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REVIEW

Challenges and research priorities to progress the impact of antimicrobial stewardship

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Abstract

Antimicrobial stewardship programmes have been playing an important role in patient care and hospital policies. These programmes are now recognised as formal strategies for curbing the upward trend in antibiotic resistance and for improving the appropriate antimicrobial and antifungal use. The role of such programs in the era of antimicrobial resistance presents several unique challenges and opportunities, most notably in the diagnostic and therapeutic setting. Controversies remain regarding the most effective interventions and the appropriate design to evaluate their impact. In this review, based on rounds of discussion, we explain the most important challenges faced by antibiotic stewardship and antifungal stewardship programmes. We also try to suggest areas for further research.

Keywords: antimicrobial stewardship, antimicrobial resistance, AMR, AMS, antifungal stewardship

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Introduction

Antimicrobial stewardship (AMS) emerged as a strategy to improve appropriate antimicrobial use in an attempt to facilitate better clinical outcomes and to stem the tide of antimicrobial resistance (AMR). Despite multiple challenges, tremendous progress has been made in the last two and a half decades since its first reference in scientific terms in 1996.[1] However, besides standardising terminology,[2–4] vital and diverse impediments need to be mastered if we were to further advance in the field.

Whilst specific determinants apply to antibiotic and antifungal stewardship, general challenges and research priorities will dictate augmentation and transformation of future antimicrobial stewardship programmes (ASP) (Table 1).

General aspect of antimicrobial stewardship

In the following paragraphs, general challenges and research priorities of ASP are presented.

Empirical evidence for the most effective AMS interventions

A recent Effective Practice and Organisation of Care (EPOC) group review of interventions to improve antibiotic prescribing practices for hospital inpatients[5] documented high-certainty evidence that both enablement and restriction were independently associated with increased compliance with antibiotic policies, and enablement enhanced the effect of restrictive interventions. Enabling (persuasive) interventions that included feedback were probably more effective than those that did not.

Notably, more research is required on unintended consequences of restrictive interventions in hospitalised patients as concerns were raised by the authors that restrictive interventions may lead to delay in treatment and negative professional culture due to a breakdown in communication and trust between infection specialists and clinicians.[5] The ideal model tailored for long-term care facilities also need to be confirmed.[6]

Appropriate design to evaluate the impact of AMS

Davey and colleagues[5] also found considerable design heterogeneity of different global interventions and that all

Table 1. Challenges and research priorities to optimise the impact of stewardship.

Antimicrobial stewardship
• Defining empirical evidence for the most effective interventions
• Defining the most appropriate design to evaluate impact
• Defining consensus metrics to evaluate impact
• Assessing next-generation clinical outcome measures
• Assessing health economics and cost-effectiveness
• Defining sufficient human resources and funding
• Incorporating behavioural science evidence-guided interventions
• Exploring barriers and facilitators to implementation
• Improving compliance to standards
• Defining and incorporating the role of nurses to augment interventions
• Managing true or perceived antibiotic allergies
• Expanding efficient interventions beyond hospitalised patients
• Universal guidance for implementation in low- and middle-income countries
Antibiotic stewardship
• Defining impact of carbapenem-sparing strategies
• Appraisal of the impact of broad-spectrum antibiotics on the gut microbiota
• Defining and improving compliance to de-escalation standards
• Delineating patient benefit of alternative antibiotic dosing strategies
• Delineating patient benefit of therapeutic drug monitoring
• Delineating patient benefit of mono or combination drug regimens
• Elucidating pathogen directed and MDR risk-stratification
• Deciphering mechanisms of resistance as confounder in antibiotic stewardship
• Defining diagnostic tools for early start–early stop antibiotic strategies
Antifungal stewardship
• Improving organisation
• Disseminating education
• Improving microbiological diagnostic methods
• Delineating patient benefit of empirical antifungal therapy
• Identifying a strategy for early stop of empirical antifungal therapy
• Improving de-escalation in patients with proven infection
• Delineating patient benefit of therapeutic drug monitoring

controlled before-after (CBAs) and non-randomised trials (NRTs) reviewed were at high risk of bias. This is evident of the fact that practising stewardship in a complex, real-world setting leads to bias and random time effects endanger the validity of causal inference.[7] In addition, the quality of reporting of interventions in this Cochrane review was poor, which makes it difficult for stewardship teams to authenticate useful interventions or to replicate or build on research findings.[5]

To progress the field of AMS, De Kraker and colleagues[7] recently provided a framework to inform the design and planning of future AMS evaluation studies specifically to negate contamination, which plays a cardinal role in AMS. Accordingly, cluster-randomised controlled studies are the reference standard, but as a consequence of high cost and other factors, using interrupted time series design with a control arm for quasi-experimental studies is also recommended. The authors also highlighted the importance of monitoring unintended consequences.[7,8] Following robust evidence using appropriate design is vital for future standards of stewardship literature.

Consensus metrics to evaluate the impact and success of AMS

Although metrics are rapidly evolving and are bound to transfigure stewardship in the future, currently optimum measures (or combinations involving antibiotic quantity, process, quality, cost, and clinical outcome) to evaluate the impact of AMS are unknown. Few metrics for measuring quality of antimicrobial use and pragmatic clinical outcome measures have been standardised and validated.[9] If we are to progress, more research is needed to develop consensus definitions of process measures, such as 'appropriateness',[3,9] 'antimicrobial de-escalation',[10] and 'time to appropriate antibiotics', for global utilisation.

The impact of novel antibiotic measures has not been documented but warrants investigation, as paradigm shifts in AMS metrics are imminent. To provide a standardised, risk-adjusted benchmark of antibiotic use, the Centers for Disease Control and Prevention (CDC) developed the Standardized Antimicrobial Administration Ratio (SAAR).[11] The SAAR is an observed-to-predicted ratio, in which reported antimicrobial days are the numerator and predicted, statistically modelled antimicrobial days are the denominator. This represents the first aggregate antibiotic use metric that uses point-of-care, antimicrobial administration data electronically reported to a national surveillance system to enable a pivotal component lacking thus far, that of risk-adjusted antibiotic use across multiple hospitals.

The urgent need to improve use of antibiotics throughout healthcare includes the prerequisite to develop appropriate stewardship metrics in the outpatient.[12] Recognising the need for practical tools for antibiotic stewardship at national and international levels, the World Health Organization (WHO) established three categories of antibiotics used for empiric treatment: access, watch, and reserve. The relative proportions of each antibiotic group prescribed form the basis of the AWaRe index (e.g. % amoxicillin use [amoxicillin index]) recently proposed by Sharland and colleagues[13] and applied globally

by Hsia and colleagues[14] to facilitate worldwide paediatric antibiotic consumption benchmarking.

Although a novel standard of measurement, such as the AWaRe metrics, might facilitate benchmarking of outpatient antibiotic use, similar to the SAAR metric for in-hospital use, the AWaRe metrics are not a definitive measure of inappropriate use.[12] Rather, they highlight areas for initiating further investigation and potentially identifying national, state, or provincial system-wide interventional strategies to negate disparate use. However, this implies that we still require universally agreed upon novel metrics to appraise the impact of patient-level stewardship intercessions.

Next-generation clinical outcome measures

Current evidence to support patient-level stewardship is impeded by the inability to provide robust association between cause (intervention) and effect (an outcome). Stewardship metrics are likely to evolve beyond length of stay (LOS), 30-day re-admission rates, and in-hospital mortality, which are subject to multiple confounding variables that are compounded particularly in critically ill patients.[9]

Notably, a structured taskforce of experts working at reliable standards for stewardship (STEWARDS) list of recommended metrics for assessing the impact of patient-level AMS interventions in the acute-care setting in the United States,[15] did not include any clinical outcome measures until further research identifies useful and feasible measures. Although a recent systematic review and meta-analysis did not identify a change in mortality associated with ASPs using audit and feedback in intensive care units (ICUs),[16] the authors also highlighted the need for reporting standardised estimates of mortality and use of more robust study designs to specifically assess mortality, when feasible. More patient-level outcomes, such as those related to dosing strategies, particularly prospective, infection-related re-admission and adverse events and toxicity, are also needed.

In this regard, in an attempt to overcome methodological constraints of stewardship-related studies to date, Evans and colleagues[17] proposed a new strategy to refine integration of both safety and clinical outcomes. The proposed desirability of outcome ranking (DOOR) and response adjusted for days of antibiotic risk (RADAR) metrics are methodological research tools that incorporate both efficacy and safety. These metrics account for a larger number of confounders, thus potentially providing superior patient-level outcomes and more comprehensible benefit and risk data, and as such, the new strategy represents an innovative approach to the clinical impact of a given AMS intervention.

AMS health economics and cost-effectiveness

Although recent evidence on the cost-effectiveness, cost-utility and cost-benefit of AMS has been described,[18] particularly for persuasive and structural interventions, a recurring theme in AMS is a general lack of sufficient data for investment decision making.[18,19]

Economic studies should address not only changes in immediate clinical outcomes and costs. Indeed, changes in resistance prevalence that could impact future outcome and costs should also be taken into account.[18,19]

In this regard, cost-effectiveness analysis of implementing an ASP *versus* standard of care in Spanish ICUs (for sepsis, community-acquired pneumonia, and nosocomial infections, including ventilator-associated pneumonia) was designed.[20] The incremental cost-effectiveness ratio (ICER) was analysed regarding the ability of the ASP to reduce multidrug-resistant (MDR) bacteria. Cost per avoided resistance was €7342, and cost-per-life-years gained (LYG) was €9788. Results from the probabilistic sensitivity analysis showed that AMS would be cost-effective at a level of €8000 per LYG in that setting and that implementing an ASP focusing on critical care patients is a long-term cost-effective tool.[20]

Notably, existing data highlight the lack of evidence on the health economic benefit of restrictive AMS strategies and AMS in the community. Regarding implementation costs of ASPs, except for a few countries and, unlike infection prevention control, a minimum standard of human resources and funding for AMS teams is lacking.[21] One may argue that paradoxically due to extremely limited cost-effectiveness evidence for AMS, decision-makers currently do not have necessary verification to assess whether ASPs provide sufficient benefits.[18]

Behavioural science evidence-guided AMS interventions

The success of ASPs is reliant on the complex challenge of changing prescribing behaviour.[22] Yet, one of the pivotal limitations surrounding existing stewardship interventions is that very few integrate behavioural theory or behaviour change techniques into the design, evaluation, and reporting of interventions to improve antimicrobial prescribing.[5,23] Increasingly, studies have been documenting complex behavioural and social influences on antimicrobial prescribing and confirming the composite effect on stewardship processes, such as adhering to guidelines, assessing benefit/risk, decision-making around initiation (drug choice, route, dose, duration, and timely drug administration), and review (switching or stopping) of treatment.

Because the behavioural and social sciences offer a range of theories, frameworks, methods, and evidence-based principles that can inform the design of behaviour change interventions that are context-specific and thus more likely to be effective and sustainable, Lorencatto and colleagues[23] recently provided fundamental tenets for the process of developing and evaluating complex behaviour change stewardship interventions. One is defining the problem in behavioural terms and understanding current behaviour in context, that is *who*

needs to do *what* differently, to *whom*, *where*, and *when*. The authors also provided a list of practical recommendations as to how to approach behaviour change in ASPs in a structured, theory- and evidence-informed way that is more likely to be effective.[23]

The Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) Working Group on Behavioural Approaches to Antibiotic Stewardship Programs also published a new consensus paper in which proposed research priority areas for optimising effective implementation of ASPs in hospital settings using a behavioural perspective were summarised.[24] There is no doubt that improving and refining research priorities for behaviour change will eventually systematically transform AMS interventional design and reporting and improve bedside enablement through curtailing negative consequences associated with inappropriate antimicrobial prescribing.

Towards improving antibiotic stewardship

Whilst universal challenges and future research priorities generally apply to anti-infective therapy, there are some unresolved controversies specific to antibiotic optimisation (Table 2).

Defining impact of carbapenem-sparing strategies

Sparing carbapenems has assumed preeminent importance in the last decade, as a consequence of the diffusion of carbapenem-resistant Gram-negative bacteria (CR-GNB).[25] The reason this strategy has been advocated by many lies in the frequently multidrug-resistant (MDR) phenotype of CR-GNB.

Table 2. Summary of challenges to improve the impact of antibiotic stewardship.

Challenge	Description
Defining impact of carbapenem-sparing strategies	• Precisely delineate efficacy and safety of different carbapenem-sparing strategies • Assess the impact of carbapenem-sparing strategies on microbiological epidemiology by means of adequate and dedicated RCT or quasi-experimental studies
Appraisal of the impact of broad-spectrum antibiotics on the gut microbiota	• Consider and measure the potentially favourable impact of antibiotic stewardship on the gut microbiota composition and the related outcomes in patients' health • Improve measuring of antibiotic-induced microbiota alterations during both drug development phases and postapproval studies
Defining and improving compliance to de-escalation standards	• Reaching consensus on the definition of de-escalation • Clarify their impact of de-escalation on the individual and population risks of developing colonisation and/or infection by resistant organisms • Detail the effects of de-escalation strategies on the human microbiota
Delineating patient benefit of alternative antibiotic dosing strategies	• Precisely identify patients who could benefit from alternative dosing strategies • Assess the impact of personalised dosing strategies on the human microbiota and resistome
Delineating patient benefit of therapeutic drug monitoring	• Obtain standardised and reproducible laboratory methods • Assess the precise impact of inadequate dosages on both patients' outcomes and resistance development
Delineating patient benefit of mono- or combination drug regimens	• Delineate the true cost-effectiveness of combination therapies by means of dedicated RCT • Evaluate the possible different effect of mono- *versus* combined regimens on the development of resistance
Elucidating pathogen directed and MDR risk stratification	• Provide external validation for most of existing risk scores • Precisely identify the contribution of biomarkers in influencing the post-test probability of colonisation or disease
Deciphering mechanisms of resistance as confounder in antibiotic stewardship	• Provide rapid identification of gene- or enzyme-level resistance determinants • Reducing the risks both of underestimating and overestimating the impact of resistance determinants
Defining diagnostic tools for early start–early stop antibiotic strategies	• Reduce the turn-around time to identification and antimicrobial susceptibility testing • Pursuing the use of appropriate comparator methods and the correct interpretation of equivocal results • Avoid operational biases and inadequate sample sizes in research studies on diagnostic tools

RCT, randomised controlled trial.

Indeed, very few dependable alternatives that were usually associated with suboptimal pharmacokinetics and/or increased toxicity (e.g. polymyxins) often remained available for treatment in the past.[26] In the light of this, relieving selective pressure for carbapenem resistance was thought to favourably impact survival, by indirectly reducing the number of patients who develop CR-GNB infections.[27] The advent of novel agents for treating CR-GNB, which show higher cure rates and better tolerability than polymyxins (e.g. novel β-lactam/β-lactamases inhibitor combinations), has slightly changed the meaning of carbapenem-sparing strategies, but their theoretical importance has remained untouched. Indeed, reducing the incidence of CR-GNB may also reduce the need for using novel agents, in turn preserving also their activity in the long term. On the other hand, some novel agents themselves have been reasonably proposed as possible carbapenem-sparing agents in specific scenarios, further complicating the current ideas and intents of carbapenem sparing in both clinical practice and research.[28,29] Considering these continuously evolving concepts, it is becoming increasingly essential to assess the impact of carbapenem-sparing strategies on microbiological epidemiology by means of adequate and dedicated RCT or quasi-experimental studies, as discussed in previous paragraphs, to guarantee comparability and reproducibility of research results.[7,8]

Another essential point about carbapenem-sparing strategies is to avoid alternatives to carbapenems possibly associated with less probability of treatment success than the latter. In this regard, results of the MERINO RCT have casted important doubts regarding the suitability of piperacillin-tazobactam as a carbapenem-sparing option in patients with bloodstream infections (BSI) due to ceftriaxone-resistant Enterobacteriaceae.[30] Other RCTs comparing piperacillin-tazobactam and meropenem in low-risk patients (e.g. NCT02437045) or evaluating intermittent *versus* continuous infusion of beta-lactams in critically ill patients (e.g. NCT03213990) are ongoing and could help to further define this scenario, in which results of observational experiences remain controversial and the need for pursuing high-level evidence is becoming paramount.

Appraisal of the impact of broad-spectrum antibiotics on the gut microbiota

Although the disruptive effect of broad-spectrum antibiotics on the gut microbiota is intuitive and has been demonstrated,[31,32] the comprehensive nature of their effect on the microbiota dynamics is complex.[33] In addition, current research on antibiotic stewardship rarely considers and measures its potentially favourable impact on the gut microbiota composition and on the related outcomes in patients' health.[34,35] This will likely change in the forthcoming years, due to the expected reduction in the costs of sophisticated diagnostics to precisely define and monitor changes in the human microbiota biodiversity that should nonetheless be subjected to standardisation of sampling and preservation procedures.[36] In addition, composite ecological scores to rank antibiotics regarding their impact on the gut and novel substitutive definitions for 'broad' and 'narrow' spectrum of activity are being proposed, with the intent of better depicting and measuring the antibiotic-induced microbiota alterations during both drug development phases and post-approval studies.[35,37]

Defining and improving compliance to de-escalation standards and appropriate duration of therapy

After an empirical broad-spectrum therapy is initially administered to guarantee adequate coverage, in as many as 40–50% patients with bacterial infections (usually in those with severe infections), de-escalation strategies are employed as soon as susceptibility test results are available.[10,38] However, no definite consensus has been reached about what clearly is de-escalation, as it may refer to different components, for example narrowing the spectrum, switching from combination therapy to monotherapy, or reducing the effect on the microbiota independent of changes in the number of administered agents.[38,39] This unresolved controversy is critical from an antimicrobial stewardship standpoint, as de-escalation has been indicated as a recommended metric for assessing both staff compliance and patient-level impact of stewardship interventions, provided further dedicated study to delineate standardised, validated definitions are conducted.[15] In addition, future efforts should be directed not only towards accurately measuring the occurrences of de-escalation events (dependent of the standardisation of de-escalation metrics) but also towards clarifying their impact on the individual and population risks of developing colonisation and/or infection by resistant organisms, as well as towards detailing their comprehensive effects on the microbiota, thereby evaluating the impact of de-escalation from a more generalised patients' health perspective.

Adequate duration of therapy is another important issue worth discussing. Indeed, fixed-therapy durations (which is almost the rule still nowadays) inevitably pose the risk of either undertreatment or overtreatment, dependent of several personalised variables, such as time to favourable response and pharmacokinetic (PK) and pharmacodynamic (PD) parameters, including the effect of antimicrobial resistance.[40,41] However, appropriate personalised duration (thus able to favourably impact stewardship procedures) cannot be separated from the availability of reliable rapid tests and more guidance on their appropriate combination/interpretation.[42–45] Finally, both pursuing reduction of the inappropriate extension of antimicrobial prophylaxis in the postoperative period and evaluating its unfavourable impact on development of resistance are important priorities for AMS research in the forthcoming future.

Delineating patient benefit of alternative antibiotic dosing strategies

Although stochastic models have shown that continuous/prolonged *versus* intermittent administration increase

the probability of target attainment in patients receiving beta-lactam antibiotics,[46] clear conclusions have still to be reached outside specific categories of patients.[47–49] Indeed, It is likely that extending the time of infusions may confer an advantage only in some conditions, linked to the individual risk of reduced concentrations, the site of infection, and the minimum inhibitory concentration (MIC) of the causative organisms.[49,50] In this regard, although it could be reasonable to apply continuous/prolonged infusion of beta-lactams to all critically ill patients pending further confirmation by additional RCTs, future research interests should also converge towards precisely identifying those patients who could benefit from alternative dosing strategies.[51] Very importantly, this does not only involve the duration of administration but also possible increases in daily dosages in the presence of specific host and/or organism characteristics. In turn, these considerations raise the question as to whether precision medicine (herein in the form of personalised dosages) could not only have a beneficial effect on patients' outcome, but also on their microbiota and resistome, thus delineating another important field of future research.

Delineating patient benefit of therapeutic drug monitoring

Therapeutic drug monitoring (TDM) is aimed both at maximising antibiotic efficacy and at minimising potential toxicity.[52,53] However, several issues have been highlighted that may hamper its widespread implementation in clinical practice (with the exclusion of the well-established TDM of aminoglycosides and vancomycin). These include lack of standardised and reproducible laboratory methods, uncertainties in defining the optimal number of samples and frequency of results reporting, and the absence of adequate prospective studies for assessing the impact of inadequate dosages on both patients' outcomes and resistance development.[10,54,55] Again, these considerations fall in the field of precision medicine, with not only personalised prescriptions but also personalised, TDM-guided adjustments representing promising tools for maximising the efficacy of our stewardship efforts, once standardised.

Delineating patient benefits of mono or combination drug regimens

Combination regimens rather than monotherapy have been frequently employed in the last decades for the treatment of severe bacterial infections caused by MDR Gram-negative bacteria.[56–61] The reason lies in the paucity of alternatives, with clinicians frequently forced to employ drugs with suboptimal PK parameters and/or increased risks of toxicity, as already discussed in previous paragraphs. Notably, several biases exist in most published studies that have precluded a comprehensive assessment of the true cost-effectiveness of combination therapies.[62,63] The growing amount of observational literature ultimately seems to suggest a possible advantage of combinations over monotherapy for severe infections due to carbapenem-resistant Enterobacteriaceae, whilst this is less clear for MDR *Acinetobacter baumannii* and MDR *Pseudomonas aeruginosa*.[26,61,63,64] As these MDR Gram-negative bacteria have been endemic in several countries for several years now, the fact that no clear high-level evidence exists for firmly guiding the use of combinations or monotherapy testifies to the need for improving our ability to rapidly provide good evidence to guide the treatment of MDR organisms in the near future.

In addition, with the advent of novel effective agents, some authors have raised the question as to whether novel agents themselves should be used in combination (with each other or with old drugs), not only aiming at improving efficacy but also at preserving their activity in the long term, by delaying the emergence of further resistance.[65] However, the possible impact on resistance development has seldom been investigated in studies comparing combination therapy *versus* monotherapy, and high-level evidences are still largely lacking.

Elucidating pathogen directed and MDR risk stratification

Stratifying the risk of acquiring colonisation and/or developing infection due to specific and/or MDR organisms is certainly a complex task. Indeed, there are various and highly overlapped individual and environmental potential risk factors, including amongst others previous exposures to healthcare facilities, previous treatment with broad-spectrum antibiotics, baseline comorbidities, travel to endemic areas, and local colonisation pressure.[66–69] Several risk-assessment tools have been proposed, with the aim of guiding the decision whether or not initiating empirical treatment, as well as which agent/s should be administered.[66–68,70,71] However, only a few of them have been externally validated, and their widespread applicability still remains uncertain. Further efforts are thus needed to validate existing scores and to precisely identify the contribution of both old and novel biomarkers in significantly influencing the post-test probability of colonisation or disease.[70–74] Very importantly, although this would allow to further increase our ability to identify specific risks, it cannot be separated from a global understanding of underlying resistance mechanisms, as well as from the implementation of adequate diagnostic stewardship procedures, as discussed in the following paragraphs.

Deciphering mechanisms of resistance as confounder in antibiotic stewardship

The potential confounding effect of resistance mechanisms in antibiotic stewardship interventions may arise from the risks of either underestimating or overestimating the impact of resistance. Indeed, on the one hand, the

presence of a given resistance mechanism may not always be associated with a resistant phenotype; on the other hand, the missed identification of the underlying resistance mechanism in the presence of full phenotypic resistance may preclude a stewardship-oriented selection of the agent to be employed.[72–74] In this regard, a rapid identification of gene- or enzyme-level resistance determinants will become increasingly essential in the future, owing to the specific activity of some novel agents against specific mechanisms.[65,75] Notably, this is also true from a research perspective, as advancements in this field are intimately related to the probability of success of all antibiotic stewardship programs based on a continuous and proactive collaboration between clinicians and the laboratory.

Defining diagnostic tools for early start–early stop antibiotic strategies

In the last few years, novel microbiology technologies have enabled a considerable reduction in the turnaround time to identification and antibiotic susceptibility testing, and the so-called 'fast microbiology' has been recognised by several scientific groups and organisations as a fundamental aspect for guiding antibiotic initiation and discontinuation within antibiotic stewardship interventions, as well as for increasing the appropriateness of therapy.[76–78] Research priorities in this area include the need for appropriate comparator methods, correct interpretation of equivocal results, and avoidance of operational biases and inadequate sample sizes.[79] In addition, for increasing comparability and reproducibility, the possible influence of local personnel availability and resources should always be considered when assessing the cost-effectiveness of laboratory workflows and algorithms involving innovative diagnostic methods.[57] Notably, the impact of rapid molecular testing on clinical outcomes and costs is maximised only in the presence of well-structured antimicrobial stewardship interventions.[80–82]

Towards improving antifungal stewardship

In recent years, antifungal stewardship (AFS) programmes have grown in interest and are now a 'hot topic' in infectious disease.[83] Similar to AMS, the aims of AFS programmes are to optimise patient outcome with appropriate selection of antifungal drugs based on patient profiles, appropriate doses, route of administration, and duration of therapy, whilst limiting consequences of misuse, such as the emergence of resistant fungal strains and adverse drug reactions[84] (Table 3). In addition, although not a primary objective, reduction in healthcare costs frequently represents a secondary AFS effect.[85]

In this section, we will review the different challenges specifically faced by AFS and suggest strategies to improve AF use in the hospital setting.

Disseminating education

Continuing education regarding adequate invasive fungal infection (IFI) management should be regularly performed for prescribers, as their knowledge may not be as good as their own perception. In a recent European survey on different aspects of IFI, significant gaps in the knowledge were mainly related to the interpretation of microbiological results (i.e. a differentiation between colonisation and real infection), appropriate antifungal selection, and dosing.[86] Medical education should, therefore, target antifungal optimisation and should be regularly repeated.[87]

Educational programmes should be developed on in-person training, internet-based resources, interactive leaflets, and sessions available at least annually. Moreover, focused sessions may be also useful for obtaining practice-specific feedback and if major deviations in prescribing are detected in a specific unit.

However, because the educational intervention is more efficient in association with other measures, audit and feedback

Table 3. Ten golden rules for adequate IFI management.

1. Restrict antifungal prophylaxis to patients who really need it (i.e. avoid universal prophylaxis in critically ill patients or in lymphoma patients)
2. Try to implement new diagnostic techniques to reduce the gap between empirical and targeted antifungal treatment
3. Start prompt 'early' antifungal treatment based on risk factors in critically ill patients
4. Select the most adequate antifungal drug according to the clinical picture of the patient and his underlying condition
5. Achieve adequate source control
6. Use an adequate dose: low dose is associated with resistance. Perform TDM to all patients receiving voriconazole and posaconazole
7. Perform biomarkers to confirm or to exclude the diagnosis and to monitor clinical evolution of the disease (galactomannan, CAGTA, Beta-d-glucan, T2MR)
8. Stop 'early' inappropriate therapy at 72–96 hours
9. De-escalate whenever possible
10. Check duration of therapy

CAGTA, *Candida albicans* germ antibodies; IFI, invasive fungal infection; T2MR, T2 magnetic resonance.

assessing antifungal prescription should be an useful tool.[76] Regular feedback of antifungal prescribing profiles, both at the facility and individual physicians levels, might also be a compelling method.[88,89]

Improving microbiological diagnostic methods

Even for infectious disease (ID) doctors with experience in IFI management, diagnosis of fungal infections can be challenging. Difficulties include non-specific symptomatology of IFI that makes their clinical manifestations indistinguishable from other infections, discrimination between colonisation and infection, and the low sensitivity of traditional cultures.[87]

In recent years, new non-culture-based microbiological techniques have been introduced in daily clinical practice, not only to confirm or to exclude more rapidly a diagnosis of IFI,[90,91] but also to determine the susceptibility profile of fungal species,[92] to identify the origin of fungemia,[92] or to predict the clinical evolution of the disease.[93] The need for more rapid results is evident and welcome, and there are several molecular and non-molecular methods that can provide results within few hours. These techniques include galactomannan (GM), matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS), the T2 magnetic resonance (T2MR), the fluorescence *in situ* hybridisation using peptide nucleic acid probes (PNA-FISH), 1-3 b-D-glucan (BDG), *Candida albicans* germ antibodies (CAGTA), *Candida* polymerase chain reaction (PCR), and *Aspergillus* PCR.[94,95]

Regarding BDG, Giacobbe and colleagues recently assessed its performance in combination with procalcitonin for the differential diagnosis between candidaemia and bacteraemia in critically ill patients.[73] They found that when both markers indicated candidaemia (BDG ≥80 pg/mL and PCT <2 ng/mL), their PPV (96%) for diagnosis of invasive candidiasis was significantly higher than that of BDG (79%) or PCT alone (66%), respectively.

Another promising tool is the T2MR, a new diagnostic method for the diagnosis of invasive candidiasis, cleared by the US Food and Drug Administration (FDA)[96] and the European Medicines Agency (EMA). In the pivotal trial involving 1801 hospitalised patients, T2MR was effective in detecting the five most common species of *Candida* in blood cultures within 3–5 hours, with an overall specificity of 99.4% and sensitivity of 91.1%.[96] The assay appears to be a promising diagnostic tool to identify patients with suspected invasive candidiasis who may benefit from empirical antifungal therapy.[90]

Although these new techniques will be useful to improve the management of patients with suspected or documented IFI, additional studies are certainly warranted to assess their real impact in the clinical context of AFS interventions.

Delineating patient benefit of empirical antifungal therapy

Reflecting the under-recognition of IFI and the diagnostic delays of the traditional fungal cultures, the empirical antifungal approach is increasingly popular in daily clinical practice[97] and now corresponds to 45–65% of all inpatient antifungal prescriptions.[98,99]

Nonetheless, deciding whether a patient actually needs empirical antifungal treatment is troublesome, especially in ICUs. As outlined by the last published consensus on invasive candidiasis management,[100] this practice is frequently based on risk scores with very low positive predictive values[101,102] that lead to unnecessary antifungal treatment. For example, in a prospective observational study performed in 36 ICUs, antifungal treatment was empirically administered to 180 out of 1017 patients included in the study (17%), but only 5% of those developed candidemia.[103]

In addition, there are no randomised controlled trials demonstrating the efficacy of empirical antifungal therapy on patients' survival, thus limiting recommendations on appropriateness and timing. Recently, Timsit and colleagues[104] compared the outcome of a 14-day empirical course of micafungin with placebo in a prospective randomised multicentre, placebo-controlled trials including 260 patients. Although many high-risk patients were included in the study, there were no differences between arms with respect to the primary study endpoint (survival to day 28 free of IFI).

In our opinion, the role of empirical therapy in high-risk patients presenting with ICU-acquired sepsis of unknown origin still remains to be determined and further studies aimed to specify criteria for early initiate antifungal therapy in critically ill patients are needed.

Identifying a strategy for early stop of empirical antifungal therapy

In the clinical scenario in which most antifungals are prescribed empirically, it is critical to reassess the need for antifungal therapy at 72–96 hours after starting the therapy, particularly in septic critically ill patients, in whom initial diagnosis could have been uncertain. To help clinicians to feel safe stopping empirical AF treatment, *Candida* biomarkers have been used for this indication. In a previous study performed in Spain, a combination of BDG and CAGTA performed on days 0, 3, and 5 during empirical antifungal therapy had a very high negative predictive value (97% for the entire population and 100% in ICU patients).[91] The same strategy was prospectively studied by Nucci and colleagues, who reported the safety of early discontinuation of empirical echinocandin therapy based on consecutive negative BDG tests in high-risk ICU patients.[91] A combination of biomarkers was also used to avoid empirical antifungal therapy in haematological patients receiving

antimould prophylaxis.[105] Moreover, a recent study showed T2MR may help to reduce the length of empirical therapy and its use led to a 21% discontinuation rate.[106]

Improving de-escalation in patients with proven infection

It is also challenging to widely implement early de-escalation of antifungal therapy in patients with proven IFI according to microbiological results. In previous studies, such a reassessment was performed in less than half of patients with fluconazole susceptible *Candida* bloodstream infection who finalised the initial treatment with echinocandins without being de-escalated to fluconazole.[107,108] In our opinion, it should be a clear objective of AFS programme in the next future.

Delineating patient benefit of therapeutic drug monitoring

Similarly to antimicrobials, also for antifungals, the systematic use of TDM is aimed to optimise patient outcomes whilst minimising potential toxicity.[107,108] Currently, both the Infectious Diseases Society of America (IDSA)[109] and the British Society of Medical Mycology guidelines[110] recommend systematic TDM in patients receiving posaconazole or voriconazole due to their pharmacokinetics variability[111] and potential relationship between serum drugs concentration and therapeutic efficacy[112] or toxicity.[112] On the other hand, the same guidelines do not support systematic TDM for fluconazole and echinocandins[110] because of the linear and predictable pharmacokinetics profile,[113] as demonstrated by studies performed *in vitro* and in healthy volunteers. However, when the pharmacokinetics of fluconazole, anidulafungin, and caspofungin were prospectively addressed in critically ill patients receiving fixed doses of antifungals, a considerable interindividual variability was observed, with a large proportion of patients (up to 33%) not attaining the optimal pharmacokinetics/pharmacodynamics target.[114]

Few AFS programmes have included systematic TDM as a part of their interventions[82] but none of them have specifically evaluated the clinical impact of TDM on patient outcomes.

Conclusion

In this review, we have outlined the current status of AMS, the evidence base for intervention strategies, and issues of education, organisation, improved diagnostic technologies and on how to optimise treatment on a patient level. However, a number of outstanding challenges in the field of stewardship and antimicrobial resistance still need to be resolved.

One important strategy to combat the potential threat of untreatable infection is to accelerate the introduction of new diagnostic techniques in daily clinical practice as well as the development of new drugs that, clearly, need to be protected by the same AMS. Future studies assessing length of antibiotic treatment are also needed.

On the other hand, the diagnosis and management of IFI remains difficult, and IFIs are still associated with high morbidity, mortality, and healthcare costs. Despite the recent introduction of new diagnostic tests, such as T2MR or PCR, and the widespread use of empirical therapy, treatment of such infections still remains a remarkable challenge.

In conclusion, multidisciplinary teams and AMS programmes should be implemented to optimise patient care and encourage the appropriate use of resources.

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