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NARRATIVE REVIEW

Antibiotic therapy for severe bacterial infections

Jean-François Timsit[1,2,3*], Lowell Ling[4], Etienne de Montmollin[1,2,3], Hendrik Bracht[5], Andrew Conway-Morris[6,7], Liesbet De Bus[8,9], Marco Falcone[10,11], Patrick N. A. Harris[12,13,14,15], Flavia R. Machado[16], José-Artur Paiva[17,18,19], David L. Paterson[12,20], Garyphallia Poulakou[21], Jason A. Roberts[12,14,22,23], Claire Roger[23], Andrew F. Shorr[24], Alexis Tabah[12,25,26] and Jeffrey Lipman[12,14,23,26,27]

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

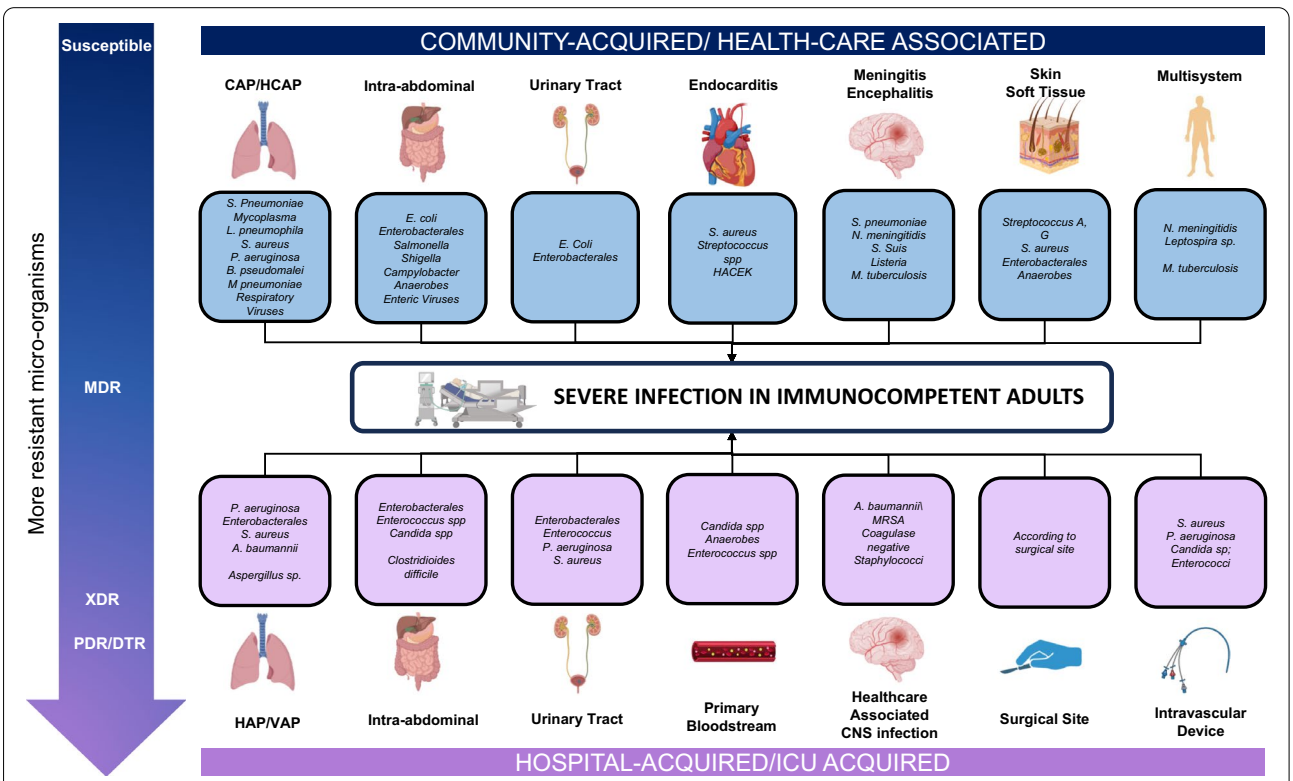

Fig. 1 Severe infection in immunocompetent individuals. *UTI* urinary tract infection; *CAP* community-acquired pneumonia; *HCAP* healthcare-associated pneumonia; *HAP* hospital-acquired pneumonia; *VAP* ventilatory-associated pneumonia; *MDR* multidrug-resistant bacteria; *XDR* extensively drug-resistant 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 Enterobacterales (CRE) and *A. baumannii* (CRAB) are on the rise [13, 14], particularly metallo-betalactamases, (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]. HCAIs 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

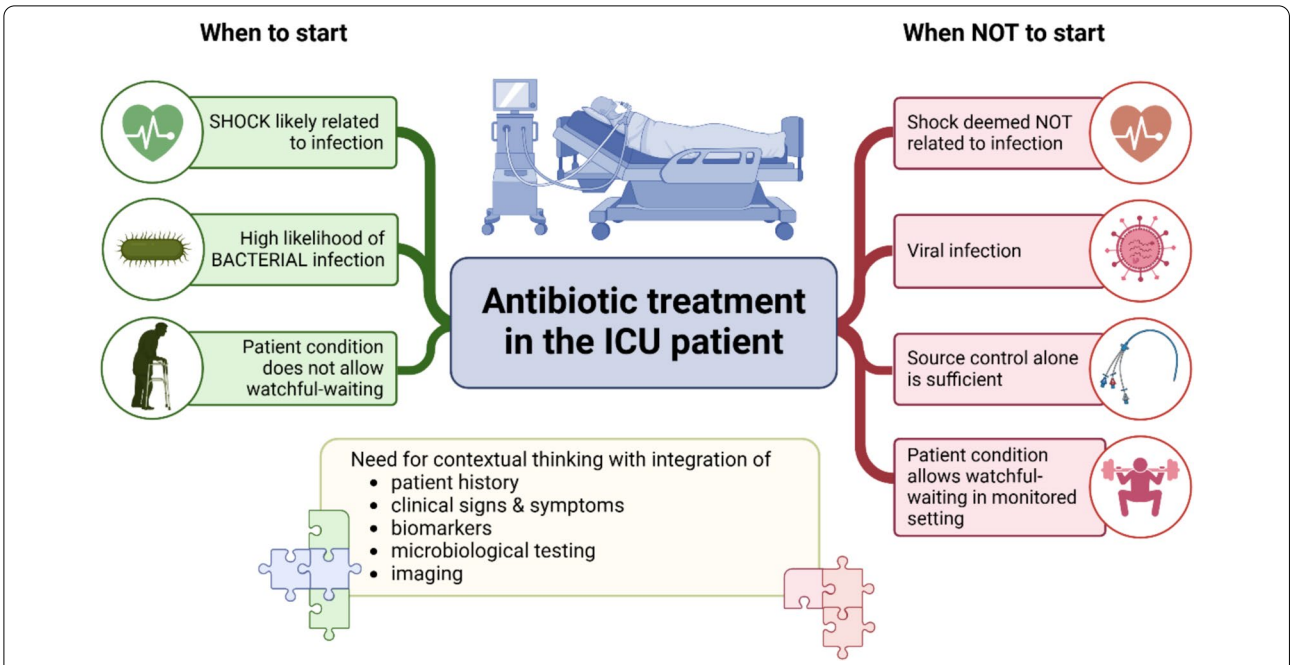

Fig. 2 When to start and when not to start antibiotic treatment in ICU patients. Created in BioRender. De Bus, L. (2025) https://BioRender.com/s05x456

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 (Plasmodium falciparum 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 *Salmonella typhi* or *S. paratyphi* 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 trial 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,

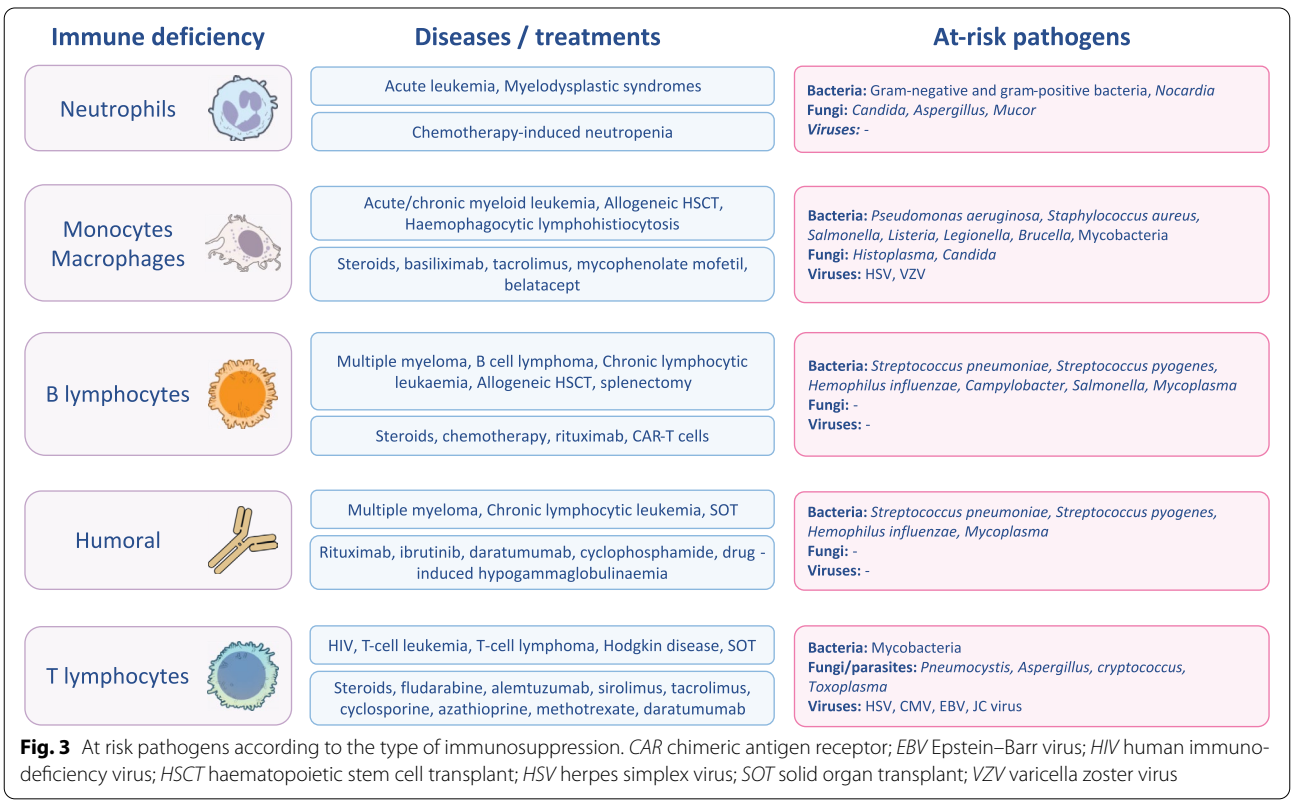

Fig. 3 At risk pathogens according to the type of immunosuppression. *CAR* chimeric antigen receptor; *EBV* Epstein–Barr virus; *HIV* human immunodeficiency virus; *HSCT* haematopoietic stem cell transplant; *HSV* herpes simplex virus; *SOT* solid organ transplant; *VZV* varicella zoster virus

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 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

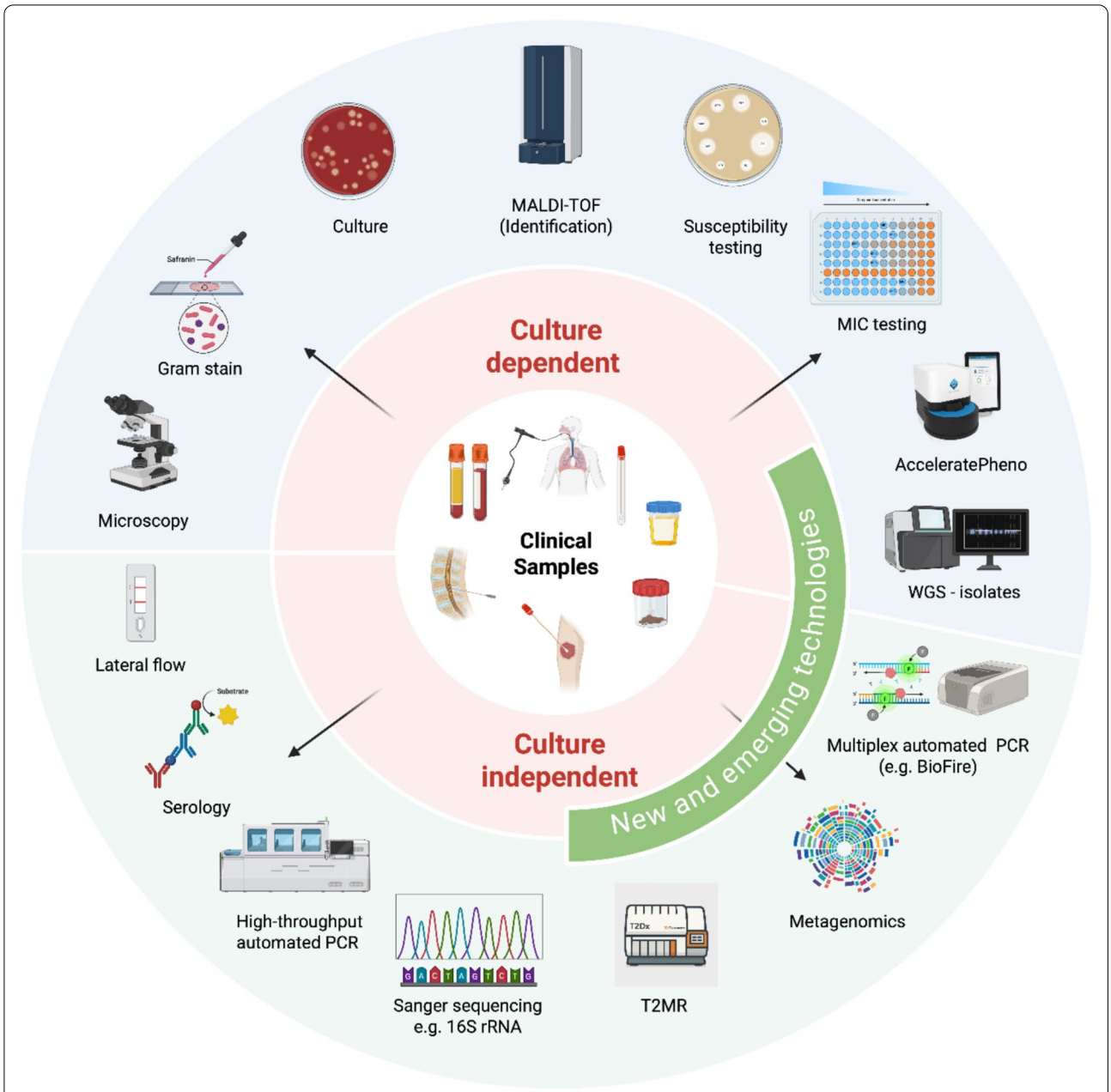

Fig. 4 Existing, new and emerging methods for microbiological diagnosis. Note some methods can be applied in a culture-dependent or culture-independent approach (e.g., BioFire instrument can be used to test cerebrospinal fluid directly [FilmArray ME Panel] or on positive blood culture bottles [BCID2 Panel]). Some novel methods are FDA-approved (e.g., AcceleratePheno, T2MR, and BioFire), others remain in clinical development (e.g. clinical metagenomics)

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].

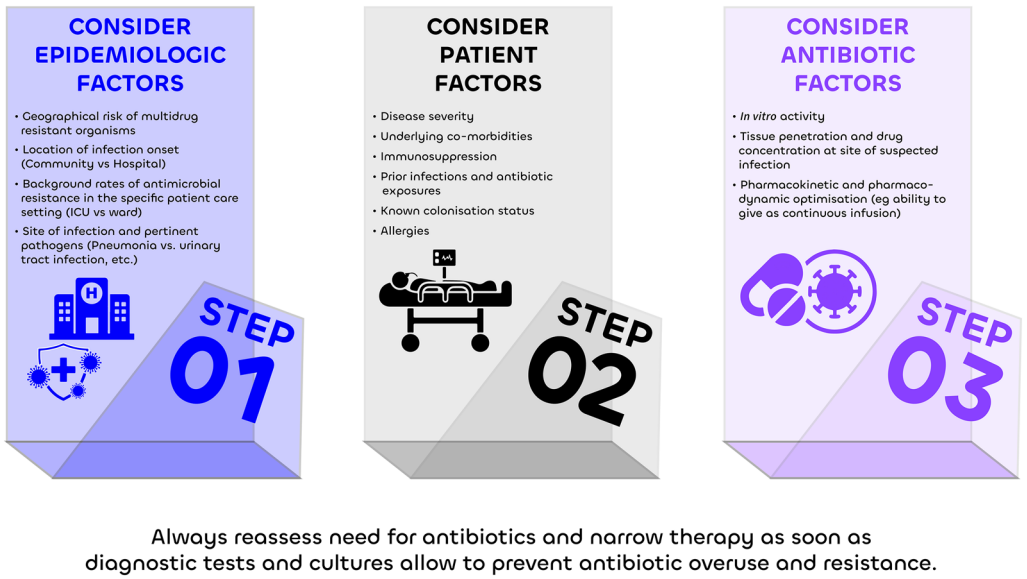

Fig. 5 Selecting appropriate antibiotic therapy: key steps and considerations

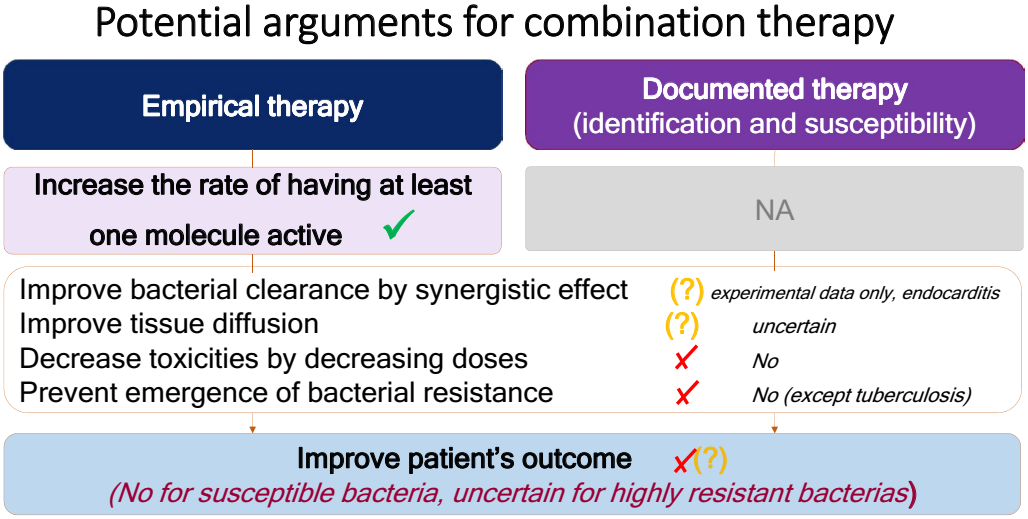

Fig. 6 The pro and con of combination therapy in severe bacterial infections: *NA* not available

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

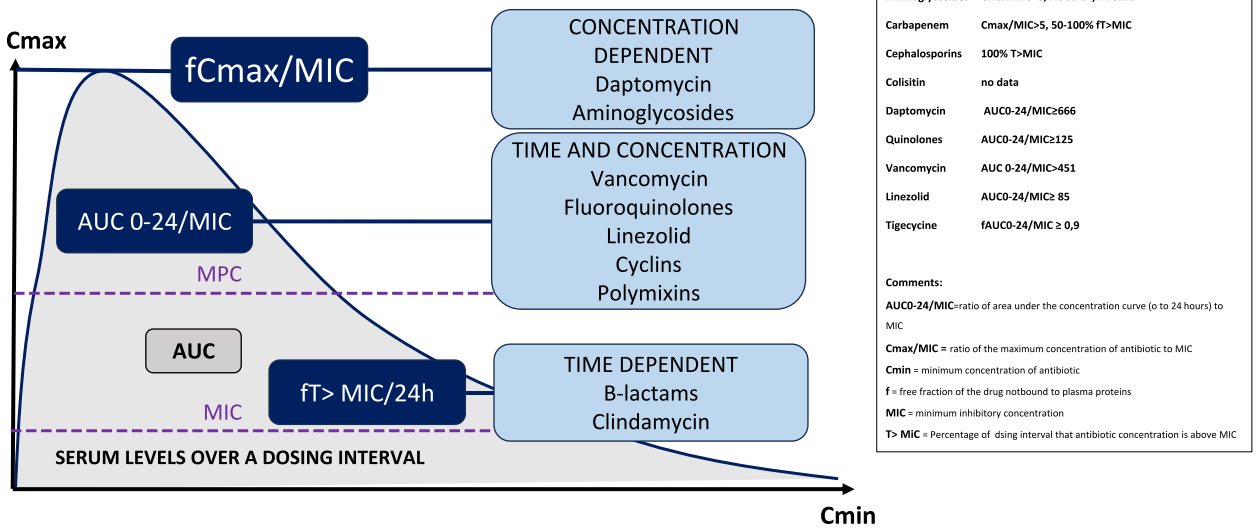

Fig. 7 Elements to consider to optimise antibiotic therapy (adapted from [81, 87]). Cmax: peak concentration; Cmin: though concentration; AUC area under the curve; MIC: minimum inhibitory concentration: is defined as the lowest concentration of a drug, which prevents visible in vitro growth of bacteria or fungi. MPC: mutation prevention concentration describes a drug concentration threshold or lowest drug concentration blocking growth of mutant bacterial sub-populations that spontaneously arise in bacterial densities of 10^7–10^9 cfu—densities seen with infection. NB: The clinical impact of other elements related to the interaction between antimicrobials and bacteria (bactericidal activity, inoculum effect, and post-antibiotic effect) are debated

duration of time that free drug concentration remains above the MIC during a dosing interval (fT > MIC; time dependency), the ratio of AUC0–24 to MIC (total exposure/time), and the ratio of Cmax 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 ß-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 ß-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

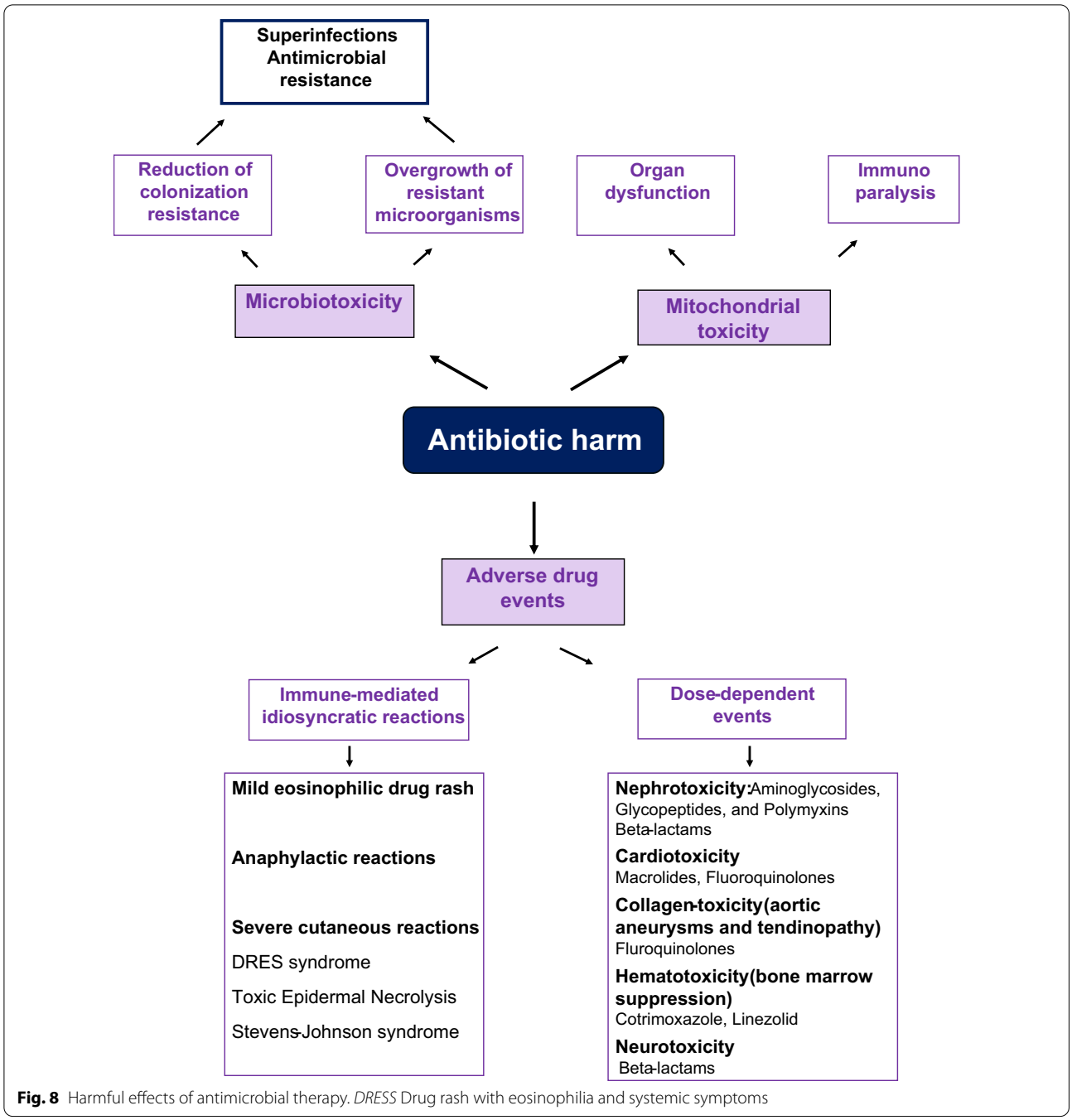

Fig. 8 Harmful effects of antimicrobial therapy. *DRESS* Drug rash with eosinophilia and systemic symptoms

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	Measuring the burden of untreated sepsis within communities is critical for identifying gaps in healthcare delivery and improving outcomes
	Understanding the pathways of care, including how patients navigate the healthcare system, and identifying specific barriers unique to different settings will be essential steps
	Gathering data on the prevention, recognition, management, and rehabilitation of sepsis in resource limited settings is key to develop targeted interventions
Rapid diagnostic tests	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
	Accurate interpretation of RDT requires expertise, and further research is necessary to evaluate their impact on AMS and patient outcomes
	The impact of syndromic mPCR including not only suspected but also very uncommon pathogens should be refined
	Rapid pan pathogen genomic-based diagnostics should be developed and tested in severe infections
TDM: use of rapid TDM and dosing softwares	Interventional dose optimization studies using rapidly applied TDM and dosing software to see if patient outcomes and healthcare costs can be improved
	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
	Further to this, the effect of dose optimization on emergence of AMR is important
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	Exposure to bactericidal antimicrobials results in mitochondrial toxicity that may contribute to development and perpetuation of organ dysfunction and to immunoparalysis in sepsis
	To evaluate the respective impact of broad spectrum antibiotics on the gut microbiota through novel metagenomic approaches
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 (*A baumanni, S maltophilia* and other difficult-to-treat gram negative bacteria)
Duration of antibiotic therapy	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
	Early cessation vs antibiotic continuation in case of culture negative sepsis
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
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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, 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, Nimes University Hospital, Nimes, 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, bioMerieux, AOP Orphan, Advanz Pharma, Fresenius, Pfizer and MSD. attended Scientific Advisory Board from bioMerieux, 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.

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