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RESEARCH AGENDA

The intensive care medicine research agenda on multidrug-resistant bacteria, antibiotics, and stewardship

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Abstract

Purpose: To concisely describe the current standards of care, major recent advances, common beliefs that have been contradicted by recent trials, areas of uncertainty, and clinical studies that need to be performed over the next decade and their expected outcomes with regard to the management of multidrug-resistant (MDR) bacteria, antibiotic use, and antimicrobial stewardship in the intensive care unit (ICU) setting.

Methods: Narrative review based on a systematic analysis of the medical literature, national and international guidelines, and expert opinion.

Results: The prevalence of infection of critically ill patients by MDR bacteria is rapidly evolving. Clinical studies aimed at improving understanding of the changing patterns of these infections in ICUs are urgently needed. Ideal antibiotic utilization is another area of uncertainty requiring additional investigations aimed at better understanding of dose optimization, duration of therapy, use of combination treatment, aerosolized antibiotics, and the integration of rapid diagnostics as a guide for treatment. Moreover, there is an imperative need to develop non-antibiotic approaches for the prevention and treatment of MDR infections in the ICU. Finally, clinical research aimed at demonstrating the beneficial impact of antimicrobial stewardship in the ICU setting is essential.

Conclusions: These and other fundamental questions need to be addressed over the next decade in order to better understand how to prevent, diagnose, and treat MDR bacterial infections. Clinical studies described in this research agenda provide a template and set priorities for investigations that should be performed in this field.

Keywords: Antibiotics, Bacteria, Stewardship, Multidrug resistance

Introduction

Antibiotic resistance has emerged as one of the most important determinants of outcome in patients with serious infections along with the virulence of the underlying pathogen. More than 700,000 healthcare-associated infections, many caused by antibiotic-resistant bacteria, occur annually in the US with almost half in critically ill patients [1]. In Europe, prevalence of carbapenemase-producing Enterobacteriaceae (CPE), in particular with the rapid spread of carbapenem-hydrolysing oxacillinase-48 (OXA-48) and New Delhi metallo-beta-lactamase (NDM)-producing Enterobacteriaceae is increasing [2]. Escalating rates of antibiotic resistance add substantially to the morbidity, mortality, and costs related to infection in hospitalized patients, especially those in the intensive care unit (ICU) setting [2, 3]. Both Gram-positive organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), and Gram-negative bacteria,

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including *Pseudomonas aeruginosa*, *Acinetobacter* species, and CPE have contributed to the escalating rates of multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) bacteria causing healthcare-associated infections [3].

The rapid evolution of antibiotic resistance impedes efforts to insure that initial appropriate antibiotic therapy (IAAT) is delivered to critically ill infected patients. IAAT is a key determinant of outcome in severe infection [4, 5], and the Surviving Sepsis Guidelines strongly support initiatives to guarantee that patients receive timely appropriate antibiotic treatment to reduce mortality [6]. Yet, because not all serious infections are due to MDR organisms, clinicians must have a strategy for determining which patients should be treated with broad-spectrum antibiotics. Minimizing the unnecessary use of antibiotics is a fundamental principle of antimicrobial stewardship that should be followed by all intensivists [7]. The challenge is how to best optimize antibiotic decision making in the ICU balancing the need for IAAT, in order to improve patient outcomes, with the need for avoidance of unnecessary antibiotics so as to reduce resistance emergence.

The goal of this research agenda is to concisely describe the current standards of care, major recent advances, areas of uncertainty, and to identify clinical studies/trials that need to be performed over the next decade in regards to the management of MDR bacteria, antibiotic use, and antimicrobial stewardship in the ICU.

Methods

A narrative review based on a systematic analysis of the medical literature was conducted with a timeline from 2006 through 2016 searching PubMed by two authors for each of the three sections using the terms "stewardship, antibiotics, antibiotic resistance and multidrug resistance". Searches were completed in December 2016. One author (M.H.K.) also manually screened reference lists of articles selected for inclusion to identify additional studies. To identify potential unpublished data, M.H.K. also (1) searched abstracts from the Society of Critical Care Medicine, European Society of Intensive Care Medicine, American Thoracic Society, CHEST, International Symposium on Intensive Care and Emergency Medicine, and Pharmacotherapy from 2006 to 2016, and (2) searched online for clinical trials registration (ClinicalTrials.gov). The selection of articles and topics for inclusion in this research agenda were based on their likely importance for yielding clinically important practice changes over the next decade as determined by the writing committee.

New antibiotics and antibiotic delivery

Standard of care

IAAT for definite infections, such as sepsis, complicated intra-abdominal infection (cIAI), severe community-acquired pneumonia (CAP) and hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP), is a critical aspect of care. Unfortunately, attempts to administer IAAT often lead to the administration of broad-spectrum antibiotics for many non-resistant infections. Rapid provision of appropriate antibiotics is most important in the presence of shock, since delays in therapy are associated with increased mortality [8]. When shock is not present, a more careful approach to the diagnosis of bacterial sepsis is warranted, as administration of broad spectrum antibiotics produces collateral damage and, in the presence of non-bacterial inflammatory conditions, selects for antibiotic-resistant bacteria [9].

Standard dosing regimens are often not adequate for critically ill patients. Two common differences in pharmacokinetic/pharmacodynamic (PK/PD) parameters encountered in the ICU that result in this are an increased volume of distribution and increased renal clearance of antibiotics [10]. Initial antibiotic doses should address the increased volume of distribution of antibiotics (particularly hydrophilic drugs) that often occurs in sepsis with fluid resuscitation [11], such that a large loading dose is required independent of subsequent clearances. Without this, time to achieve optimal bacterial killing is delayed due to under-dosing which also predisposes to the emergence of newly resistant bacterial overgrowth. After empirical broad spectrum and/or combination treatments are prescribed, secondary re-evaluation and focused therapy following documentation of the etiology of infection is strongly recommended. Despite this basic tenet of antibiotic stewardship, conflicting results have been generated on the overall benefits of antimicrobial de-escalation [12, 13].

The optimal duration of antibiotic therapy remains controversial but has significantly decreased over the past two decades. In VAP, a shorter treatment course of 7–8 days has been validated, even though for some specific pathogens or clinical situations a longer treatment course may still be recommended [14, 15]. For cIAI, a treatment course of 4 days may also be acceptable when septic shock is not present [16]. Serial biomarkers such as procalcitonin can also help to accurately identify patients appropriate for shorter courses of antibiotics [17].

Major recent advances

When compared to the twentieth century, few new antibiotics have been recently marketed or even developed. Because of the importance of both antibiotic resistance

Table 1 Recently approved antibiotics and drugs in development

	Drug name	Drug class	Potential indications
Recently approved	Ceftazidine/ Avibactam	Cephalosporin/ β-Lactamase inhibitor	cIAI, cUTI, HAP/VAP
	Ceftaroline	Extended spectrum cephalosporin	Pneumonia, skin infections
	Solithromycin	Macrolide (fluoroketolide)	CAP
	Tedizolid	Oxazolidinone	HAP/VAP, skin infections
	Ceftolozane/ Tazobactam	Cephalosporin/ β-Lactamase inhibitor	HAP/VAP, cIAI, cUTI
In development	Aztreonam/ Avibactam	Monobactam/ β-Lactamase inhibitor	cIAI
	Cadazolid	Quinolonyl-oxazolidinone	*C. difficile* infection
	Ceftaroline/ Avibactam	Cephalosporin/ β-Lactamase inhibitor	Bacterial infections
	Delafloxacin	Fluoroquinolone	Skin infections, CAP, cUTI
	Eravacycline	Tetracycline	cIAI, cUTI
	Finafloxacin11	Fluoroquinolone	cUTI, cIAI, skin infections
	Iclaprim	Dihydrofolate reductase inhibitor	Skin infections, HAP/VAP
	Imipenem/ Relebactam	Carbapenem/ β-Lactamase inhibitor	cUTI, cIAI, HAP/VAP
	Meropenem/ Vaborbactam	Meropenem/boronic β-Lactamase inhibitor	cUTI, cIAI, HAP/VAP, BSI
	Nemonoxacin8	Quinolone	CAP, skin infections
	Omadacycline	Tetracycline	CAP, skin infections, cUTI
	Plazomicin	Aminoglycoside	cUTI, BSI, HAP/VAP, cIAI
	S-649266	Siderophore cephalosporin	BSI, HAP/VAP, cUTI
	Zabofloxacin	Fluoroquinolone	CAP

cIAI complicated intra-abdominal infection, *cUTI* complicated urinary tract infection, *HAP/VAP* hospital-acquired pneumonia/ventilator-associated pneumonia, *CAP* community-acquired pneumonia, *BSI* bloodstream infection

and emerging infectious diseases, the scientific community and national governments have decided to support both discovery and research in the anti-infective field. Therefore, both large pharmaceutical and smaller biotech companies have re-invested in this endeavor.

Accordingly, a few antibiotics with some ICU indications (especially HAP/VAP and cIAI) have recently been approved and others should become available in the near future. Potentially interesting new options include broad-spectrum antibiotics covering both resistant Gram-negative bacteria and MRSA which could be used as first-line empiric therapy in clinical situations where a high risk of antibiotic resistance is suspected or confirmed, especially with mixed infections. Additionally, options to cover MDR pathogens including CPE and NDM-producing Enterobacteriaceae have recently been approved or are forthcoming, including novel β-lactamase inhibitors (Table 1). The concern with these new antibiotics is that they may be utilized indiscriminately, especially in locations with suboptimal infection control and antimicrobial stewardship practices, thereby allowing resistance to rapidly arise.

Ceftolozane/tazobactam is a recently approved antibiotic that is especially active against *Pseudomonas aeruginosa* (from the intrinsic activity of ceftolozane), while the addition of tazobactam confers activity against most extended-spectrum β-lactamase (ESBL) producers. It is currently approved for the treatment of complicated urinary tract infection (cUTI) and cIAI [18]. Avibactam is a novel β-lactamase inhibitor that inactivates class A [including *Klebsiella pneumoniae* carbapenemase (KPC)], class C (AmpC), and some class D (OXA) β-lactamases. It is licensed in combination with ceftazidime and approved for cUTI and cIAI. The REPROVE trial (NCT01808092) has assessed the efficacy of ceftazidime-avibactam compared to meropenem for the treatment of HAP/VAP. The results have not yet been published but preliminary data confirm that the primary objective of statistical non-inferiority, employed by regulatory agencies for drug approval, has been reached with crude mortality rates at day 28 being similar for both groups [19].

While developing new antimicrobials is an essential task, emphasizing the importance of proper antibiotic

dosing in order to optimize cures and prevent resistance is also paramount. Several studies have shown that subtherapeutic antibiotic concentrations are often achieved in critically ill patients when standard dosage regimens are administered, particularly when dealing with difficult-to-treat pathogens [20, 21]. β-Lactam antibiotics have a large therapeutic ratio (i.e., toxicity is rare in usual therapeutic doses). However, β-lactam efficacy is now being questioned, with possible under-dosing in difficult-to-treat groups including ICU patients [22]. To improve PK/PD target attainment in critically ill patients, higher doses than those currently accepted by the regulatory agencies may be required. This may include the use of continuous or extended infusions with front-loading doses, as opposed to traditional intermittent bolus doses, for time-dependent antibiotics (e.g., β-lactams). For concentration-dependent antibiotics (e.g., aminoglycosides), once daily dosing to achieve high peak antibiotic concentrations is now accepted as the standard of care [23]. Increased awareness of these issues suggests the need for clinical trials of routine therapeutic dose monitoring (TDM) for β-lactams and other antibiotic classes to assess whether clinical and microbiologic outcomes can be improved.

Common beliefs contradicted by recent trials

ICU patients are often considered as primarily having renal impairment requiring dose reduction of antibiotics especially with more severe renal dysfunction. Nevertheless, recent clinical studies have shown that supranormal renal clearances, especially in young patients, are associated with suboptimal plasma concentrations of antibiotics and treatment failures [10, 14, 22].

In mechanically ventilated patients, antibiotic concentrations in the airways can be 100-fold higher when given through the aerosol route. Several studies have demonstrated a reduction of bacterial load and an interesting safety profile with both aerosolized colistin and aminoglycosides [24]. Accordingly, aerosolized antibiotics are now widely used, especially in Gram-negative VAP and more specifically with MDR pathogens. Despite the overall findings of the recent negative randomized trial of adjunctive aerosolized fosfomycin:amikacin for VAP, subgroup analysis suggested that patients infected with PDR *Acinetobacter* might still benefit from aerosolized antibiotics [25].

In severe sepsis, because of their time-dependent activity, continuous or prolonged β-lactam infusion could improve outcome due to better PK/PD target attainment, and many physicians are using this approach as their standard of care. Nevertheless, in two large multicenter prospective trials, clinical outcomes were not different by type of infusion [14, 26]. However, a significant increase in clinical cure with prolonged antibiotic infusions in a recent trial keeps this as an open question [27, 28].

Remaining areas of uncertainty

Despite several improvements in the use of antibiotics in the ICU, numerous scientific questions remain to be addressed. The optimal duration of antibiotic therapy remains uncertain and, aside from 7–8 days therapy in HAP/VAP and 4 days therapy in cIAI, little is known, and "one duration size" may not fit all indications.

The need for combination antibiotic therapy in critically ill patients remains highly debated, and is often prescribed based on patient severity without taking into account other important factors including pathogen virulence and resistance.

Nebulized antibiotics are currently used in critically ill patients with VAP and ventilator-associated tracheobronchitis (VAT) due to the low penetration of systemic antibiotics into the lung compartment [29]. Nebulized antibiotics aim to increase antibiotic efficacy by delivering higher drug concentrations to the distal areas of the lung in order to reduce systemic drug toxicity and to minimize the risk of resistance. Several factors can influence the delivery of aerosolized antibiotics to the lungs, although aerosol particle size seems to be the most important factor [30]. Currently available nebulizers include jet, ultrasonic and vibrating mesh devices whose antibiotic delivery efficiency to the lung parenchyma ranges from 15 to 60% across this continuum of devices [31]. To date, the efficacy and safety of aerosolized antibiotics for VAP has been examined in heterogeneous studies and meta-analyses yielding conflicting results [24, 25, 32].

Evolution of high-efficiency vibrating mesh nebulizers including the Pulmonary Drug Delivery System (PDDS) (NKTR-061) and the PARI eFlow® Inline rapid nebulizer are under development and could improve overall drug delivery to the lung. The PDDS system employs a new formulation of Amikacin Inhalation Solution (BAY41-6551) and provides antibiotic delivery of up to 60% of the administered dose [33]. The PARI eFlow® system is a single-patient, multiple-use device developed to deliver uniform small particles of an amikacin:fosfomycin formulation over a short time of nebulization. The observed mean values of tracheal concentrations with this system are 12,985 and 9000 μg/g, respectively, for amikacin and fosfomycin [34]. Unfortunately, a phase 2 study of aerosolized amikacin:fosfomycin delivered via the eFlow® Inline system in mechanically ventilated patients with Gram-negative bacterial pneumonia (IASIS study, NCT01969799) demonstrated no overall outcome benefit compared to optimal standard of care parenteral antibiotic therapy [24].

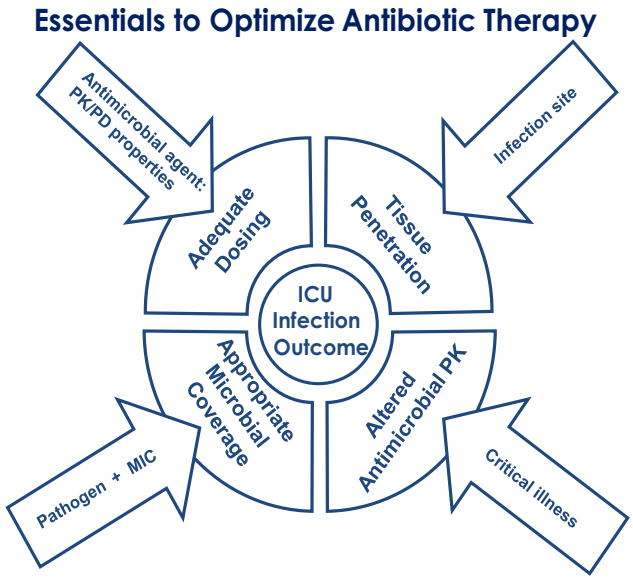

Fig. 1 Schematic representing the essential factors needing to be considered in order to optimize antibiotic treatment and outcomes in critically ill patients. *PK* pharmacokinetic; *PD* pharmacodynamics; *MIC* minimum inhibitory concentration

Mdr bacteria

Standard of care

MDR bacteria are now prevalent all over the world, with XDR and PDR pathogens also being increasingly encountered [1, 2]. Emergence of antimicrobial resistance is largely attributed to the indiscriminate and often abusive use of antimicrobials, including inadequate dosages and prolonged durations, both within hospitals and other healthcare settings such as nursing homes and the community. Moreover, there is also increasing spread of resistance genes between bacteria and of resistant bacteria between humans and the environment including waterborne and agricultural sources. Even in areas hitherto known for having relatively minor resistance problems, 5–10% of hospitalized patients on a given day have been found to harbor ESBL-producing Enterobacteriaceae in their gut flora, as seen in a French ICU study [35].

The number of different mechanisms by which bacteria can become resistant to an antimicrobial agent is increasing, as is the variety of encountered resistance genes, the number of clones within a species which carry resistance, and the number of different species harboring resistance genes. This all contributes to accelerating antibiotic resistance development with spread of antibiotic-resistant pathogens leading to life-threatening diseases [36]. Local outbreaks of antibiotic resistant infections have been reported with MRSA, *Escherichia coli*, *K. pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa* and *Enterococcus faecalis* or *faecium* (the latter species being difficult to treat when glycopeptide resistance is present). These outbreaks have typically occurred in highly specialized healthcare settings such as neonatal wards, ICUs, transplant units and hematology/oncology areas. The rising incidence of MDR bacteria results in two important consequences: increase of initial inappropriate antibiotic therapy (IIAT) and greater overall consumption of broad-spectrum antibiotics [36]. Since no truly new antimicrobial classes have been approved recently for the treatment of resistant bacteria, interest in "rediscovered" older antimicrobials has also increased [37]. At present, the best current option for optimizing antibiotic use and minimizing further resistance is to select antibiotic regimens with the highest level of effectiveness for the infection, while also minimizing collateral damage in the form of colonization with resistant clones (Fig. 1).

Major recent advances

Several rapid microbiological identification methods are currently being developed for clinical use, such as PCR, PNA FISH, and mass spectrometry. Some of these techniques can potentially be brought "to the bedside", with microbiological results being available within a few hours. This could completely change the landscape of bacterial species and susceptibility documentation, especially in bacteremia and VAP [38], and could even be considered as a companion diagnostic for specific targeted therapies such as anti-infective monoclonal antibodies (mAbs).

Anti-infective mAbs represent a promising class of infectious disease drugs in the ICU, with a very innovative mechanism of action via one or several specific virulence targets. Several ICU studies have found encouraging preliminary results, especially when targeting *P. aeruginosa* [39]. With the current technological progress and the increasing need for alternative therapeutic options to standard antibiotics in critically ill infected patients, numerous anti-infective mAbs are being developed targeting the most frequent ICU pathogens including *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, *A. baumannii* and *E. coli* [40].

Similarly, there has been growing interest in the use of bacterial viruses (i.e., bacteriophage therapy) to treat infections by MDR bacteria. Bacteriophage lysins are classified as peptidoglycan hydrolases, being able to cleave a variety of bonds in the bacterial peptidoglycan. Preliminary in vitro and in vivo studies suggest high efficiency of such peptides to kill *A. baumannii*, supporting further clinical development [41].

Common beliefs contradicted by recent trials

In the recent era, characterized by the lack of novel antibiotic class development, several clinical trials have yielded frustrating results. New antimicrobials targeting antibiotic-resistant pathogens (i.e. doripenem, tigecycline, ceftobiprole) have unfortunately failed to demonstrate non-inferiority for the primary endpoint of clinical cure in patients with VAP [14, 42, 43]. The presence of young adults with augmented creatinine clearance enrolled in these studies combined with antibiotic under dosing, resulting in reduced antibiotic plasma concentrations, may partly explain these negative study results [44].

Remaining areas of uncertainty

Improved accuracy and timeliness to detect drug susceptibility, including the ability to detect heteroresistance, inducible enzymes, and highly resistant subpopulations, is increasingly being desired to improve overall antibiotic therapy and outcomes. While PCR is now widely used in the ICU, and thus allows for a more rapid detection of antibiotic resistance genes, additional efforts are required to develop patient profiles with the use of these technologies in order to optimize antimicrobial stewardship in the ICU. Similarly, the development of a toolkit to accurately and objectively detect successful versus unsuccessful therapy in MDR/XDR/PDR infections, is clearly needed.

As suggested above, experiences with rapid diagnostics for the evaluation of blood culture specimens suggests that rapid diagnostics may play an important role in enhancing antimicrobial prescribing practices in hospitalized patients [45]. The benefits to this can be numerous, including optimizing clinical outcomes, reducing toxicity, and facilitating clinical trials for new anti-infective agents by stratifying patients eligible for the trial at the earliest possible opportunity. However, it is also important to understand the limitations of these new technologies, including that they cannot differentiate colonization from infection, which could be highly problematic in mechanically ventilated patients, nor give us the true susceptibility patterns of the responsible pathogens. The latter is true with the exception of a few specific mechanisms of resistance provided by molecular techniques and automated microscopy which has the potential to provide real-time susceptibility data [46].

The potential role of rapid diagnostics in improving antimicrobial therapy and outcome when embedded in a well-organized antimicrobial stewardship program (ASP) is illustrated by the study by Huang et al. from the University of Michigan [47]. These investigators performed a study to analyze the impact of MALDI-TOF MS in conjunction with an ASP in patients with bloodstream infections. The ASP provided antibiotic recommendations after receiving real-time notification following blood culture Gram stain, organism identification, and antimicrobial susceptibilities using conventional microbiology methods in the before-period and MALDI-TOF MS in the after-period. Use of MALDI-TOF MS significantly decreased time to organism identification, and improved time to optimal directed antibiotic therapy. Similarly, the PCR-based GeneXpert MRSA/SA diagnostic platform (Cepheid, Sunnyvale, CA, USA) for MRSA bacteremia has been shown to reduce the mean time to initiation of appropriate therapy and the duration of unnecessary MRSA drug therapy [48]. A recent systematic review also demonstrated that rapid diagnostic testing was associated with decreases in mortality risk in the presence of an ASP [49].

The use of rapid diagnostics may hold the key for achieving a proper balance between the need to provide timely appropriate antibiotic therapy while minimizing the unnecessary use of antibiotics in the ICU. There is an urgent need for clinical studies aimed at understanding how to best integrate the use of antibiotics in critically ill patients with the emerging rapid diagnostic technologies in a way that is cost-effective and sustainable for the long run [50].

Antibiotic stewardship

Standard of care

Antimicrobial stewardship involves a multifaceted and multidisciplinary approach to achieving the following goals: (1) combating antimicrobial resistance, (2) improving clinical outcomes, and (3) controlling costs by improving antimicrobial use. As one of the largest

consumers of antibiotics in the hospital, ICUs are well situated to reap benefit from an effective ASP. Recent guidelines provide evidence-based criteria for implementation and self-evaluation of such a program [51]. ASPs are necessary and effective in critical care settings, resulting in reductions in drug-resistant pathogen infections, reduced broad-spectrum antimicrobial use, and reduced antimicrobial costs, all without increases in mortality [52, 53].

All ASPs in ICUs should include prospective audit and feedback of antimicrobial prescriptions, therapeutic drug monitoring, formulary restrictions, use of local antibiograms, and partnership with infection prevention services when available. Underlining the importance of a multidisciplinary approach to antimicrobial stewardship, a recent study showed the importance of infectious disease (ID) fellowship programs, full-time ID physicians, and clinical pharmacists with ID training in reducing antimicrobial use [54].

A recently performed systematic review found that the quality of evidence supporting specific antimicrobial stewardship interventions was low, but did recommend audit and feedback, guideline implementation, and decision support [55]. Additional strategies for ASPs have been tested in studies with poorly defined outcomes, resulting in low-quality evidence for their efficacy. Unfortunately, this poor-quality evidence limits knowledge of the advantages and disadvantages of individual stewardship strategiesthough ASP implementation does not seem to result in harm. Table 2 provides some strategies of plausible benefit in an ASP.

Table 2 Components to be considered for inclusion into Antimicrobial Stewardship Programs (*ASPs*) in the intensive care unit (*ICU*) (stratified by likelihood of efficacy)

Requirements for ASPs in the ICU
Prospective audit and feedback of antimicrobial prescriptions
Therapeutic drug monitoring of vancomycin, aminoglycosides, and azole antifungals
Formulary restrictions
Use of local antibiograms
Partnership with infection prevention services
Partnership with infectious diseases fellows, faculty, pharmacists (when available)
Of likely benefit for ASPs in the ICU
Stewardship education programs for all providers
Guideline implementation
Antimicrobial de-escalation strategies
Use of rapid diagnostics, guided by institutional requirements
Unlikely to be of benefit for ASPs in the ICU
Antibiotic cycling

Major recent advances

Advances in molecular biology have paved the way for imminent revolutions in antimicrobial stewardship. Though not uniformly ready for routine clinical use, rapid diagnostics have the potential to dramatically alter the field of antimicrobial stewardship [56]. Rapid diagnostic tools have the potential to identify bacterial, fungal, and viral causes of sepsis at a much earlier stage than traditional culture methods, which should reduce time to appropriate therapy, a known determinant of sepsis mortality [4, 5, 57].

Emerging diagnostics can produce susceptibility results more rapidly than traditional methods [46]. Accelerated susceptibility testing will allow for appropriate antimicrobial choices to occur much earlier in the course of infection, with the potential for improvements in mortality, other clinical outcomes, and reduced usage of broad spectrum antimicrobials. Reduced broad spectrum antimicrobial use will likely result in fewer *Clostridium difficile* infections, fewer gut microbiome disturbances, fewer MDR infections, and the preservation of the remaining antibiotics in our armamentarium for antibiotic-resistant infections. Similarly to local antibiograms, it is likely that rapid diagnostics will need to be tailored to each institution's needs, as local prevalence of organisms varies [58]. For example, a rapid diagnostic aimed at detecting MRSA would likely be of little value in an area of low MRSA prevalence such as northern Europe.

Another growing area of research that could transform empiric antimicrobial decision making is host gene expression analysis. Host transcriptome analyses were able to differentiate non-infectious inflammatory syndromes from sepsis with modest sensitivity and specificity [59, 60]. After distinguishing non-infectious inflammatory syndromes from sepsis, bacterial and viral infections were also differentiated using transcriptome analysis [60]. Host gene expression analysis requires clinical trial verification of predictive validity, further research on the host transcriptome profiles in mixed infections, fungal infections, mycobacterial infections, and more robust recognition of when infections are not present. Though not ready for clinical use, it is a promising area of research that will likely be more feasible as molecular technology continues to advance and become more affordable.

Common beliefs contradicted by recent trials

Physicians may continue to feel that ASPs are too intrusive and interfere with autonomy [61]. Yet, ASPs may result in reduced mortality [62, 63]. With continuously mounting evidence in support of improved patient outcomes due to ASPs, physicians can be further convinced

Table 3 Top trials to be done in the future

New antibiotics and antibiotic delivery
1. Novel trial designs assessing new antimicrobials targeting resistant bacteria are needed to determine their efficacy for specific infections and to insure that proper PK/PD targets are met. This is in contrast to the typical non-inferiority studies required by regulatory agencies that frequently do not have significant numbers of MDR/XDR/PDR bacteria.
2. Clinical trials designed to determine the precise PK/PD targets to be reached in order to optimize bacterial killing for specific drug classes.
3. Given that tissue levels of antibiotics can differ dramatically from blood targets, such as the lung in which penetration of systemic antibiotics is notoriously difficult, properly designed trials addressing this issue are required.
4. Clinical trials assessing TDM of β-lactams versus standard dosing based on "optimal" PK/PD assessments are required. A better understanding of antibiotic dosing along with more accurate target attainment of day-to-day antibiotic administration should prevent treatment failures, improve clinical outcome, and reduce toxicity from antibiotics.
5. Given the experience of recent clinical trials, a careful evaluation of aerosolized antibiotics in patients with PDR VAP should be a priority. It is expected that increased microbiological cure and reduced resistance emergence will be observed, and that clinical outcomes, including both mortality and duration of mechanical ventilation, will be improved.
MDR bacteria
1.Given the high mortality associated with PDR infections, alternative or adjunctive therapies should urgently be sought and subject to clinical trials, especially with the growing numbers of MDR/XDR/PDR pathogens and the inevitability of resistance emergence to new antibiotics in the future.
2. Trials evaluating mAbs targeting virulence factors related to *Staphylococcus aureus* and *Pseudomonas aeruginosa* are needed. We anticipate that such studies will demonstrate that preemptive or adjunctive therapy with mAbs will reduce the overall need for antibiotics, the number of treatment failures and infection recurrence.
3. The potential for rapid microbiologic diagnostics to provide etiologic identification of pathogens and their antibiotic susceptibility mandates that an evaluation of rapid diagnostic platforms compared to usual culture-based diagnosis of potential antibiotic-resistant infections be performed. It is expected that earlier targeted therapy is likely to have equal, if not superior, outcomes with a significant reduction of empirical broad spectrum antibiotic therapy.
4. Future investigation in the development of non-traditional anti-infective agents such as bacteriophage and endolysins is needed to provide alternative treatment pathways for antibiotic resistant bacteria.
Antibiotic stewardship
1. With growing numbers of immunocompromised patients in ICUs, trials of ASPs to reduce unnecessary antibiotic use in this population will be critical. Future trials should utilize antimicrobial stewardship to reduce unnecessary antimicrobial prophylaxis, reduce adverse drug events, and prove that ASPs are effective in hematology/oncology patients.
2. Patients' purported antibiotic allergies are known to alter antimicrobial prescribing and result in greater risk of adverse events [72]. Recently, it has been shown that interventions aimed at increasing test doses of alleged hypersensitivity-inducing antibiotics were effective at increasing β-lactam exposure without increased adverse drug reactions [73]. Future trials should seek to implement similar guideline-based interventions or protocols to improve appropriateness of therapy and minimize adverse reactions from non-preferred antimicrobials.
3. Future clinical trials of ASPs in ICUs should incorporate antifungal stewardship and cost reduction as an outcome measure. Antifungal stewardship has great potential for reducing the costs associated with antifungal use [74]. Implementation of antifungal stewardship as part of an ICU ASP is likely to reduce costs without adverse outcomes, similar to stewardship outcomes with antibacterial agents.
4. In general, cost-effectiveness of novel and traditional treatments, preventive approaches and stewardship programs should be carefully analyzed, also with respect to the presence of increasing resistance patterns.

ASP Antimicrobial stewardship program, *HAP* hospital-acquired pneumonia, *ICU* intensive care unit, *mAbs* monoclonal antibody, *MDR* multidrug-resistant, *PK/PD* pharmacokinetic/pharmacodynamics, *PDR* pandrug-resistant, *TDM* therapeutic drug monitoring, *VAP* ventilator-associated pneumonia, *XDR* extensively-drug resistant

of the benefit of a multidisciplinary approach to antimicrobial stewardship.

Despite guidelines that place nominal emphasis on the importance of education in antimicrobial stewardship [51], there is still clearly a great need for education among providers who treat infections, as evidenced by several recent studies [64, 65].

Remaining areas of uncertainty

Due to the low quality of evidence in trials of antimicrobial stewardship, many areas of uncertainty remain. It is clear that ASPs do not result in harm and likely improve patient outcomes. However, which individual components of ASPs provide the greatest benefits is less clear. Some ASP strategies also have potential harm, such as requiring ASP team approval for certain antibiotics for hypotensive patients at risk for MDR pathogens. These higher risk interventions should be prospectively studied. Funding limitations and variability in resources for ASPs at different institutions make it unlikely that each component of an ASP will be systematically studied in a clinical trial.

For ICUs looking to implement ASPs, one major area of uncertainty is the concept of antimicrobial de-escalation. Further research must be done to determine what defines antimicrobial de-escalation, when it is appropriate, when to "re-escalate," and how to transition antimicrobial decision making when patients move from the ICU to the hospital ward. Antimicrobial de-escalation is also uncertain in pathogen-negative sepsis, particularly

whether it is safe to de-escalate and the optimal duration of antimicrobials. With improving culture methods and rapid diagnostics, it is possible that the proportion of patients with pathogen-negative sepsis will diminish over time, resulting in fewer uncertainties.

Other areas of uncertainty include outpatient antimicrobial stewardship, stewardship in immunocompromised patients, and agricultural stewardship. Stewardship in these areas will reduce the global burden of antimicrobial use with subsequent reductions in antimicrobial resistance. With global reductions in antimicrobial resistance, patients will be at lower risk for IIAT when admitted to ICUs.

Limitations

Although this narrative review is based on a systematic analysis of the medical literature, the research agenda presented reflects the inherent biases of the writing committee. Moreover, this document does not reflect all possible novel interventions that could or should be explored over the next decade [66–68]. We attempted to layout the most compelling areas of future investigation based on the available literature and the experience of the writing committee. Certainly, as new clinical trial information becomes available, modification in the priorities and direction of this research agenda should be considered.

Conclusion

Important fundamental studies examining questions regarding the development and use of new antibiotics, novel strategies for the treatment and prevention of MDR/XDR/PDR bacterial infections, and optimizing antimicrobial stewardship in the ICU, as outlined in this document, should be carried out over the next decade (Table 3). The development of sustainable clinical trial networks represents an important operational goal to successfully carry out these investigations [69]. Moreover, advances in the design of clinical trials, biostatistics, electronic data collection, and randomization tools will enhance our ability to carry out such trials, as illustrated by recent antibiotic studies [25, 69]. The rising prevalence of infections due to MDR/XDR/PDR bacteria in the ICU emphasizes the urgent need to advance this research agenda over the next decade [70, 71].

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Compliance with ethical standards

Conflicts of interest

Dr. Kollef is an investigator for the Arsanis and Aridis monoclonal antibody studies. Dr. Francois is an investigator for the Aridis monoclonal antibody study.

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References

1. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, Lynfield R, Maloney M, McAllister-Hollod L, Nadle J, Ray SM, Thompson DL, Wilson LE, Fridkin SK, Infections Emerging Infections Program Healthcare-Associated, Team Antimicrobial Use Prevalence Survey (2014) Multistate point-prevalence survey of health care-associated infections. N Engl J Med 370(13):1198––1208. doi:10.1056/NEJMoa1306801
2. Albiger B, Glasner C, Struelens MJ, Grundmann H, Monnet DL, Europe-anSurveyof Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) working group (2015) Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. Euro Surveill. doi:10.2807/1560-7917.ES.2015.20.45.30062
3. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL (2012) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 18(3):268––281. doi:10.1111/j.1469-0691.2011.03570.x
4. Kollef MH, Sherman G, Ward S, Fraser VJ (1999) Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 115:462––474
5. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C (2003) Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 31:2742––2751. doi:10.1097/01.CCM.0000098031.24329.10
6. Dellinger RP, Levy MM, Rhodes A et al (2013) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 41:580––637. doi:10.1097/CCM.0b013e31827e83af
7. Kollef MH, Micek ST (2012) Antimicrobial stewardship programs: mandatory for all ICUs. Crit Care 16:179. doi:10.1186/cc11853
8. Kumar A (2014) Antimicrobial delay and outcome in severe sepsis. Crit Care Med 42:e802. doi:10.1097/CCM.0000000000000620
9. de Groot B, Ansems A, Gerling DH, Rijpsma D, van Amstel P, Linzel D, Kostense PJ, Jonker M, de Jonge E (2015) The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study. Crit Care 19:194. doi:10.1186/s13054-015-0936-3

10. Roberts JA, Taccone FS, Lipman J (2016) Understanding PK/PD. Intensive Care Med 42(11):1797––1800. doi:10.1007/s00134-015-4032-6
11. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, Hope WW, Farkas A, Neely MN, Schentag JJ, Drusano G, Frey OR, Theuretzbacher U, Kuti JL (2014) Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 14:498––509. doi:10.1016/S1473-3099(14)70036-2
12. Garnacho-Montero J, Gutiérrez-Pizarraya A, Escoresca-Ortega A, Corcia-Palomo Y, Fernández-Delgado E, Herrera-Melero I, Ortiz-Leyba C, Márquez-Vácaro JA (2014) De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. Intensive Care Med 40:32––40. doi:10.1007/s00134-013-3077-7
13. Leone M, Bechis C, Baumstarck K, Lefrant JY, Albanèse J, Jaber S, Lepape A, Constantin JM, Papazian L, Bruder N, Allaouchiche B, Bézulier K, Antonini F, Textoris J, Martin C, Network Investigators AZUREA (2014) De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. Intensive Care Med 40:1399––1408. doi:10.1007/s00134-014-3411-8
14. Kollef MH, Chastre J, Clavel M, Restrepo MI, Michiels B, Kaniga K, Cirillo I, Kimko H, Redman R (2012) A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia. Crit Care 16(6):R218. doi:10.1186/cc11862
15. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jusserand D, Asfar P, Perrin D, Fieux F, Aubas S, Pneum A, Trial Group (2003) Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 290(19):2588––2598. doi:10.1001/jama.290.19.2588
16. Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, Cook CH, O'Neill PJ, Mazuski JE, Askari R, Wilson MA, Napolitano LM, Namias N, Miller PR, Dellinger EP, Watson CM, Coimbra R, Dent DL, Lowry SF, Cocanour CS, West MA, Banton KL, Cheadle WG, Lipsett PA, Guidry CA, Popovsky K (2015) Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med 372(21):1996––2005. doi:10.1056/NEJMoa1411162
17. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE et al (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. doi:10.1016/S1473-3099(16)00053-0
18. van Duin D, Bonomo RA (2016) Ceftazidime/Avibactam and Ceftolozane/Tazobactam: Second-generation β-Lactam/β-Lactamase Inhibitor Combinations. Clin Infect Dis 63:234––241. doi:10.1093/cid/ciw243
19. https://www.astrazeneca.com/media-centre/press-releases/2016/AstraZenecas-antibiotic-Zavicefta-met-primary-endpoints-in-Phase-lll-trial-for-treatment-of-hospital-acquired-pneumonia-21072016.html. Accessed Oct 21 2016
20. Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney BC, Ungerer JP, Lipman J, Roberts JA (2012) Subtherapeutic initial β-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 142:30––39. doi:10.1378/chest.11-1671
21. Udy AA, Lipman J, Jarrett P, Klein K, Wallis SC, Patel K, Kirkpatrick CM, Kruger PS, Paterson DL, Roberts MS, Roberts JA (2015) Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance? Crit Care 19:28. doi:10.1186/s13054-015-0750-y
22. Huttner A, Harbarth S, Hope WW, Lipman J, Roberts JA (2015) Therapeutic drug monitoring of the β-lactam antibiotics: what is the evidence and which patients should we be using it for? J Antimicrob Chemother 70:3178––3183. doi:10.1093/jac/dkv201
23. Udy AA, Roberts JA, Lipman J (2013) Clinical implications of antibiotic pharmacokinetic principles in the critically ill. Intensive Care Med 39:2070––2082. doi:10.1007/s00134-013-3088-4
24. Wenzler E, Fraidenburg DR, Scardina T, Danziger LH (2016) Inhaled antibiotics for Gram-negative infections. Clin Microbiol Rev 29:581––632. doi:10.1128/CMR.00101-15
25. Kollef MH, Ricard JD, Roux D, Francois B, Ischaki E, Rozgonyi Z, Boulain T, Ivanyi Z, János G, Garot D, Koura F, Zakynthinos E, Dimopoulos G, Torres A, Danker W, Montgomery AB (2016) A randomized trial of the amikacin fosfomycin inhalation system for the adjunctive therapy of Gram-negative ventilator-associated pneumonia: IASIS Trial. Chest. doi: 10.1016/j.chest.2016.11.026 **[Epub ahead of print]**
26. Dulhunty JM, Roberts JA, Davis JS, Webb SAR, Bellomo R, Gomersall C, Shirwadkar C, Eastwood GM, Myburgh J, Paterson DL, Starr T, Paul SK, Lipman J (2015) A multicenter randomized trial of continuous versus intermittent β-lactam infusion in Severe Sepsis. Am J Resp Crit Care Med 192:1298––1305. doi:10.1164/rccm.201505-0857OC
27. Abdul-Aziz MH, Sulaiman H, Mat-Nor MB, Rai V, Wong KK, Hasan MS, Abd Rahman AN, Jamal JA, Wallis SC, Lipman J, Staatz CE, Roberts JA (2016) Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis. Intensive Care Med 42(10):1535––1545. doi:10.1007/s00134-015-4188-0
28. Roberts JA, Abdul-Aziz MH, Davis JS, Dulhunty JM, Cotta MO, Myburgh J, Bellomo R, Lipman J (2016) Continuous versus intermittent β-lactam infusion in severe sepsis. a meta-analysis of individual patient data from randomized trials. Am J Respir Crit Care Med 194(6):681––691. doi:10.1164/rccm.201601-0024OC
29. Palmer LB, Smaldone GC (2014) Reduction of bacterial resistance with inhaled antibiotics in the intensive care unit. Am J Respir Crit Care Med 189(10):1225––1233. doi:10.1164/rccm.201312-2161OC
30. Kollef MH (2016) Counterpoint: Should inhaled antibiotic therapy be routinely used for the treatment of bacterial lower respiratory tract infections in the ICU setting? No. Chest. doi: 10.1016/j.chest.2016.11.007 **[Epub ahead of print]**
31. Daniels T, Mills N, Whitaker P (2013) Nebuliser systems for drug delivery in cystic fibrosis. Cochrane Database Syst Rev 4:CD007639. doi: 10.1002/14651858.CD007639.pub2
32. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratalà J, El Solh AA, Ewig S, Fey PD, File TM Jr, Restrepo MI, Roberts JA, Waterer GW, Cruse P, Knight SL, Brozek JL (2016) Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 63:575––582. doi:10.1093/cid/ciw504
33. Luyt CE, Eldon MA, Stass H, Gribben D, Corkery K, Chastre J (2011) Pharmacokinetics and tolerability of amikacin administered as BAY41-6551 aerosol in mechanically ventilated patients with gram-negative pneumonia and acute renal failure. J Aerosol Med Pulm Drug Deliv 24(4):183––190. doi:10.1089/jamp.2010.0860
34. PARI eFlow rapid, Technical Data. http://www.pari.de/uk-en/products/lower-airways-1/eflow-rapid-nebuliser-system-1/ Accessed 2 Aug 2016
35. Razazi K, Derde LP, Verachten M, Legrand P, Lesprit P, Brun-Buisson C (2012) Clinical impact and risk factors for colonization with extended-spectrum β-lactamase-producing bacteria in the intensive care unit. Intensive Care Med 38(11):1769––1778. doi:10.1007/s00134-012-2675-0
36. Bassetti M, Poulakou G, Timsit JF (2016) Focus on antimicrobial use in the era of increasing antimicrobial resistance in ICU. Intensive Care Med 42(6):955––958. doi:10.1007/s00134-016-4341-4
37. ESCMID Conference on Reviving Old Antibiotics, 22–24 October 2014, Vienna, Austria https://www.escmid.org/research_projects/escmid_conferences/reviving_old_antibiotics/.
38. Bogaerts P, Hamels S, de Mendonca R, Huang TD, Roisin S, Remacle J, Markine-Goriaynoff N, de Longueville F, Plüster W, Denis O, Glupczynski Y (2013) Analytical validation of a novel high multiplexing real-time PCR array for the identification of key pathogens causative of bacterial ventilator-associated pneumonia and their associated resistance genes. J Antimicrob Chemother 68:340––347. doi:10.1093/jac/dks392
39. François B, Luyt CE, Dugard A, Wolff M, Diehl JL, Jaber S, Forel JM, Garot D, Kipnis E, Mebazaa A, Misset B, Andremont A, Ploy MC, Jacobs A, Yarranton G, Pearce T, Fagon JY, Chastre J (2012) Safety and pharmacokinetics of an anti-PcrV PEGylated monoclonal antibody fragment in mechanically ventilated patients colonized with Pseudomonas aeruginosa: a randomized, double-blind, placebo-controlled trial. Crit Care Med 40(8):2320––2326. doi:10.1097/CCM.0b013e31825334f6
40. François B, Chastre J, Eggiman P, Laterre PF, Torres A, Sanchez M, Esser M, Bishop B, Bonten M, Goosens H, Jafri HS (2016) The SAATELLITE and EVADE clinical studies within the COMBACTE consortium: a collaborative effort between academic institutions and pharmaceutical industry in advancing the conduct and feasibility of clinical trials to evaluate novel antibacterial drugs to treat hospital acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Clin Infect Dis 63(Suppl 2):S46––S51. doi:10.1093/cid/ciw245

41. Thandar M, Lood R, Winer BY, Deutsch DR, Euler CW, Fischetti VA (2016) Novel engineered peptides of a phage lysin as effective antimicrobials against multidrug-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 60(5):2671––2679. doi:10.1128/AAC.02972-15
42. Freire AT, Melnyk V, Kim MJ, Datsenko O, Dzyublik O, Glumcher F, Chuang YC, Maroko RT, Dukart G, Cooper CA, Korth-Bradley JM, Dartois N, Gandjini H, 311 Study Group (2010) Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. Diagn Microbiol Infect Dis 68:140––151. doi:10.1016/j.diagmicrobio.2010.05.012
43. Awad SS, Rodriguez AH, Chuang YC, Marjanek Z, Pareigis AJ, Reis G, Scheeren TW, Sánchez AS, Zhou X, Saulay M, Engelhardt M (2014) A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. Clin Infect Dis 59:51––61. doi:10.1093/cid/ciu219
44. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J, DALI Study (2014) DALI defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 5:1072––1083. doi:10.1093/cid/ciu027
45. Banerjee R, Teng CB, Cunningham SA et al (2015) Randomized trial of rapid multiplex polymerase chain reaction-based blood culture identification and susceptibility testing. Clin Infect Dis 61:1071––1080
46. Kollef MH, Burnham CAD (2016) Ventilator-associated pneumonia: the role of emerging diagnostic technologies. Semin Respir Crit Care Med **[In press]**
47. Huang A, Newton D, Kunapuli A et al (2013) Impact of rapid organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. Clin Infect Dis 57:1237––1245
48. Parta M, Goebel M, Thomas J, Matloobi M, Stager C, Musher DM (2010) Impact of an assay that enables rapid determination of Staphylococcus species and their drug susceptibility on the treatment of patients with positive blood culture results. Infect Control Hosp Epidemiol 31:1043––1048
49. Timbrook TT, Morton JB, McConeghy KW, Caffrey AR, Mylonakis E, LaPlante KL (2016) The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: a systematic review and meta-analysis. Clin Infect Dis **[Epub ahead of print]**
50. Kollef MH, Micek ST (2014) Rational use of antibiotics in the ICU: balancing stewardship and clinical outcomes. JAMA 312:1403––1404
51. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, Srinivasan A, Dellit TH, Falck-Ytter YT, Fishman NO, Hamilton CW, Jenkins TC, Lipsett PA, Malani PN, May LS, Moran GJ, Neuhauser MM, Newland JG, Ohl CA, Samore MH, Seo SK, Trivedi KK (2016) Executive summary: implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 62:1197––1202. doi:10.1093/cid/ciw217
52. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N (2011) Impact of antimicrobial stewardship in critical care: a systematic review. J Antimicrob Chemother 66:1223––1230. doi:10.1093/jac/dkr137
53. 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 60:4840––4852. doi:10.1128/AAC.00825-16
54. Chou AF, Graber CJ, Jones M, Zhang Y, Goetz MB, Madaras-Kelly K, Samore M, Kelly A, Glassman PA (2016) Characteristics of Antimicrobial Stewardship Programs at Veterans Affairs Hospitals: results of a Nationwide Survey. Infect Control Hosp Epidemiol 37:647––654. doi:10.1017/ice.2016.26
55. Wagner B, Filice GA, Drekonja D, Greer N, MacDonald R, Rutks I, Butler M, Wilt TJ (2014) Antimicrobial stewardship programs in inpatient hospital settings: a systematic review. Infect Control Hosp Epidemiol 35:1209––1228. doi:10.1086/678057
56. Doern CD (2013) Integration of technology into clinical practice. Clin Lab Med 33:705––729. doi:10.1016/j.cll.2013.03.004
57. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH (2002) Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 122:262––268
58. Bauer KA, Perez KK, Forrest GN, Goff DA (2014) Review of rapid diagnostic tests used by antimicrobial stewardship programs. Clin Infect Dis 59(Suppl 3):S134––S145. doi:10.1093/cid/ciu547
59. Sweeney TE, Shidham A, Wong HR, Khatri P (2015) A comprehensive time-course-based multicohort analysis of sepsis and sterile inflammation reveals a robust diagnostic gene set. Sci Transl Med 7:287ra271. doi:10.1126/scitranslmed.aaa5993
60. Sweeney TE, Wong HR, Khatri P (2016) Robust classification of bacterial and viral infections via integrated host gene expression diagnostics. Sci Transl Med 8:346ra391. doi:10.1126/scitranslmed.aaf7165
61. Steinberg M, Dresser LD, Daneman N, Smith OM, Matte A, Marinoff N, Bell CM, Morris AM (2016) A national survey of critical care physicians' knowledge, attitudes, and perceptions of antimicrobial stewardship programs. J Intensive Care Med 31:61––65. doi:10.1177/0885066614541922
62. Rosa RG, Goldani LZ, dos Santos RP (2014) Association between adherence to an antimicrobial stewardship program and mortality among hospitalised cancer patients with febrile neutropaenia: a prospective cohort study. BMC Infect Dis 14:286. doi:10.1186/1471-2334-14-286
63. Wolf J, Sun Y, Tang L, Newland JG, Gerber JS, Van Dyke CJ, Hymes SR, Yu D, Carias DC, Bryant PA (2016) Antimicrobial stewardship barriers and goals in pediatric oncology and bone marrow transplantation: a survey of antimicrobial stewardship practitioners. Infect Control Hosp Epidemiol 37:343––347. doi:10.1017/ice.2015.295
64. Jump RL, Heath B, Crnich CJ, Moehring R, Schmader KE, Olds D, Higgins PA (2015) Knowledge, beliefs, and confidence regarding infections and antimicrobial stewardship: a survey of Veterans Affairs providers who care for older adults. Am J Infect Control 43:298––300. doi:10.1016/j.ajic.2014
65. Grigoryan L, Naik AD, Horwitz D, Cadena J, Patterson JE, Zoorob R, Trautner BW (2016) Survey finds improvement in cognitive biases that drive overtreatment of asymptomatic bacteriuria after a successful antimicrobial stewardship intervention. Am J Infect Control doi: 10.1016/j.ajic.2016.04.238**(Epub ahead of print)**
66. Czaplewski L, Bax R, Clokie M, Dawson M, Fairhead H, Fischetti VA, Foster S, Gilmore BF, Hancock RE, Harper D, Henderson IR, Hilpert K, Jones BV, Kadioglu A, Knowles D, Ólafsdóttir S, Payne D, Projan S, Shaunak S, Silverman J, Thomas CM, Trust TJ, Warn P, Rex JH (2016) Alternatives to antibiotics-a pipeline portfolio review. Lancet Infect Dis 16:239––251. doi:10.1016/S1473-3099(15)00466-1
67. Hauser AR, Mecsas J, Moir DT (2016) Beyond antibiotics: new therapeutic approaches for bacterial infections. Clin Infect Dis 63:89––95. doi:10.1093/cid/ciw200
68. Knisely JM, Liu B, Ranallo RT, Zou L (2016) Vaccines for healthcare-associated infections: promise and challenge. Clin Infect Dis 63:657––662. doi:10.1093/cid/ciw333
69. McDonnell A, Rex JH, Goossens H, Bonten M, Fowler VG Jr, Dane A (2016) Efficient delivery of investigational antibacterial agents via sustainable clinical trial networks. Clin Infect Dis 63(Suppl 2):S57––S59. doi:10.1093/cid/ciw244
70. Cillóniz C, Gabarrús A, Ferrer M, Puig de la Bellacasa J, Rinaudo M, Mensa J, Niederman MS, Torres A (2016) Community-Acquired Pneumonia Due to Multidrug- and Non-Multidrug-Resistant Pseudomonas aeruginosa. Chest 150:415––425. doi:10.1016/j.chest.2016.03.042
71. Grundmann H, Glasner C, Albiger B, Aanensen DM, Tomlinson CT, Andrasević AT, Cantón R, Carmeli Y, Friedrich AW, Giske CG, Glupczynski Y, Gniadkowski M, Livermore DM, Nordmann P, Poirel L, Rossolini GM, Seifert H, Vatopoulos A, Walsh T, Woodford N, Monnet DL (2016) Occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study. Lancet Infect Dis. doi:10.1016/S1473-3099(16)30257-2
72. MacFadden DR, LaDelfa A, Leen J, Gold WL, Daneman N, Weber E, Al-Busaidi I, Petrescu D, Saltzman I, Devlin M, Andany N, Leis JA (2016) Impact of reported beta-lactam allergy on inpatient outcomes: a multicenter prospective cohort study. Clin Infect Dis 63:904––910. doi:10.1093/cid/ciw462
73. Blumenthal KG, Shenoy ES, Varughese CA, Hurwitz S, Hooper DC, Banerji A (2015) Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. Ann Allergy Asthma Immunol 115:294––300. doi:10.1016/j.anai.2015.05.011
74. Valerio M, Rodriguez-Gonzalez CG, Munoz P, Caliz B, Sanjurjo M, Bouza E (2014) Evaluation of antifungal use in a tertiary care institution: antifungal stewardship urgently needed. J Antimicrob Chemother 69:1993––1999. doi:10.1093/jac/dku053