

NARRATIVE REVIEW



Antimicrobial-associated harm in critical care: a narrative review

Nishkantha Arulkumaran¹, Matthew Routledge^{2,3}, Sanmarié Schlebusch^{4,5}, Jeffrey Lipman^{4,6,7} and Andrew Conway Morris^{8,9*} 

© 2020 Springer-Verlag GmbH Germany, part of Springer Nature

Abstract

The belief that, for the individual patient, the benefit of prompt and continued use of antimicrobials outweighs any potential harm is a significant barrier to improved stewardship of these vital agents. Antimicrobial stewardship may be perceived as utilitarian rationing, seeking to preserve the availability of effective antimicrobials by limiting the development of resistance in a manner which could conflict with the immediate treatment of the patient in need. This view does not account for the growing evidence of antimicrobial-associated harm to individual patients. This review sets out the evidence for antimicrobial-associated harm and how this should be balanced with the need for prompt and appropriate therapy in infection. It describes the mechanisms by which antimicrobials may harm patients including: mitochondrial toxicity; immune cell toxicity; adverse drug reactions; selection of resistant organisms within a given patient; and disruption of the microbiome. Finally, the article indicates how the harms of antimicrobials may be mitigated and identifies areas for research and development in this field.

Keywords: Antibiotics, Antifungals, Drug-related side effects and adverse reactions, Critical care

Introduction

One of the major barriers to improved antimicrobial stewardship is the widespread belief amongst both medical professionals and the public that, for the individual patient, the benefits of prompt and continued use of antimicrobials outweigh any potential harm. Antimicrobial stewardship is sometimes perceived as the utilitarian rationing of a vital resource, sacrificing the wellbeing of the present individual for a less immediate collective good. For the clinician, their principal duty to the patient in need outweighs this wider and more nebulous benefit. This view is perhaps most pertinent to critically ill

patients, who are the highest per-capita consumers of antimicrobials [1] and who are at greatest risk of harm from untreated or undertreated infection [2, 3].

However, there is growing evidence of the harm caused to individual patients by unnecessary or unduly prolonged antimicrobial use [4]. If consideration is given to potential harms in the individual patient, clinicians may be more judicious about antimicrobial prescribing. Several studies conducted within the intensive care unit (ICU) setting have provided compelling evidence that over-zealous use of antimicrobials can translate into adverse patient outcomes, including increased mortality [4–6].

This review sets out the evidence for antimicrobial-associated harm, with a specific focus on the critically ill patient. It explores potential mechanisms underlying antimicrobial toxicity, including antimicrobial-induced cellular and mitochondrial toxicity, adverse drug reactions, selection of resistant organisms at individual patient level and disruption of the microbiome. Finally, it discusses approaches to limit antimicrobial-associated harm and highlights research priorities.

*Correspondence: ac926@cam.ac.uk

⁹ Division of Anaesthesia, Department of Medicine, University of Cambridge, Level 4, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK

Full author information is available at the end of the article
Nishkantha Arulkumaran, Matthew Routledge and Sanmarié Schlebusch contributed equally to this manuscript.

The evidence for antimicrobial-associated harm

Initiation of antimicrobial therapy

Early initiation of antimicrobial therapy in bacteraemic septic shock on ICU admission is associated with a mortality benefit [3, 7, 8]. This led to the Surviving Sepsis Campaign guidelines emphasizing the importance of timely, empirical, broad spectrum antimicrobial therapy [9]. However, the effect of the timing of initiation of antimicrobials in patients already in ICU is less clear cut, a large observational multi-centre study possibly suggested that adequacy of antimicrobial coverage may be more critical than time of initiation [10]. In clinical practice, the Surviving Sepsis Campaign guidelines have sometimes resulted in the indiscriminate of empirical broad-spectrum antimicrobials in patients who have uncomplicated infections (an area where the evidence base is far less certain) and in those who have no bacterial infection at all [11]. There is some evidence that suggests that an early empiric approach may cause harm. A quasi-experimental, before and after cohort study [12], performed on patients suspected of having an infection on a single Surgical ICU, compared early antimicrobial administration based solely on clinical grounds to a more conservative strategy, based on waiting for microbiological evidence of infection. There was a significant all-cause mortality benefit among patients treated with the more conservative approach (odds of death ratio 2.5, 95% CI 1.5–4.0), despite a median 10-h prolongation in time to antimicrobial therapy, suggesting inappropriate antimicrobial therapy was associated with significant harm. This approach also appeared to translate into more appropriate antimicrobial choice and a shorter overall course duration.

However, it is important to note several caveats with these data. The data concerning initiation of antimicrobials in ICU comes from observational studies which are subject to inherent biases. For example, in observational studies there may be systematic differences between patients who received earlier and later antimicrobial therapy which were not measured and may influence the effects seen. Equally, Hranjec et al.'s quasi-experimental study [12] occurred in a selected group of patients in a single ICU and may not be generalisable.

Although it is plausible that early initiation of appropriate antimicrobials is beneficial in severe sepsis and septic shock, their over-zealous use in patients without infection is likely to lead to harm [13].

Although beyond the scope of this review, it should be emphasised that prompt source control can be vital in managing sepsis, improving the physiological status of the patient as well as providing samples for microbiological investigation [8, 10, 14].

Take-home message

Antimicrobial stewardship is sometimes perceived by frontline clinicians as the utilitarian rationing of a vital healthcare resource; sacrificing the wellbeing of the present individual for a less immediate collective good. This review sets out the evidence that antimicrobials can cause harm for the individual patient and proposes a research and quality improvement agenda to address this pressing but underacknowledged issue.

Duration of antimicrobial therapy

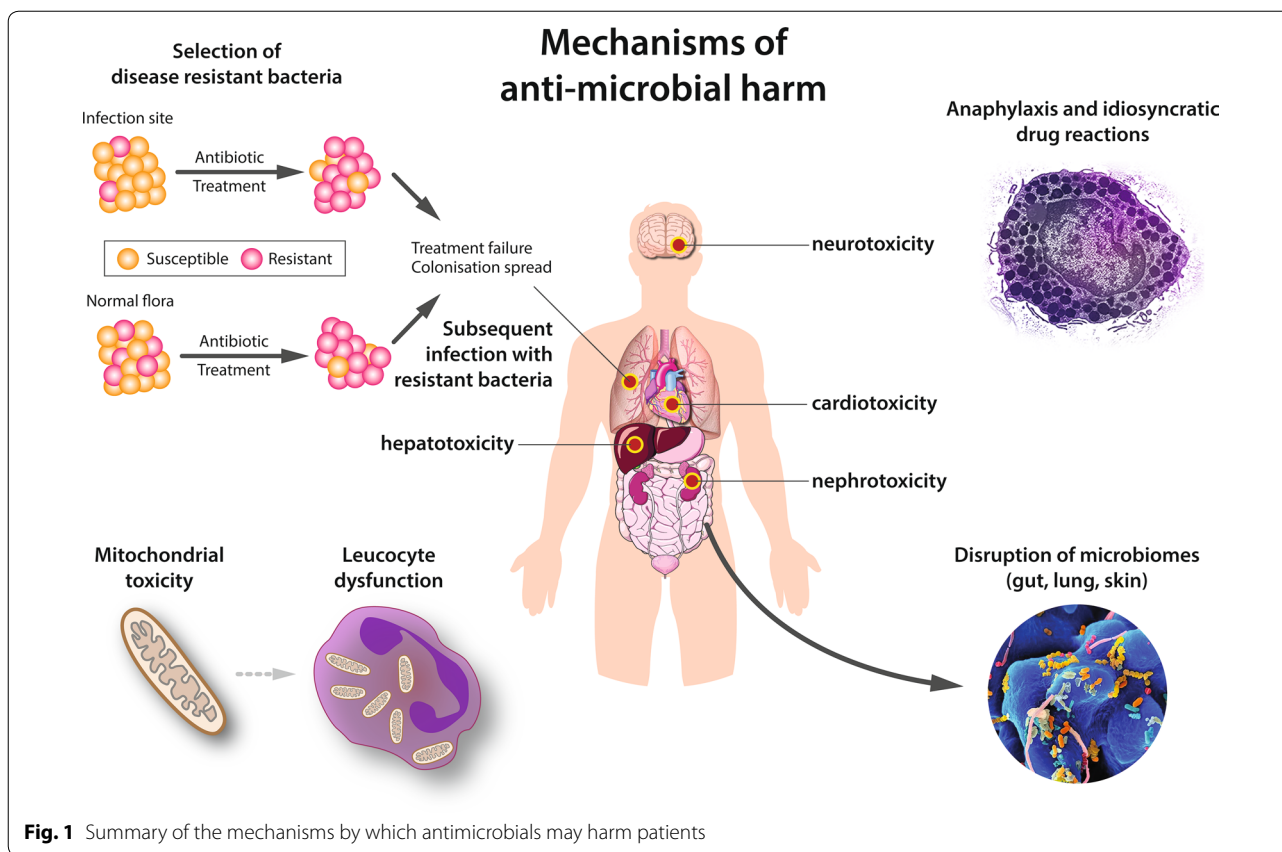
Arguably of greater concern for stewardship efforts in the ICU is the inappropriate continuation of antimicrobials following initiation. The potential harms of this were illustrated in a randomised controlled trial (RCT) of invasive versus non-invasive diagnostic strategies for ventilator-associated pneumonia (VAP). Patients in the invasive group had significantly reduced antimicrobial exposure which was associated with reduced risk-adjusted mortality [15]. Subsequent studies of diagnostic technique did not result in significant reduction in antimicrobial use or mortality [16, 17], implying that it was the reduction in antimicrobials rather than the method of diagnosis that was the key factor. Similarly, in the largest RCT evaluating procalcitonin (PCT) guided cessation of antimicrobials, PCT-guided treatment was associated with lower overall antimicrobial use and mortality [4]. However, the association between shorter duration of antimicrobial use and mortality was not demonstrated by other, smaller, studies [18].

Broad-spectrum antimicrobial combination

Another area where there is evidence that antimicrobials cause harm is in the co-administration of agents. A prospective observational study evaluating the impact of American Thoracic Society/Infectious Diseases Society of America guideline compliance in management of potentially resistant pneumonia demonstrated an excess mortality associated with guideline compliance [5]. The main reasons for non-compliance were non-use of dual treatment for Gram negative pathogens and non-coverage for methicillin-resistant *Staphylococcus aureus*. This suggests that empirical, concomitant use of several antimicrobials is associated with an excess mortality risk compared to monotherapy [5].

Excessive prolongation

There is a growing body of evidence that antimicrobial course durations are excessive [19]. These have led to calls to abandon the concept of a defined 'antimicrobial course' and move to a more individualised approach



to antimicrobial duration [20]. An RCT looking at the management of community acquired pneumonia (CAP) showed no significant difference in mortality between median antimicrobial treatment duration of 5 versus 10 days. There was, however, a significant increase in readmission at 30 days in those treated for longer durations; Intriguingly this appears not to have been caused by CAP recurrence, which was similar between the two groups [21].

Several randomised trials have evaluated the duration of antimicrobials in ICU patients. Three studies including patients with VAP [22–24] and one with undifferentiated sepsis [25], demonstrated that shorter duration of antimicrobials was not associated with increased mortality risk. It should be noted that, in general, these trials were powered for non-inferiority, which may explain why many of them failed to identify any significant reduction in antimicrobial-associated harm. De-escalation of antimicrobials, being the reduction in spectrum and duration of agents, has been assessed in a number of observational studies in intensive care and one RCT [26], which did not show a survival advantage in de-escalation. However, this literature should give the intensivist confidence that in many cases the

duration of antimicrobial courses can be safely shortened and de-escalated, thereby minimising the risk of adverse effects.

Mechanisms of anti-microbial associated harm

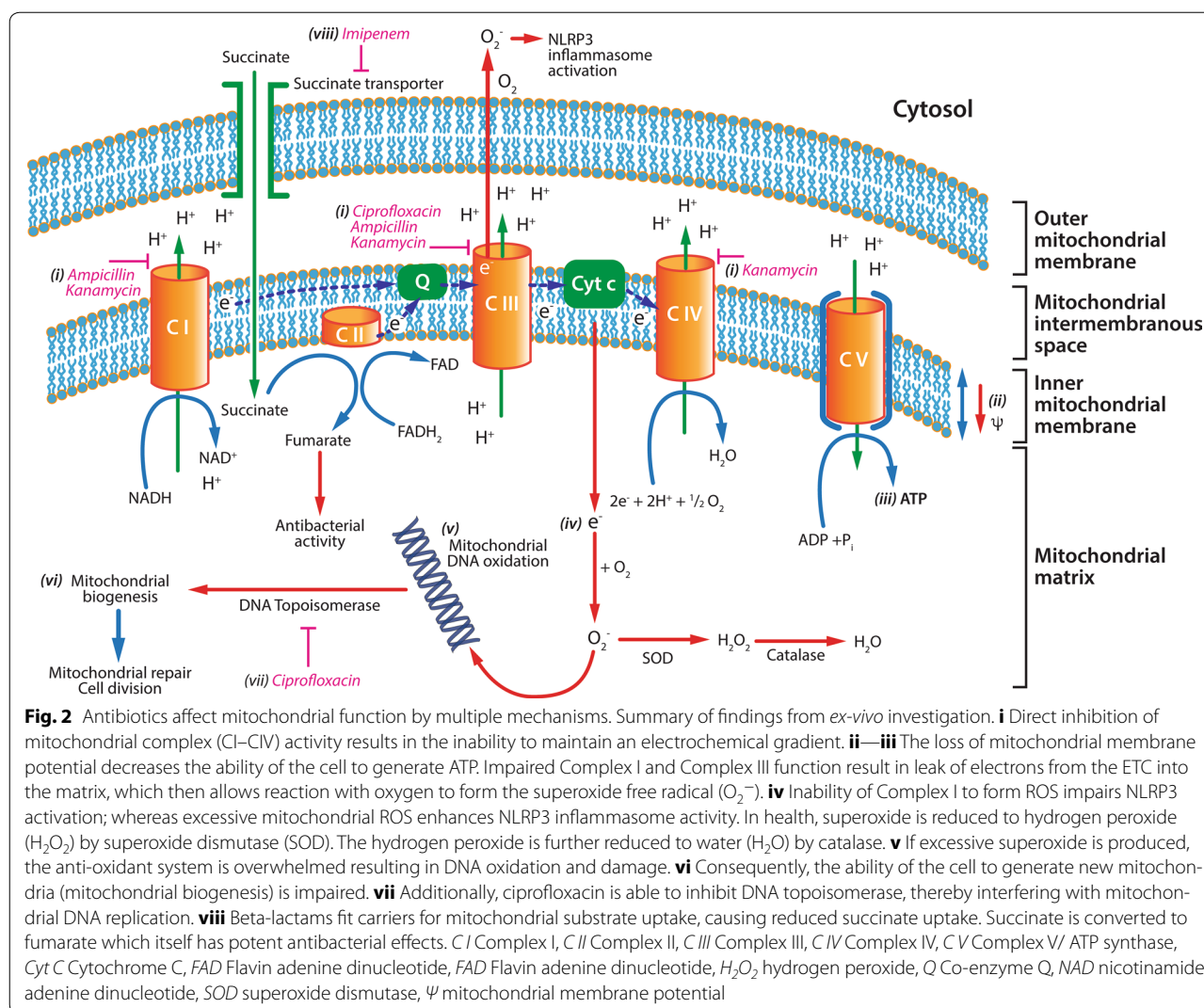
Antimicrobials are able to harm patients by various mechanisms (Fig. 1).

Mechanism: drug toxicity

Antimicrobials are associated with a wide range of well-recognised detrimental side effects including hepatotoxicity, nephrotoxicity, and cytopenias. The multiple pathophysiological mechanisms underlying these toxicities is not completely understood. The common phylogenetic origin between mitochondria and bacteria [27] suggest that antimicrobials may directly affect human mitochondrial function and may contribute to the mitochondrial dysfunction and associated organ failure in sepsis.

Mechanism: mitochondrial dysfunction and organ dysfunction

Mitochondrial dysfunction is implicated in the pathophysiology of organ dysfunction in sepsis [28], although



the mechanisms are poorly understood. At clinically relevant doses, exposure to bactericidal antimicrobials results in mitochondrial dysfunction, reactive oxygen species (ROS) overproduction, reduced ATP, and oxidative damage in mammalian cells *ex vivo* [29]. Similar changes have been described in patients with sepsis [30, 31]. The diverse mechanisms that underlie antimicrobial-induced mitochondrial damage may provide insight into therapies that aim to mitigate toxicity (Fig. 2).

ROS production, antioxidant depletion, and associated oxidative damage in sepsis has been described in several clinical studies [32]. The mitochondrial electron transport chain (ETC) is the major source of ROS production in non-immune cells [33]. A number of antimicrobials including ciprofloxacin and ampicillin inhibit ETC complexes I and III [29]. This disrupts the flow of electrons through the ETC, allowing the leak of electrons into the

matrix which react with oxygen to form superoxide [34]. Excessive ROS production can lead to irreversible protein nitration, DNA damage, perpetuation of mitochondrial dysfunction, and cellular dysfunction.

Beta-lactams and cephalosporins fit carriers for mitochondrial substrate uptake, causing reversible inhibition [35] and prolonged exposure to beta-lactams results in irreversible change due to acylation of the transporters [35]. At high doses, several antimicrobials are able to inhibit mitochondrial oxidative phosphorylation [36]. The resulting impairment in substrate availability, ETC complex activity, and decreased ATP production may contribute to organ dysfunction in sepsis [30].

Recovery from sepsis is heralded by increased mitochondrial biogenesis [31]. Mitochondrial topoisomerase II is required for mtDNA replication and transcription; a key feature of mitochondrial biogenesis. This enzyme is

susceptible to direct inhibition by antimicrobials including ciprofloxacin, resulting in a loss of mtDNA [37]. Prolonged use of antimicrobials may, therefore, perpetuate organ dysfunction by impairing mitogenesis.

Therapeutic strategies to mitigate antimicrobial-induced cellular dysfunction may be of benefit where prolonged courses of antimicrobials are required. Although mitochondrial-targeted anti-oxidants have demonstrated benefit in experimental sepsis [38], none have been used in clinical trials in septic patients. Clinical trials evaluating non-specific anti-oxidants have failed to demonstrate any clinical benefit [39], reflecting the complexity of the underlying pathology and the difficulty of targeting a mediator as ubiquitous and pluripotent as reactive oxygen species.

Immune function and mitochondria

Many patients with sepsis develop immunoparalysis and are at increased risk of secondary infections [40]. Mitochondria are integral to regulating immune function, and defects in energy metabolism of leukocytes are associated with immunoparalysis in septic patients [41]. Although the adverse effects of antimicrobials on immune cell function have been known for decades [42], their specific impact on immunoparalysis in sepsis and critical illness is unknown. Mitochondria regulate wide-ranging functional responses in innate and adaptive immune cells which may be altered by antimicrobials (Fig. 2).

As an example, electron transport chain adaptations serve as an early immunological-metabolic checkpoint that adjust innate immune responses to bacterial infection [43]. Increased mitochondrial complex II conversion of succinate to fumarate is required for macrophage phagocytic activity. Beta-lactams and cephalosporins fit carriers for mitochondrial substrate uptake [35] and may limit the activity of Complex II. The highly energy-dependent respiratory burst required for bacterial killing by macrophages is impaired by ciprofloxacin through a dose-dependent inhibition of mitochondrial respiratory activity [44].

Whilst excessive ROS may be detrimental, mitochondrial ROS has important signalling roles in immune homeostasis. Cytosolic oxidized mtDNA associates with the NLRP3 inflammasome complex and is required for its activation after the engagement of Toll-like receptors [45]. Inhibition of mitochondrial complex I-induced-ROS impairs NLRP3 inflammasome activity [46], and impaired monocyte NLRP3 activity is associated with mitochondrial dysfunction and increased risk of death in sepsis [47].

The effect of antimicrobials on immune system function are, however, complex, and observations from ex vivo experiments may not always translate to in vivo

function. Therefore, whilst the hypothesis that antimicrobials are key drivers of immune cell dysfunction in sepsis and other critical illness syndromes is plausible and supported by mechanistic data, it requires further investigation at a whole organism and patient level.

Mechanism: adverse drug reactions

Commonly encountered manifestations of antimicrobial harm are the various forms of adverse drug reactions that they can provoke. These can be broadly divided into 'dose dependent' or predictable reactions, and 'immunological' or idiosyncratic reactions. The topic of adverse drug reactions to antimicrobials in intensive care has been reviewed in depth [48], and will be briefly summarised below.

Dose-dependent reactions result from pharmacodynamic interactions between antimicrobials and mammalian cells. Aminoglycosides, glycopeptides, and polymyxins have dose-dependent risks of nephrotoxicity, and these agents are amongst those most commonly managed with therapeutic drug monitoring (TDM) as a result [49]. Routine TDM is seldom employed for other antimicrobial classes, although they too can have organ-specific reactions such as beta-lactam and macrolide-induced neurotoxicities [50]. Fluoroquinolones and macrolides lead to cardiac dysrhythmias through interaction with the rapidly activating delayed rectifier potassium channel (I_{Kr}) [51]. Fluoroquinolones are also associated with collagen-toxicity which leads to aortic aneurysms and tendinopathy, whilst bone marrow suppression is seen with co-trimoxazole and linezolid. Beyond direct drug toxicity, antimicrobials may alter the plasma levels of other drugs through effects on plasma protein binding or impact on the cytochrome P450 metabolism system. These adverse drug reactions are frequently missed in critically ill patients as they may be misinterpreted as part of the underlying disease process.

Antimicrobials are common triggers of Immune-mediated idiosyncratic reactions such as anaphylaxis [52]. Beyond type I (anaphylactic) reactions, there are a range of other idiosyncratic immune responses that range from mild eosinophilic drug rash to the severe cutaneous adverse reactions (including Toxic Epidermal Necrolysis and Stevens-Johnson syndrome). Within this spectrum there are also a variety of systemic and organ-specific reactions such as serum sickness, hypersensitivity vasculitis, angioedema, acute interstitial nephritis [53]. There is a growing recognition that some of these reactions are not simple immune system-drug interactions, but also involve interactions with viral pathogens. Examples include the rash observed with penicillin treatment in Epstein-Barr Virus infection and the role of Human Herpes Viruses 6/7 in drug rash with eosinophilia and

systemic symptoms (DRESS) syndrome [54]. Again, these reactions can, at times, be difficult to distinguish from the underlying disease process.

Conversely, there is an increasing focus on the problem of the documentation of antimicrobial allergy. Rates of reported penicillin allergy far outstrip rates of actual allergy on skin prick testing [55]. This can result in antimicrobial choices with unnecessarily broad spectrum or adverse toxicity profiles, increasing the risk of antimicrobial-induced harm.

Mechanism: antimicrobial resistance

The most widely recognised mechanism of antimicrobial-associated harm is the emergence of antimicrobial resistance (AMR). Whilst the global threat of AMR is now widely acknowledged [56, 57], what has received less attention is the role of antimicrobial therapy in developing subsequent multi-drug resistant (MDR) infections in the patients receiving those antimicrobials.

Infections caused by MDR pathogens are associated with increased mortality and length of stay [58]. They are more likely to be resistant to commonly prescribed empirical antimicrobials and thus introduce delays to appropriate, effective therapy. They also often necessitate treatment with antimicrobials that have inferior bactericidal activity and undesirable pharmacological properties/toxicities, as seen in the comparison between beta-lactam and glycopeptide therapy for *S. aureus* infection [59]. MDR pathogens are common causes of ICU-acquired infection with one European estimate suggesting that more than two-thirds of cases of ICU-acquired bacteraemia are caused by MDR bacteria [60].

Common MDR bacteria encountered in Intensive Care are linked to the antimicrobials used in critically ill patients. Examples include Gram positive organisms such as methicillin resistant *S. aureus* (MRSA) and vancomycin resistant enterococci (VRE) the prevalence of which appears to have been relatively stable [61]. Conversely, rates of MDR Gram negative bacteria (e.g. Carbapenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and Carbapenem-resistant/extended spectrum beta-lactamase (ESBL) producing Enterobacterales) appear to be rising [62].

Patients in ICU are particularly susceptible to acquiring MDR organisms, either as pathogens or colonisers. One of the causes is the large antimicrobial burden critical care patients are exposed to prior and during their ICU stay. Case-control studies examining risk factors for isolating Carbapenemase-resistant Enterobacterales (CRE) found recent antimicrobial administration, and carbapenems specifically, to be the largest risk factor [63, 64]. Likewise a recent meta-analysis, specifically looking at the risk factors for MDR Gram negative bacteria

infection in ICUs, found previous antimicrobial therapy to be key [65].

Respiratory tract infections and VAP [1] account for the majority of hospital-acquired infections. An observational cohort study in suspected VAP and a RCT in microbiologically proven VAP have shown a significant increase in subsequent MDR-related superinfection in patients treated with longer duration of antimicrobial therapy [23, 66]. Crucially neither study showed a mortality benefit with longer antimicrobial use.

It is established that the oropharynx of ventilated patients become colonised with multi-resistant bacteria within a few days of ICU admission [67] and that this is related to antimicrobial use [67]. What is also increasingly being appreciated is that exposure to antimicrobials can lead to colonisation/infection with pathogens resistant to not only the same class, but also different classes of antimicrobials. A study looking at the development of piperacillin-resistant *P. aeruginosa* VAP showed an association with prior fluoroquinolone treatment [68]. This likely underscores the complex selection pressures driven by antimicrobial therapy on the host microbiome, and how antimicrobial-associated dysbiosis (see below) relates to the selection of MDR organisms. A study performed in two ICUs in the Netherlands, utilizing mathematical modelling, suggested that the predominant route of acquisition of MDR Enterobacterales was endogenous (i.e. from selection pressure applied to the patient's own gut microbiome), rather than by exogenous cross-contamination (i.e. from other patients, healthcare workers or the environment) [69]. This suggests that infection control/hand hygiene precautions, that have been very effective at reducing rates of MRSA infection [70], may not be as effective in preventing MDR Gram negative infections and that antimicrobial therapy may well be a driver of MDR Gram-negative colonisation in the individual patient.

Mechanism: disruption of the microbiome

When an imbalance of commensal and pathogenic bacteria occurs in a microbiome, known as dysbiosis, the risk increases for local and systemic disease including healthcare-acquired infection (HAI) and associated complications [69, 71]. Not only can alteration of the microbiome and dysbiosis increase risk of infection, it also has the potential to contribute to increase of antimicrobial resistance genes and become a source for MDR organisms such as the ESKAPE organisms [72, 73]. ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Enterobacter* species) are of worldwide concern as major causes of HAI and can cause life-threatening infections in critical care patients [74]. The impact of dysbiosis

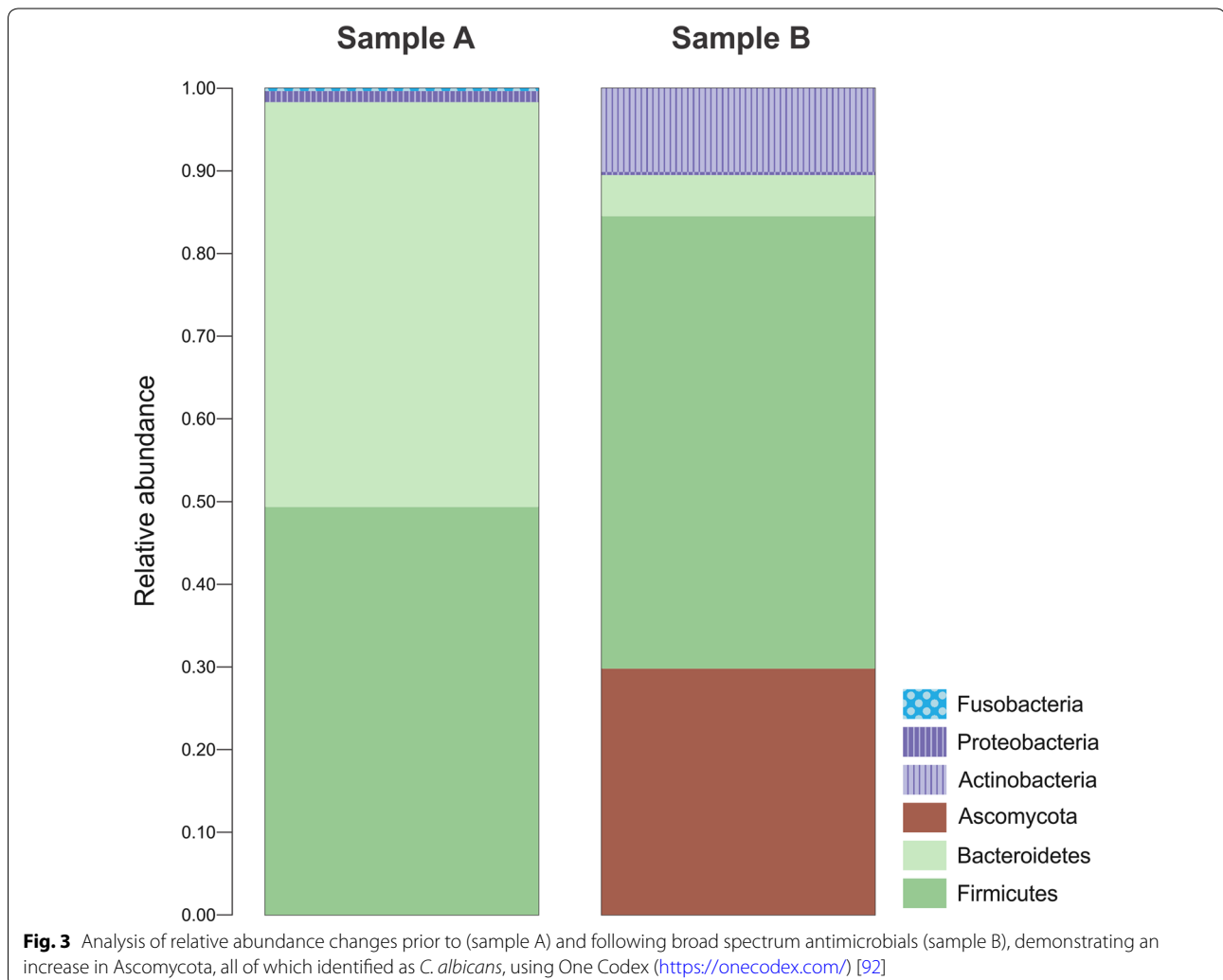
extends beyond overgrowth of pathogenic organisms, and a loss of diversity can upset the metabolic symbiosis between the host and its microbiome which may drive inflammation and organ dysfunction directly [75].

Critical illness results in changes to the human microbiome and dysbiosis [72, 76]. A decrease in diversity and commensal organisms, with a concomitant increase in potential pathogens, has been described for the skin, oral, respiratory, and gastrointestinal microbiota of ICU patients [76–78]. In mechanically ventilated patients, a decrease in the diversity of the lung microbiome and increase in the abundance of potential pathogens such as staphylococci and *Pseudomonas* spp. has been reported [77]. Greater lung dysbiosis was demonstrated in patients with VAP compared to ventilated patients without VAP [79]. Despite inter-individual variation in the gut microbiome, marked reductions in bacterial diversity have been described in septic and non-septic critically ill patients [80]. Prolonged ICU admission has also been associated

with low gut microbiome diversity and presence of MDR organisms [72]. Whilst the process of critical illness itself contributes to gut microbiome disruption, the frequent use of antimicrobials in ICU can further adversely impact gut microbiome diversity [72, 81]. The high frequency of antimicrobial administration in ICU, makes it challenging to disentangle these processes in human illness [76, 82] although animal models do imply both play a major role [83].

Impact of antimicrobials on the microbiome

Significant loss of gut microbiome diversity has been observed in intensive care patients following the use of broad spectrum antimicrobials such as meropenem [84]. In a study currently being conducted at the ICU of the Royal Brisbane Hospital, Australia, similar findings are observed using shotgun metagenomics. In one particular patient, admitted with burns, classified *Candida albicans* reads increases to nearly 30% relative abundance



following the receipt of antimicrobials including meropenem. Figure 3 illustrates the significant increase of *C. albicans* in this patient following broad-spectrum antimicrobials (Schlebusch S. pers comm). This finding is consistent with observations by Ravi and colleagues [84]. *C. albicans* is recognised as a serious concern in critically ill patients and colonization with *Candida* predisposes for invasive *Candida* infections in intensive care patients [85].

In 75% of long-stay ICU patients, most of whom received antimicrobials [84], Ravi and colleagues further describe increases in the relative abundance of ESKAPE pathogens such as *E. faecium*, *K.pneumoniae*, and *E. cloacae*, illustrating the selective effect of antimicrobial therapy on resistant microbial populations. In this study 23 of 24 patients received antimicrobials, with meropenem especially being associated with increased abundance of pathogens and loss of putative beneficial species such as *Faecalibacterium prauznetzii* and *Akkermansia muciniphila* [84].

Although it is clear that dysbiosis occurs amongst critically ill patients, and that antimicrobials are a major driver of this, it is less clear how this impacts patient outcomes as we do not currently have effective interventions to modify the microbiome. However, there is considerable plausibility from animal models, where antimicrobial-induced dysbiosis worsens spinal cord injury [86], increases the risk of pseudomonal lung infection by affecting mucosal IgA levels [87], and impairs the immune response to Influenza A [88]. In terms of human disease, perhaps the clearest example of a disease arising from dysbiosis is *Clostridium difficile*-associated diarrhoea (CDAD). Whilst the association between antimicrobial exposure and CDAD is long established, the realisation that this was not simply selection of a resistant organism has come more recently [89]. The role of dysbiosis in CDAD is underlined by the impressive response to faecal microbial transplant [90] and its ability to restore gut microbiota [91].

Reducing harm: the research agenda

What remains to be elucidated is how to mitigate against these harms given the centrality played by antimicrobials in the treatment of infections. Antimicrobial stewardship programmes to reduce the use of antimicrobials in non-bacterial infections and non-infectious conditions reduce harm by reducing exposure [93], whilst efforts to shorten courses avoid unnecessarily broad-spectrum or multiple agents may also be expected to reduce harm. In this area, the domain of healthcare improvement science, we believe that research efforts should focus on determining the optimal components of antimicrobial stewardship programmes and how to drive behaviour change [94].

Secondary infections are common amongst patients in intensive care [40] and efforts to reduce these through prevention programmes can have a significant impact on antimicrobial use [95]. Molecular diagnostic techniques allow more rapid and sensitive testing for infecting organisms [96], whilst host-focussed diagnostics can identify patients with infection as opposed to colonization [94]. However, the impact of these tests on antimicrobial prescribing is not clearly established and should be a focus for future research. The heightened sensitivity of pathogen-focussed tests especially may inappropriately increase the use of antimicrobials. Limiting this inappropriate increase will require distinguishing between invasive infection and benign colonisation and may require the combination of both host and pathogen-focussed tests.

The use of gut microbiome testing for monitoring and guiding antimicrobial choice is promising; however, although direct to consumer testing is available, accredited clinical testing remains elusive [97]. Further research underpinning the clinical validation of gut microbiome testing to progress clinical accreditation of testing is much needed.

A recent meta-analysis of pro-biotics in intensive care patients suggested that administration of these organisms to either the oropharynx or GI tract could reduce development of VAP [98]; however, this approach has not yet found widespread acceptance [99]. Further work in this area would provide vital testing of the mechanistic hypothesis that dysbiosis plays a causative role in adverse outcomes in our patients. However, a note of caution is sounded by reports of both faecal microbiota transplant and probiotic therapy being implicated in bacteraemia [100, 101].

Even with improved stewardship and diagnostics, patients with infections will continue to require antimicrobial therapy, and often resistance patterns will demand the use of broad-spectrum agents with adverse toxicity profiles. We do not know if there are ways of preventing the immuno-suppressive and metabolic side effects of mitochondrial impairment, and similarly beyond avoiding excessive dosing there is limited evidence on how to prevent direct organ toxicity. The development of mitochondrially protective strategies which may counteract the mitochondrial toxicity of antimicrobials are of urgent need. This should be combined with further mechanistic studies on the effects of antimicrobials on immune and solid-organ tissues, which may lead to targeted mitochondrially protective strategies. The successful development of such agents would open up an entirely novel branch of therapeutics.

Ultimately, mitigation of antimicrobial-associated harm is likely to require a multi-faceted approach, combining many or all the approaches discussed above which

will need to be both individually proven and then implemented in a bundle of proven interventions.

Summary and conclusions

In conclusion, there is evidence that reducing antimicrobial use in critical care can have a direct impact on individual patients, reducing mortality. The mechanisms by which antimicrobials may worsen outcomes are varied, ranging from direct drug toxicity to dysbiosis, immune cell dysfunction to idiosyncratic drug reactions. Mitigation of these will require a multi-faceted approach. However, the first step in dealing with the problem posed by antimicrobial-associated harm is widespread acknowledgement of this issue. We need to develop an understanding that antimicrobial stewardship is about more than simply attempting to limit the development of microbial resistance and undertake research and quality improvement focusing on understanding and mitigating the serious adverse effects of these vital drugs.

Author details

¹ Bloomsbury Institute for Intensive Care Medicine, University College, London, UK. ² Clinical Microbiology and Public Health Laboratory, Addenbrooke's Hospital, Cambridge, UK. ³ Department of Medicine, University of Cambridge, Cambridge, UK. ⁴ Faculty of Medicine, The University of Queensland, Brisbane, Australia. ⁵ Forensic and Scientific Services, Queensland Health, Brisbane, Australia. ⁶ Intensive Care Services, Royal Brisbane and Womens' Hospital, Brisbane, Australia. ⁷ Scientific Consultant, Nimes University Hospital University of Montpellier, Nimes, France. ⁸ John V Farman Intensive Care Unit, Addenbrooke's Hospital, Cambridge, UK. ⁹ Division of Anaesthesia, Department of Medicine, University of Cambridge, Level 4, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK.

Acknowledgement

We are grateful to Rudma Tek Pty Ltd and Phillip M Ball for their assistance with the illustrations for this article.

Author contribution

NA reviewed and appraised the literature, drafted and revised the manuscript and approves the final version. MR reviewed and appraised the literature, drafted and revised the manuscript and approves the final version. SS reviewed and appraised the literature, drafted and revised the manuscript and approves the final version. JL conceived the article, reviewed and appraised the literature, revised the manuscript and approves the final version. ACM conceived the article, reviewed and appraised the literature, drafted and revised the manuscript and approves the final version.

Funding

ACM is supported by a Clinical Research Career Development Fellowship from the Wellcome Trust (WT 2055214/Z/16/Z).

Compliance with ethical standards

Conflicts of interest

JL has received honoraria from Pfizer and MSD. All other authors declare that they have no relevant conflicts of interest.

Publisher's Note

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

Received: 14 November 2019 Accepted: 9 January 2020

Published online: 29 January 2020

References

- Vincent J-L, Rello J, Marshall J et al (2009) International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 302(21):2323–2329
- Kollef MH (2000) Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. *Clin Infect Dis* 31:S131–S138
- Kumar A, Roberts D, Wood KE et al (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 34(6):1589–1596
- de Jong E, van Oers JA, Beishuizen A, Infectious PVTL (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(7):819–827
- Kett DH, Cano E, Quartin AA et al (2011) Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. *Lancet Infect Dis* 11(3):181–189
- Cotten CM, Taylor S, Stoll B et al (2009) Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. *Pediatrics* 123(1):58–66
- Seymour CW, Gesten F, Prescott HC et al (2017) Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med* 376(23):2235–2244
- Bloos F, Rüdgel H, Thomas-Rüdgel D et al (2017) Effect of a multi-faceted educational intervention for anti-infectious measures on sepsis mortality: a cluster randomized trial. *Intensive Care Med* 43(11):1602–1612
- Rhodes A, Evans LE, Alhazzani W et al (2017) Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 43:304–377
- Bloos F, Thomas-Rüdgel D, Rüdgel H et al (2014) Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study. *Crit Care* 18(2):R42
- Wachter RM, Flanders SA, Fee C, Pronovost PJ (2008) Public reporting of antibiotic timing in patients with pneumonia: lessons from a flawed performance measure. *Ann Intern Med* 149(1):29–32
- Hranjec T, Rosenberger LH, Swenson B et al (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(10):774–780
- Prescott HC, Iwashyna TJ (2019) Improving sepsis treatment by embracing diagnostic uncertainty. *Annals ATS* 16(4):426–429
- De Waele JJ (2010) Early source control in sepsis. *Langenbecks Arch Surg* 395(5):489–494
- Fagon JY, Chastre J, Wolff M et al (2000) Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med* 132(8):621–630
- Canadian Critical Care Trials Group (2006) A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med* 355(25):2619–2630
- Ruiz M, Torres A, Ewig S et al (2000) Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome. *Am J Respir Crit Care Med* 162(1):119–125
- Bouadma L, Luyt C-E, Tubach F et al (2010) Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 375(9713):463–474
- Onakpoya IJ, Walker AS, Tan PS et al (2018) Overview of systematic reviews assessing the evidence for shorter versus longer duration antibiotic treatment for bacterial infections in secondary care. *PLoS ONE* 13(3):e0194858

20. Llewelyn MJ, Fitzpatrick JM, Darwin E et al (2017) The antibiotic course has had its day. *BMJ* 358:j3418
21. Uranga A, España PP, Bilbao A et al (2016) Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial. *JAMA Intern Med* 176(9):1257–1265
22. Capellier G, Mockly H, Charpentier C, et al. (2012) Early-onset ventilator-associated pneumonia in adults randomized clinical trial: comparison of 8 versus 15 days of antibiotic treatment. Spellberg B, ed. *PLoS One* 7(8):e41290–12
23. Chastre J, Wolff M, Fagon J-Y et al (2003) Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 290(19):2588–2598
24. Kollef MH, Chastre J, Clavel M et al (2012) A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia. *Crit Care* 16(6):R218
25. Scawn N, Saul D, Pathak D et al (2012) A pilot randomised controlled trial in intensive care patients comparing 7 days' treatment with empirical antibiotics with 2 days' treatment for hospital-acquired infection of unknown origin. *Health Technol Assess* 16(36):1–94
26. Leone M, Bechis C, Baumstarck K et al (2014) De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. *Intensive Care Med* 40(10):1399–1408
27. Carvalho DS, Andrade RFS, Pinho STR et al (2015) What are the evolutionary origins of mitochondria? A complex network approach. *PLoS ONE* 10(9):e0134988–e135021
28. Singer M (2013) The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. *Virulence* 5(1):66–72
29. Kalghatgi S, Spina CS, Costello JC et al (2013) Bactericidal antibiotics induce mitochondrial dysfunction and oxidative damage in mammalian cells. *Science Trans Med* 5(192):192
30. Brealey D, Brand M, Hargreaves I et al (2002) Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet* 360(9328):219–223
31. Carré JE, Orban J-C, Re L et al (2010) Survival in critical illness is associated with early activation of mitochondrial biogenesis. *Am J Respir Crit Care Med* 182(6):745–751
32. Galley HF (2011) Oxidative stress and mitochondrial dysfunction in sepsis. *Br J Anaesth* 107(1):57–64
33. Turrens JF (2003) Mitochondrial formation of reactive oxygen species. *J Physiol* 552(2):335–344
34. Dröse S, Brandt U (2008) The mechanism of mitochondrial superoxide production by the cytochrome bc1 complex. *J Biol Chem* 283(31):21649–21654
35. Tune BM, Hsu CY (1990) The renal mitochondrial toxicity of beta-lactam antibiotics: in vitro effects of cephaloglycin and imipenem. *J Am Soc Nephrol* 1(5):815–821
36. Duetwelhenke N, Krut O, Eysel P (2007) Influence on mitochondria and cytotoxicity of different antibiotics administered in high concentrations on primary human osteoblasts and cell lines. *Antimicrob Agents Chemother* 51(1):54–63
37. Lawrence JW, Claire DC, Weissig V, Rowe TC (1996) Delayed cytotoxicity and cleavage of mitochondrial DNA in ciprofloxacin-treated mammalian cells. *Mol Pharmacol* 50(5):1178–1188
38. Mantzaris K, Tsolaki V, Zakyntinos E (2017) Role of oxidative stress and mitochondrial dysfunction in sepsis and potential therapies. *Ox Med Cell Long* 2017(7):1–10
39. Manzanares W, Lemieux M, Elke G, Langlois PL, Bloos F, Heyland DK (2016) High-dose intravenous selenium does not improve clinical outcomes in the critically ill: a systematic review and meta-analysis. *Crit Care* 20:356
40. Morris AC, Datta D, Shankar-Hari M et al (2018) Cell-surface signatures of immune dysfunction risk-stratify critically ill patients: INFECT study. *Intensive Care Med* 44(5):627–635
41. Cheng S-C, Scicluna BP, Arts RJW et al (2016) Broad defects in the energy metabolism of leukocytes underlie immunoparalysis in sepsis. *Nat Immunol* 17(4):406–413
42. Hauser WE, Remington JS (1982) Effect of antibiotics on the immune response. *Am J Med* 72(5):711–716
43. Garaude J, Acín-Pérez R, Martínez-Cano S et al (2016) Mitochondrial respiratory-chain adaptations in macrophages contribute to antibacterial host defense. *Nat Immunol* 17(9):1037–1045
44. Yang JH, Bhargava P, McCloskey D, Mao N, Palsson BO, Collins JJ (2017) Antibiotic-induced changes to the host metabolic environment inhibit drug efficacy and alter immune function. *Cell Host Microbe* 22(6):757–765.e3
45. Zhong Z, Liang S, Sanchez-Lopez E et al (2018) New mitochondrial DNA synthesis enables NLRP3 inflammasome activation. *Nature* 560(7717):198–203
46. Kelly B, Tannahill GM, Murphy MP, O'Neill LAJ (2015) Metformin inhibits the production of reactive oxygen species from NADH: ubiquinone oxidoreductase to limit induction of interleukin-1 β (IL-1 β) and boosts interleukin-10 (IL-10) in lipopolysaccharide (LPS)-activated macrophages. *J Biol Chem* 290(33):20348–20359
47. Martínez-García JJ, Martínez-Banaclocha H, Angosto-Bazarra D et al (2019) P2X7 receptor induces mitochondrial failure in monocytes and compromises NLRP3 inflammasome activation during sepsis. *Nature Comms* 10(1):2711
48. Granowitz EV, Brown RB (2008) Antibiotic adverse reactions and drug interactions. *Crit Care Clin* 24(2):421–442
49. Jager NGL, van Hest RM, Lipman J, Taccone FS, Roberts JA (2016) Therapeutic drug monitoring of anti-infective agents in critically ill patients. *Expert Rev Clin Pharm* 9(7):961–979
50. Bhattacharyya S, Darby RR, Raibagkar P, Gonzalez Castro LN, Berkowitz AL (2016) Antibiotic-associated encephalopathy. *Neurology* 86(10):963–971
51. Cornett E, Novitch MB, Kaye AD et al (2017) Macrolide and fluoroquinolone mediated cardiac arrhythmias: clinical considerations and comprehensive review. *Postgrad Med* 129(7):715–724
52. Harper NJN, Cook TM, Garcez T et al (2018) Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 121(1):159–171
53. Kanji S, Chant C (2010) Allergic and hypersensitivity reactions in the intensive care unit. *Critical Care Med* 38:5162–5168
54. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ (2019) Antibiotic allergy. *Lancet* 393(10167):183–198
55. Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES (2017) The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis* 66(3):329–336
56. Tackling antimicrobial resistance 2019–2024 The UK's five-year national action plan, HM Government (2019) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf. Accessed 20 Dec 2019
57. Global action plan on antimicrobial resistance, WHO (2015) <https://www.who.int/antimicrobial-resistance/global-action-plan/en/>. Accessed 20 Dec 2019
58. Neidell MJ, Cohen B, Furuya Y et al (2012) Costs of healthcare- and community-associated infections with antimicrobial-resistant versus antimicrobial-susceptible organisms. *Clin Infect Dis* 55(6):807–815
59. Apellaniz G, Valdés M, Perez R et al (1991) Comparison of the effectiveness of various antibiotics in the treatment of methicillin-susceptible *Staphylococcus aureus* experimental infective endocarditis. *J Chemother* 3(2):91–97
60. Tabah A, Koulenti D, Laupland K et al (2012) Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. *Intensive Care Med* 38(12):1930–1945
61. Global priority list of antibiotic-resistant bacteria to guide research, discovery and development of new antibiotics (2017) https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf. Accessed 20 Dec 2019
62. Munoz-Price LS, Poirer L, Bonomo RA et al (2013) Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. *Lancet Infect Dis* 13(9):785–796
63. Marchaim D, Chopra T, Bhargava A et al (2015) recent exposure to antimicrobials and carbapenem-resistant Enterobacteriaceae: the role of antimicrobial stewardship. *Infect Control Hosp Epidemiol* 33(8):817–830

64. Armand-Lefèvre L, Angebault C, Barbier F et al (2013) Emergence of imipenem-resistant gram-negative bacilli in intestinal flora of intensive care patients. *Antimicrob Agents Chemother* 57(3):1488–1495
65. Ang H, Sun X (2018) Risk factors for multidrug-resistant Gram-negative bacteria infection in intensive care units: a meta-analysis. *Int J Nurs Pract* 24(4):e12644–e12713
66. Raman K, Nailor MD, Nicolau DP, Aslanzadeh J, Nadeau M, Kuti JL (2013) Early antibiotic discontinuation in patients with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoscopy cultures. *Crit Care Med* 41(7):1656–1663
67. Ewig S, Torres A, El-Ebiary M, et al. (1999) Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury. Incidence, risk factors, and association with ventilator-associated pneumonia. *Am J Respir Crit Care Med* 159(1): 188–198
68. Trouillet JL, Vuagnat A, Combes A, Kassis N, Chastre J, Gibert C (2002) *Pseudomonas aeruginosa* ventilator-associated pneumonia: comparison of episodes due to piperacillin-resistant versus piperacillin-susceptible organisms. *Clin Infect Dis* 34(8):1047–1054
69. Bootsma M, Bonten M, Nijssen S, Fluit A, Diekmann O (2007) An Algorithm to estimate the importance of bacterial acquisition routes in hospital settings. *Am J Epidemiol* 166(7):841–851
70. Derde LPG, Cooper BS, Goossens H et al (2014) Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. *Lancet Infect Dis*. 14(1):31–39
71. Wischmeyer PE, McDonald D, Knight R (2016) Role of the microbiome, probiotics, and “dysbiosis therapy” in critical illness. *Curr Opin Crit Care* 22(4):347–353
72. Zaborin A, Smith D, Garfield K, et al. (2014) Membership and behavior of ultra-low-diversity pathogen communities present in the gut of humans during prolonged critical illness Clemente J, Dominguez Bello MG, eds. *mBio* 5(5): 01361–14
73. Baron SA, Diene SM, Rolain JM (2018) Human microbiomes and antibiotic resistance. *Human Microbiome J* 10:43–52
74. Santajit S, Indrawattana N (2016) Mechanisms of antimicrobial resistance in ESKAPE pathogens. *BioMed Res Int*. <https://doi.org/10.1155/2016/2475067>
75. Saltzman ET, Palacios T, Thomsen M, Vitetta L (2018) Intestinal microbiome shifts, dysbiosis, inflammation, and non-alcoholic fatty liver disease. *Front Microbiol* 9:307–311
76. McDonald D, Ackermann G, Khalilova L, et al. (2016) Extreme dysbiosis of the microbiome in critical illness. Green Tringe S, ed. *mSphere* 1(4):207–6
77. Alagna L, Bandera A, Patrino A, Muscatello A, Citerio G, Gori A (2019) Microbiota in ICU, not only a gut problem. *Intensive Care Med* 45(5):733–737
78. Yeh A, Rogers MB, Firek B, Neal MD, Zuckerbraun BS, Morowitz MJ (2016) Dysbiosis across multiple body sites in critically ill adult surgical patients. *Shock* 46(6):649–654
79. Zakharkina T, Martin-Loeches I, Matamoros S et al (2017) The dynamics of the pulmonary microbiome during mechanical ventilation in the intensive care unit and the association with occurrence of pneumonia. *Thorax* 72(9):803–810
80. Lankelma JM, Vught LA, Belzer C et al (2016) Critically ill patients demonstrate large interpersonal variation in intestinal microbiota dysregulation: a pilot study. *Intensive Care Med* 43(1):59–68
81. Pettigrew MM, Gent JF, Kong Y et al (2018) Gastrointestinal microbiota disruption and risk of colonization with carbapenem-resistant *Pseudomonas aeruginosa* in Intensive Care Unit Patients. *Clin Infect Dis* 69(4):604–613
82. Otani S, Chihade DB, Coopersmith CM (2019) Critical illness and the role of the microbiome. *Acute Med Surg* 6(2):91–94
83. Dickson RP, Singer BH, Newstead MW et al (2016) Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome. *Nat Microbiol* 1(10):16113
84. Ravi A, Halstead FD, Bamford A et al (2019) Loss of microbial diversity and pathogen domination of the gut microbiota in critically ill patients. *bioRxiv* 9:151–236
85. Hankovszky P, Társy D, Öveges N, Molnár Z (2015) Invasive *Candida* infections in the ICU: diagnosis and therapy. *J Crit Care Med* 1(4):129–139
86. Kigerl KA, Hall JCE, Wang L, Mo X, Yu Z, Popovich PG (2016) Gut dysbiosis impairs recovery after spinal cord injury. *J Exp Med* 213(12):2603–2620
87. Robak OH, Heimesaat MM, Kruglov AA et al (2018) Antibiotic treatment-induced secondary IgA deficiency enhances susceptibility to *Pseudomonas aeruginosa* pneumonia. *J Clin Invest* 128(8):3535–3545
88. Ichinohe T, Pang IK, Kumamoto Y et al (2011) Microbiota regulates immune defense against respiratory tract influenza A virus infection. *Proc Natl Acad Sci USA* 108(13):5354–5359
89. Johanesen P, Mackin K, Hutton M et al (2015) Disruption of the gut microbiome: clostridium difficile infection and the threat of antibiotic resistance. *Genes* 6(4):1347–1360
90. Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs vancomycin for the treatment of recurrent *Clostridium difficile* infection. *Aliment Pharmacol Ther* 41(9): 835–843
91. Staley C, Kelly CR, Brandt LJ, Khoruts A, Sadowsky MJ (2016) Complete microbiota engraftment is not essential for recovery from recurrent *Clostridium difficile* infection following fecal microbiota transplantation. *mBio* 7(6):2074–2079
92. Minot SS, Krumm N, Greenfield NB (2015) One codex: a sensitive and accurate data platform for genomic microbial identification. *bioRxiv*. <https://doi.org/10.1101/027607>
93. Karanika S, Paudel S, Grigoras C, Kalbasi A, Mylonakis E (2016) Systematic review and meta-analysis of clinical and economic outcomes from the implementation of hospital-based antimicrobial stewardship programs. *Antimicrob Agents Chemother* 60(8):4840–4852
94. Hellyer TP, McAuley DF, Walsh TS et al (2019) Biomarker-guided antibiotic stewardship in suspected ventilator-associated pneumonia (VAPrapid2): a randomised controlled trial and process evaluation. *Lancet Resp Med*. [https://doi.org/10.1016/S2213-2600\(19\)30367-4](https://doi.org/10.1016/S2213-2600(19)30367-4)
95. Morris AC, Hay AW, Swann DG et al (2011) Reducing ventilator-associated pneumonia in intensive care: Impact of implementing a care bundle. *Crit Care Med* 39(10):2218–2224
96. Gadsby NJ, Russell CD, McHugh MP et al (2016) Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. *Clin Infect Dis* 62(7):817–823
97. Chiu CY, Miller SA (2019) Clinical metagenomics. *Nature Rev Genet* 20(6):341–355
98. Weng H, Li J-G, Mao Z et al (2017) Probiotics for preventing ventilator-associated pneumonia in mechanically ventilated patients: a meta-analysis with trial sequential analysis. *Front Pharmacol* 8:517–536
99. Wheeler KE, Cook DJ, Mehta S et al (2016) Use of probiotics to prevent ventilator-associated pneumonia: a survey of pharmacists’ attitudes. *J Crit Care* 31(1):221–226
100. De Filipp Z, Bloom PP, Torres Soto M et al (2019) Drug-resistant *E coli* bacteremia transmitted by fecal microbiota transplant. *N Engl J Med* 381(21):2043–2050
101. Yelin I, Flett KB, Merakou C et al (2019) Genomic and epidemiological evidence of bacterial transmission from probiotic capsule to blood in ICU patients. *Nat Med* 25:1728–1732