis* 79:502–515
64. Enne VI, Stirling S, Barber JA, High J, Russell C, Brealey D, Dhesis Z, Colles A, Singh S, Parker R, Peters M, Cherian BP, Riley P, Dryden M, Simpson R,

- Patel N, Cassidy J, Martin D, Welters ID, Page V, Kandil H, Tudtud E, Turner D, Horne R, O'Grady J, Swart AM, Livermore DM, Gant V, Group IWS, Committees (2025) INHALE WP3, a multicentre, open-label, pragmatic randomised controlled trial assessing the impact of rapid, ICU-based, syndromic PCR, versus standard-of-care on antibiotic stewardship and clinical outcomes in hospital-acquired and ventilator-associated pneumonia. *Intensive Care Med* 51:272–286
65. Voirit G, Argaud L, Cohen Y et al (2025) Combined use of a multiplex PCR and serum procalcitonin to reduce antibiotic exposure in critically ill patients with community-acquired pneumonia: the MULTI-CAP randomized controlled trial. *Intensive Care Med* 51:1417–1430. <https://doi.org/10.1007/s00134-025-08026-5>
 66. Aissaoui Y, Derkaoui A, Hachimi A, Bouchama A, Dendane T, Doumiri M, ElAidaoui K, Ziadi A, Essafti M, Oualili L, Khaddouri M, Mroune O, Oudrhiri Safiani M, Khallouki M, Berdai A, Boukatta B, El Adib AR, Madani N, Soraia N, Belhadj A, Kohen JE, Abouqal R (2025) Diagnostic performance and impact on antimicrobial treatment of a multiplex polymerase chain reaction in critically ill patients with pneumonia: a multicenter observational study (the MORICUP-PCR study: morocco ICU pneumonia-PCR study). *Crit Care Explor* 7:e1220
 67. Conway Morris A, Bos LDJ, Nseir S (2022) Molecular diagnostics in severe pneumonia: a new dawn or false promise? *Intensive Care Med* 48:740–742
 68. Vazquez-Guillamet C, Scolari M, Zilberberg MD, Shorr AF, Micek ST, Kollef M (2014) Using the number needed to treat to assess appropriate antimicrobial therapy as a determinant of outcome in severe sepsis and septic shock. *Crit Care Med* 42:2342–2349
 69. Zasowski EJ, Bassetti M, Blasi F, Goossens H, Rello J, Sotgiu G, Tavoschi L, Arber MR, McCool R, Patterson JV, Longshaw CM, Lopes S, Manissero D, Nguyen ST, Tone K, Aliberti S (2020) A systematic review of the effect of delayed appropriate antibiotic treatment on the outcomes of patients with severe bacterial infections. *Chest* 158:929–938
 70. Loiodice A, Bailly S, Ruckly S, Buetti N, Barbier F, Staiquily Q, Tabah A, Timsit JF, Eurobact-2 Study Group tESolCMtESoCMtIDSGfiICIP, the ON (2024) Effect of adequacy of empirical antibiotic therapy for hospital-acquired bloodstream infections on intensive care unit patient prognosis: a causal inference approach using data from the Eurobact2 study. *Clin Microbiol Infect* 30:1559–1568
 71. Webb BJ, Sorensen J, Jephson A, Mecham I, Dean NC (2019) Broad-spectrum antibiotic use and poor outcomes in community-onset pneumonia: a cohort study. *Eur Respir J* 54:1900057
 72. Chanderraj R, Baker JM, Kay SG, Brown CA, Hinkle KJ, Fergle DJ, McDonald RA, Falkowski NR, Metcalf JD, Kaye KS, Woods RJ, Prescott HC, Sjoding MW, Dickson RP (2023) In critically ill patients, anti-anaerobic antibiotics increase risk of adverse clinical outcomes. *Eur Respir J* 61(2):2200910. <https://doi.org/10.1183/13993003.00910-2022>
 73. Rhee C, Kadri SS, Dekker JP, Danner RL, Chen HC, Fram D, Zhang F, Wang R, Klompas M, Program CDCPE (2020) Prevalence of antibiotic-resistant pathogens in culture-proven sepsis and outcomes associated with inadequate and broad-spectrum empiric antibiotic use. *JAMA Netw Open* 3:e202899
 74. Leone M, Bechis C, Baumstarck K, Lefrant JY, Albanese J, Jaber S, Lepape A, Constantin JM, Papazian L, Bruder N, Allaouchiche B, Bezulier K, Antonini F, Textoris J, Martin C, Investigators AN (2014) De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. *Intensive Care Med* 40:1399–1408
 75. Lopez-Cortes LE, Delgado-Valverde M, Moreno-Mellado E, Goikoetxea Aguirre J, Guio Carrion L, Blanco Vidal MJ, Lopez Soria LM, Perez-Rodriguez MT, Martinez Lamas L, Revillas FADL, Arminanzas C, Ruiz de Alegria-Puig C, Jimenez Aguilar P, Martinez-Rubio MDC, Saez-Bejar C, Cuevas CDL, Martin-Aspas A, Galan F, Yuste JR, Leiva-Leon J, Bou G, Capon Gonzalez P, Boix-Palop L, Xercavins-Valls M, Goenaga-Sanchez MA, Anza DV, Caston JJ, Rufian MR, Merino E, Rodriguez JC, Loeches B, Cuervo G, Guerra Laso JM, Plata A, Perez Cortes S, Lopez Mato P, Sierra Monzon JL, Rosso-Fernandez C, Bravo-Ferrer JM, Retamar-Gentil P, Rodriguez-Bano J, Group SS (2024) Efficacy and safety of a structured de-escalation from antipseudomonal beta-lactams in bloodstream infections due to Enterobacteriales (SIMPLIFY): an open-label, multicentre, randomised trial. *Lancet Infect Dis* 24:375–385
 76. Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA (2024) Infectious diseases society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections. *Clin Infect Dis*. <https://doi.org/10.1093/cid/ciae403>
 77. Kaye KS, Marchaim D, Thamlikitkul V, Carmeli Y, Chiu CH, Daikos G, Dhar S, Durante-Mangoni E, Gikas A, Kotanidou A, Paul M, Roilides E, Rybak M, Samarkos M, Sims M, Tancheva D, Tsiodras S, Kett D, Patel G, Calfee D, Leibovici L, Power L, Munoz-Price S, Stevenson K, Susick L, Latack K, Daniel J, Chiou C, Divine GW, Ghazyan V, Pogue JM (2023) Colistin monotherapy versus combination therapy for carbapenem-resistant organisms. *NEJM Evid* 2(1). <https://doi.org/10.1056/EVIDoa2200131>
 78. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, Skiada A, Andini R, Eliakim-Raz N, Nutman A, Zusman O, Antoniadou A, Pafundi PC, Adler A, Dickstein Y, Pavleas I, Zampino R, Daitch V, Bitterman R, Zayyad H, Koppel F, Levi I, Babich T, Friberg LE, Mouton JW, Theuretzbacher U, Leibovici L (2018) Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. *Lancet Infect Dis* 18:391–400
 79. Abdul-Aziz MH, Lipman J, Mouton JW, Hope WW, Roberts JA (2015) Applying pharmacokinetic/pharmacodynamic principles in critically ill patients: optimizing efficacy and reducing resistance development. *Semin Respir Crit Care Med* 36:136–153
 80. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, Hope WW, Farkas A, Neely MN, Schentag JJ, Drusano G, Frey OR, Theuretzbacher U, Kuti JL, International Society of Anti-Infective P, the P, Pharmacodynamics Study Group of the European Society of Clinical M, Infectious D (2014) Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. *Lancet Infect Dis* 14:498–509
 81. Roberts JA, Kumar A, Lipman J (2017) Right Dose, Right Now: Customized Drug Dosing in the Critically Ill. *Crit Care Med* 45:331–336
 82. Udy AA, Roberts JA, Lipman J (2011) Implications of augmented renal clearance in critically ill patients. *Nat Rev Nephrol* 7:539–543
 83. Abdul-Aziz MH, Hammond NE, Brett SJ, Cotta MO, De Waele JJ, Devaux A, Di Tanna GL, Dulhunty JM, Elkady H, Eriksson L, Hasan MS, Khan AB, Lipman J, Liu X, Monti G, Myburgh J, Novy E, Omar S, Rajbhandari D, Roger C, Sjovalf F, Zaghi I, Zangrillo A, Delaney A, Roberts JA (2024) Prolonged vs intermittent infusions of beta-lactam antibiotics in adults with sepsis or septic shock: a systematic review and meta-analysis. *JAMA* 332:638–648
 84. Dulhunty JM, Brett SJ, De Waele JJ, Rajbhandari D, Billot L, Cotta MO, Davis JS, Finfer S, Hammond NE, Knowles S, Liu X, McGuinness S, Mysore J, Paterson DL, Peake S, Rhodes A, Roberts JA, Roger C, Shirwadkar C, Starr T, Taylor C, Myburgh JA, Lipman J, Investigators BIS (2024) Continuous vs intermittent beta-lactam antibiotic infusions in critically ill patients with sepsis: the BLING III randomized clinical trial. *JAMA* 332:629–637
 85. Vardakas KZ, Voulgaris GL, Maliaros A, Samonis G, Falagas ME (2018) Prolonged versus short-term intravenous infusion of antipseudomonal beta-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. *Lancet Infect Dis* 18:108–120
 86. Yixuan I, Roberts JA, Abdul-Aziz MH, Sime FB (2025) Continuous or extended versus intermittent i 1 nfusions of beta-lactam antibiotics in ICU patients with pneumonia: a systematic review and meta-analysis of randomized controlled trials. *Antimicrob Agents Chemother*: in press
 87. Abdul-Aziz MH, Alffenaar JC, Bassetti M, Bracht H, Dimopoulos G, Marriott D, Neely MN, Paiva JA, Pea F, Sjovalf F, Timsit JF, Udy AA, Wicha SG, Zeitlinger M, De Waele JJ, Roberts JA, Infection Section of European Society of Intensive Care M, Pharmacokinetic/pharmacodynamic, Critically Ill Patient Study Groups of European Society of Clinical M, Infectious D, Infectious Diseases Group of International Association of Therapeutic Drug M, Clinical T, Infections in the ICU, Sepsis Working Group of International Society of Antimicrobial C (2020) Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper(). *Intensive Care Med* 46:1127–1153
 88. Leguelinel-Blache G, Nguyen TL, Louart B, Poujol H, Lavigne JP, Roberts JA, Muller L, Kinowski JM, Roger C, Lefrant JY (2018) Impact of quality bundle enforcement by a critical care pharmacist on patient outcome and costs. *Crit Care Med* 46:199–207

89. Buetti N, Tabah A, Setti N, Ruckly S, Barbier F, Akova M, Aslan AT, Leone M, Bassetti M, Morris AC, Arvaniti K, Paiva JA, Ferrer R, Qiu H, Montrucchio G, Cortegiani A, Kayaaslan B, De Bus L, De Waele JJ, Timsit JF, Eurobact-2 Study Group tESolCMTESoCMTIDSGflicIP, the ON (2024) The role of centre and country factors on process and outcome indicators in critically ill patients with hospital-acquired bloodstream infections. *Intensive Care Med* 50:873–889
90. Luxton T, King N, Walti C, Jeuken L, Sandoe J (2022) A systematic review of the effect of therapeutic drug monitoring on patient health outcomes during treatment with penicillins. *J Antimicrob Chemother* 77:1532–1541
91. Pai Mangalore R, Ashok A, Lee SJ, Romero L, Peel TN, Udy AA, Peleg AY (2022) Beta-lactam antibiotic therapeutic drug monitoring in critically ill patients: a systematic review and meta-analysis. *Clin Infect Dis* 75:1848–1860
92. Novy E, Martiniere H, Roger C (2023) The current status and future perspectives of beta-lactam therapeutic drug monitoring in critically ill patients. *Antibiotics* 12(4):681. <https://doi.org/10.3390/antibiotics12040681>
93. Hagel S, Bach F, Brenner T, Bracht H, Brinkmann A, Annecke T, Hohn A, Weigand M, Michels G, Kluge S, Nierhaus A, Jarczak D, König C, Weismann D, Frey O, Witzke D, Müller C, Bauer M, Kiehntopf M, Neugebauer S, Lehmann T, Roberts JA, Pletz MW, Investigators TT (2022) Effect of therapeutic drug monitoring-based dose optimization of piperacillin/tazobactam on sepsis-related organ dysfunction in patients with sepsis: a randomized controlled trial. *Intensive Care Med* 48:311–321
94. Chai MG, Roberts JA, Kelly CF, Ungerer J, McWhinney BC, Lipman J, Farkas A, Cotta MO (2023) Efficiency of dosing software using Bayesian forecasting in achieving target antibiotic exposures in critically ill patients, a prospective cohort study. *Anaesth Crit Care Pain Med* 42:101296
95. Theodosiou AA, Jones CE, Read RC, Bogaert D (2023) Microbiotoxicity: antibiotic usage and its unintended harm to the microbiome. *Curr Opin Infect Dis* 36:371–378
96. Eljaaly K, Enani MA, Al-Tawfiq JA (2018) Impact of carbapenem versus non-carbapenem treatment on the rates of superinfection: a meta-analysis of randomized controlled trials. *J Infect Chemother* 24:915–920
97. Prescott HC, Washyna TJ (2019) Improving sepsis treatment by embracing diagnostic uncertainty. *Ann Am Thorac Soc* 16:426–429
98. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, Loef BG, Dormans T, van Melsen GC, Kluiters YC, Kemperman H, van den Elsen MJ, Schouten JA, Streefkerk JO, Krabbe HG, Kieft H, Kluge GH, van Dam VC, van Pelt J, Bormans L, Otten MB, Reidinga AC, Endeman H, Twisk JW, van de Garde EMW, de Smet A, Kesecioglu J, Girbes AR, Nijsten MW, de Lange DW (2016) Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis* 16:819–827
99. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE (2017) Association of adverse events with antibiotic use in hospitalized patients. *JAMA Intern Med* 177:1308–1315
100. Webb BJ, Subramanian A, Lopansri B, Goodman B, Jones PB, Ferraro J, Stenehjem E, Brown SM (2020) Antibiotic Exposure and Risk for Hospital-Associated Clostridioides difficile Infection. *Antimicrob Agents Chemother* 64. <https://doi.org/10.1128/aac.02169-19>
101. Bliziotis IA, Samonis G, Vardakas KZ, Chrysanthopoulou S, Falagas ME (2005) Effect of aminoglycoside and beta-lactam combination therapy versus beta-lactam monotherapy on the emergence of antimicrobial resistance: a meta-analysis of randomized, controlled trials. *Clin Infect Dis* 41:149–158
102. Curran J, Lo J, Leung V, Brown K, Schwartz KL, Daneman N, Garber G, Wu JHC, Langford BJ (2022) Estimating daily antibiotic harms: an umbrella review with individual study meta-analysis. *Clin Microbiol Infect* 28:479–490
103. Arulkumaran N, Routledge M, Schlebusch S, Lipman J, Conway Morris A (2020) Antimicrobial-associated harm in critical care: a narrative review. *Intensive Care Med* 46:225–235
104. Roger C, Louart B (2021) Beta-lactams toxicity in the intensive care unit: an underestimated collateral damage? *Microorganisms* 9(7):1505. <https://doi.org/10.3390/microorganisms9071505>
105. Payne LE, Gagnon DJ, Riker RR, Seder DB, Glisic EK, Morris JG, Fraser GL (2017) Cefepime-induced neurotoxicity: a systematic review. *Crit Care* 21:276
106. Blevins AM, Lashinsky JN, McCammon C, Kollef M, Micek S, Juang P (2019) Incidence of acute kidney injury in critically ill patients receiving vancomycin with concomitant piperacillin-tazobactam, cefepime, or meropenem. *Antimicrob Agents Chemother* 63:10.1128/aac.02658-18. <https://doi.org/10.1128/aac.02658-18>
107. de Nies L, Kobras CM, Stracy M (2023) Antibiotic-induced collateral damage to the microbiota and associated infections. *Nat Rev Microbiol* 21:789–804
108. Ferrer M, Mendez-Garcia C, Rojo D, Barbas C, Moya A (2017) Antibiotic use and microbiome function. *Biochem Pharmacol* 134:114–126
109. Palleja A, Mikkelsen KH, Forslund SK, Kashani A, Allin KH, Nielsen T, Hansen TH, Liang S, Feng Q, Zhang C, Pyl PT, Coelho LP, Yang H, Wang J, Typas A, Nielsen MF, Nielsen HB, Bork P, Wang J, Vilsbøll T, Hansen T, Knop FK, Arumugam M, Pedersen O (2018) Recovery of gut microbiota of healthy adults following antibiotic exposure. *Nat Microbiol* 3:1255–1265
110. Reyman M, van Houten MA, Watson RL, Chu M, Arp K, de Waal WJ, Schiering I, Plotz FB, Willems RJL, van Schaik W, Sanders EAM, Bogaert D (2022) Effects of early-life antibiotics on the developing infant gut microbiome and resistome: a randomized trial. *Nat Commun* 13:893
111. Anthony WE, Wang B, Sukhum KV, D'Souza AW, Hink T, Cass C, Seiler S, Reske KA, Coon C, Dubberke ER, Burnham CD, Dantas G, Kwon JH (2022) Acute and persistent effects of commonly used antibiotics on the gut microbiome and resistome in healthy adults. *Cell Rep* 39:110649
112. Stracy M, Snitser O, Yelin I, Amer Y, Parizade M, Katz R, Rimler G, Wolf T, Herzl E, Koren G, Kuint J, Foxman B, Chodick G, Shalev V, Kishony R (2022) Minimizing treatment-induced emergence of antibiotic resistance in bacterial infections. *Science* 375:889–894
113. Diaz Caballero J, Wheatley RM, Kapel N, Lopez-Causape C, Van der Schalk T, Quinn A, Shaw LP, Ogunlana L, Recanatini C, Xavier BB, Timmermont L, Kluytmans J, Ruzin A, Esser M, Malhotra-Kumar S, Oliver A, MacLean RC (2023) Mixed strain pathogen populations accelerate the evolution of antibiotic resistance in patients. *Nat Commun* 14:4083
114. Zimmermann M, Patil KR, Typas A, Maier L (2021) Towards a mechanistic understanding of reciprocal drug-microbiome interactions. *Mol Syst Biol* 17:e10116
115. Maier L, Goemans CV, Wirbel J, Kuhn M, Eberl C, Pruteanu M, Müller P, Garcia-Santamarina S, Caccace E, Zhang B, Gekeler C, Banerjee T, Anderson EE, Milanese A, Lober U, Forslund SK, Patil KR, Zimmermann M, Stecher B, Zeller G, Bork P, Typas A (2021) Unravelling the collateral damage of antibiotics on gut bacteria. *Nature* 599:120–124
116. Ubeda C, Taur Y, Jenq RR, Equinda MJ, Son T, Samstein M, Viale A, Soccì ND, van den Brink MR, Kamboj M, Pamer EG (2010) Vancomycin-resistant Enterococcus domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. *J Clin Invest* 120:4332–4341
117. Zhai B, Ola M, Rolling T, Tosini NL, Joshowitz S, Littmann ER, Amoretti LA, Fontana E, Wright RJ, Miranda E, Veelken CA, Morjaria SM, Peled JU, van den Brink MRM, Babady NE, Butler G, Taur Y, Hohl TM (2020) High-resolution mycobiota analysis reveals dynamic intestinal translocation preceding invasive candidiasis. *Nat Med* 26:59–64
118. Falcone M, Russo A, Iraci F, Carfagna P, Goldoni P, Vullo V, Venditti M (2016) Risk factors and outcomes for bloodstream infections secondary to Clostridium difficile infection. *Antimicrob Agents Chemother* 60:252–257
119. Kalghatgi S, Spina CS, Costello JC, Liesa M, Morones-Ramirez JR, Slo-movic S, Molina A, Shirihai OS, Collins JJ (2013) Bactericidal antibiotics induce mitochondrial dysfunction and oxidative damage in Mammalian cells. *Sci Transl Med* 5:192ra185
120. Cheng SC, Scicluna BP, Arts RJ, Gresnigt MS, Lachmandas E, Giamarellos-Bourboulis EJ, Kox M, Manjeri GR, Wagenaar JA, Cremer OL, Leentjens J, van der Meer AJ, van de Veerdonk FL, Bonten MJ, Schultz MJ, Willems PH, Pickkers P, Joosten LA, van der Poll T, Netea MG (2016) Broad defects

- in the energy metabolism of leukocytes underlie immunoparalysis in sepsis. *Nat Immunol* 17:406–413
121. Balouiri M, Sadiki M, Ibsouda SK (2016) Methods for in vitro evaluating antimicrobial activity: a review. *J Pharm Anal* 6:71–79
 122. Chuang YC, Chang SC, Wang WK (2012) Using the rate of bacterial clearance determined by real-time polymerase chain reaction as a timely surrogate marker to evaluate the appropriateness of antibiotic usage in critical patients with *Acinetobacter baumannii* bacteremia. *Crit Care Med* 40:2273–2280
 123. Jeffrey M, Denny KJ, Lipman J, Conway Morris A (2023) Differentiating infection, colonisation, and sterile inflammation in critical illness: the emerging role of host-response profiling. *Intensive Care Med* 49:760–771
 124. Nielsen ND, Dean JT, 3rd, Shald EA, Conway Morris A, Povoja P, Schouten J, Parchim N (2024) When to Stop Antibiotics in the Critically Ill? *Antibiotics* 13(3):272. <https://doi.org/10.3390/antibiotics13030272>
 125. Wald-Dickler N, Spellberg B (2019) Short-course antibiotic therapy-replacing constantine units with “shorter is better.” *Clin Infect Dis* 69:1476–1479
 126. Daneman N, Rishu A, Pinto R, Rogers BA, Shehabi Y, Parke R, Cook D, Arabi Y, Muscedere J, Reynolds S, Hall R, Dwivedi DB, McArthur C, McGuinness S, Yahav D, Coburn B, Geagea A, Das P, Shin P, Detsky M, Morris A, Fralick M, Powis JE, Kandel C, Sligl W, Bagshaw SM, Singhal N, Belle-Cote E, Whitlock R, Khwaja K, Morpeth S, Kazemi A, Williams A, MacFadden DR, McIntyre L, Tsang J, Lamontagne F, Carignan A, Marshall J, Friedrich JO, Cirone R, Downing M, Graham C, Davis J, Duan E, Neary J, Evans G, Alraddadi B, Al Johani S, Martin C, Elsayed S, Ball I, Lauzier F, Turgeon A, Stelfox HT, Conly J, McDonald EG, Lee TC, Sullivan R, Grant J, Kagan I, Young P, Lawrence C, O’Callaghan K, Eustace M, Choong K, Aslanian P, Buehner U, Havey T, Binnie A, Prazak J, Reeve B, Litton E, Lother S, Kumar A, Zarychanski R, Hoffman T, Paterson D, Daley P, Commons RJ, Charbonney E, Naud JF, Roberts S, Tiruvoipati R, Gupta S, Wood G, Shum O, Miyakis S, Dodek P, Kwok C, Fowler RA, Balance Investigators ftCCCTGtAoMM, Infectious Disease Canada Clinical Research Network tA, New Zealand Intensive Care Society Clinical Trials G, the Australasian Society for Infectious Diseases Clinical Research N (2025) Antibiotic treatment for 7 versus 14 days in patients with bloodstream infections. *N Engl J Med* 392:1065–1078
 127. Davar K, Clark D, Centor RM, Dominguez F, Ghanem B, Lee R, Lee TC, McDonald EG, Phillips MC, Sendi P, Spellberg B (2023) Can the future of ID escape the inertial dogma of its past? The exemplars of shorter is better and oral is the new IV. *Open Forum Infect Dis* 10:ofac706
 128. Gajdos L, Buetti N, Tabah A, Ruckly S, Akova M, Sjoval F, Arvanti K, de Waele J, Bracht H, Barbier F, Timsit JF, Euroact-2, ESICM, ESCMID, ESGCIP, OUTCOMEREA (2025) Shortening antibiotic therapy duration for hospital-acquired bloodstream infections in critically ill patients: a causal inference model from the international EUROACT-2 database. *Intensive Care Med* 51:518–528
 129. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jusserand D, Asfar P, Perrin D, Fieux F, Aubas S, Pneum ATG (2003) Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 290:2588–2598
 130. Montravers P, Tubach F, Lescot T, Veber B, Esposito-Farese M, Seguin P, Paugam C, Lepape A, Meistelman C, Cousson J, Tesniere A, Planteveve G, Blasco G, Asehnoune K, Jaber S, Lasocki S, Dupont H, Group DT (2018) Short-course antibiotic therapy for critically ill patients treated for post-operative intra-abdominal infection: the DURAPOP randomised clinical trial. *Intensive Care Med* 44:300–310
 131. Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, Cook CH, O’Neill PJ, Mazuski JE, Askari R, Wilson MA, Napolitano LM, Namias N, Miller PR, Dellinger EP, Watson CM, Coimbra R, Dent DL, Lowry SF, Cocanour CS, West MA, Banton KL, Cheadle WG, Lipsett PA, Guidry CA, Popovsky K, Investigators S-IT (2015) Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med* 372:1996–2005
 132. Pandolfo AM, Horne R, Jani Y, Reader TW, Bidad N, Brealey D, Enne VI, Livermore DM, Gant V, Brett SJ, Group IWS (2022) Understanding decisions about antibiotic prescribing in ICU: an application of the Necessity Concerns Framework. *BMJ Qual Saf* 31:199–210
 133. Hedrick TL, Evans HL, Smith RL, McElearney ST, Schulman AS, Chong TW, Pruett TL, Sawyer RG (2006) Can we define the ideal duration of antibiotic therapy? *Surg Infect (Larchmt)* 7:419–432
 134. Dark P, Hossain A, McAuley DF, Brealey D, Carlson G, Clayton JC, Felton TW, Ghuman BK, Gordon AC, Hellyer TP, Lone NI, Manazar U, Richards G, McCullagh IJ, McMullan R, McNamee JJ, McNeil HC, Mouncey PR, Naisbitt MJ, Parker RJ, Poole RL, Rostron AJ, Singer M, Stevenson MD, Walsh TS, Welters ID, Whitehouse T, Whiteley S, Wilson P, Young KK, Perkins GD, Lall R, Collaborators AD-S (2025) Biomarker-guided antibiotic duration for hospitalized patients with suspected sepsis: the ADAPT-sepsis randomized clinical trial. *JAMA* 333:682–693
 135. Papp M, Kiss N, Baka M, Trasy D, Zubek L, Fehervari P, Harnos A, Turan C, Hegyi P, Molnar Z (2023) Procalcitonin-guided antibiotic therapy may shorten length of treatment and may improve survival—a systematic review and meta-analysis. *Crit Care* 27:394
 136. Schouten J, De Angelis G, De Waele JJ (2020) A microbiologist consultant should attend daily ICU rounds. *Intensive Care Med* 46:372–374
 137. Chiu CY, Miller SA (2019) Clinical metagenomics. *Nat Rev Genet* 20:341–355
 138. Rodino KG, Simner PJ (2024) Status check: next-generation sequencing for infectious-disease diagnostics. *J Clin Invest* 134:e178003
 139. Gaston DC, Miller HB, Fissel JA, Jacobs E, Gough E, Wu J, Klein EY, Carroll KC, Simner PJ (2022) Evaluation of metagenomic and targeted next-generation sequencing workflows for detection of respiratory pathogens from bronchoalveolar lavage fluid specimens. *J Clin Microbiol* 60:e0052622
 140. Abdul-Aziz MH, Sulaiman H, Mat-Nor MB, Rai V, Wong KK, Hasan MS, Abd Rahman AN, Jamal JA, Wallis SC, Lipman J, Staatz CE, Roberts JA (2016) Beta-lactam infusion in severe sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis. *Intensive Care Med* 42:1535–1545
 141. Friberg LE (2021) Pivotal role of translation in anti-infective development. *Clin Pharmacol Ther* 109:856–866
 142. Hussein M, Han ML, Zhu Y, Zhou Q, Lin YW, Hancock REW, Hoyer D, Creek DJ, Li J, Velkov T (2019) Metabolomics study of the synergistic killing of polymyxin B in combination with amikacin against polymyxin-susceptible and -resistant *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 64:e01587
 143. Sela U, Euler CW, Correa da Rosa J, Fischetti VA (2018) Strains of bacterial species induce a greatly varied acute adaptive immune response: The contribution of the accessory genome. *PLoS Pathog* 14:e1006726
 144. van der Poll T, Shankar-Hari M, Wiersinga WJ (2021) The immunology of sepsis. *Immunity* 54:2450–2464
 145. Bulman ZP, Wicha SG, Nielsen EI, Lenhard JR, Nation RL, Theuretzbacher U, Derendorf H, Tangden T, Zeitlinger M, Landersdorfer CB, Bulitta JB, Friberg LE, Li J, Tsuji BT, International Society of Anti-Infective P, European Society of Clinical M, Infectious Diseases P, Pharmacodynamics of Anti-Infectives Study G, International Society of Antimicrobial Chemotherapy Anti-Infective Pharmacology Working G (2022) Research priorities towards precision antibiotic therapy to improve patient care. *Lancet Microbe* 3:e795–e802
 146. Antcliffe DB, Burrell A, Boyle AJ, Gordon AC, McAuley DF, Silversides J (2025) Sepsis subphenotypes, theragnostics and personalized sepsis care. *Intensive Care Med* 51:756–768
 147. Blot S, Ruppe E, Harbarth S, Asehnoune K, Poulakou G, Luyt CE, Rello J, Klompas M, Depuydt P, Eckmann C, Martin-Loeches I, Povoja P, Bouadma L, Timsit JF, Zahar JR (2022) Healthcare-associated infections in adult intensive care unit patients: Changes in epidemiology, diagnosis, prevention and contributions of new technologies. *Intensive Crit Care Nurs* 70:103227