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Review Article

Optimization of antimicrobial prescription in the hospital☆

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ABSTRACT

Internal Medicine wards are an appropriate focus of antibiotic stewardship, along with emergency departments and intensive care units, because a large proportion of patients are with parenteral broad-spectrum antibiotics. Given the unmet clinical need of antibiotic optimization in the hospital and the importance of front-line practitioners for antibiotic stewardship, the barriers and tactics to overcome them were discussed in a round table at the European Congress of Internal Medicine. Better rapid diagnostic tests should help to increase appropriate early antibiotic rates, favoring diversity in antibiotic choices adapted to the awareness of local resistance patterns. Providing such is a greater challenge in low-resource settings. Prescriptions should be personalized, adjusting dosage and source control to specific patients' conditions. Shorter antibiotic duration and de-escalation are major drivers to reduce adverse events, with mortality and recurrence rates being independent of antimicrobial duration. Appropriate diagnostic tests with quick turnaround times decrease excessive antibiotic use. Antimicrobial optimization requires a multidisciplinary approach and it should be a core competence of training specialists, improving opportunities to provide safer patient care.

Many obstacles in antimicrobial stewardship (AMS) are shared across high-income countries (HICs) and low and middle-income countries (LMICs). Some of the issues raised in a workshop by the American Thoracic Society on AMS in the Intensive Care Unit (ICU) [1] are universal and could be applied to many different settings: excessively larger-spectrum drugs are often prescribed due to the fear of not covering a specific pathogen with narrow-spectrum antibiotics while waiting on cultures; unnecessary therapy escalation often occurs when a new clinical event, such as fever or hypotension, manifests within hours of therapy initiation, at a time when treatment response did not had enough time to occur or when such events are due to other reasons. The lack of awareness of adverse events related to antibiotic prescription also applies to LMIC settings, as nephrotoxicity, increased risk for *Clostridioides difficile* infection, selection of drug-resistant species and other side effects are often neglected during antibiotic prescription. Nevertheless, many challenges are exclusive of or more often experienced by healthcare workers in resource-limited settings. In this review, we aim to discuss current challenges in providing AMS at the hospital in both low and high resource settings. Barriers to implement antimicrobial optimization in the hospital, tactics to overcome and the role of internists in multidisciplinary teams was convened in a specific workshop at the 10th European Congress of Internal Medicine (ECIM), that was held in Malaga (Spain), on 10th June 2022. This report is a synthesis of the lecture and subsequent major discussion that emerged among participants.

1. Diagnostic workup

Blood cultures and specimens from infectious sites should be collected as early as possible near the infection onset. In sepsis, patients with vasopressors or immunocompromised it is not appropriate to delay antibiotic start to collect samples because clinical outcomes remain the primary concern. Over the past years, many tests have been developed aiming to provide more rapid results for microbiological tests: point-of-care antimicrobial susceptibility tests [2], rapid tests for identifying extended-spectrum β-lactamases (ESBLs) [3], carbapenemases [4] and resistance to polymyxin/colistin [5], for example. Non-culture methods, including nucleic acid amplification technologies, transcriptomic tests, and predictive biomarkers also aid on sepsis diagnosis [6,7]. Although there are no studies, up to our knowledge, evaluating the impact of

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incorporating such technologies using clinical outcomes, reducing time to diagnosis might improve clinical outcomes of patients with sepsis and ultimately reduce length of hospital stay [8].

Diagnostic resources represent an important difference between low and high-resource settings. LMICs have lower availability of culture methods, rapid tests and molecular diagnostic tools [9]. Additionally, in some scenarios these tests are available, but must be either paid by the patient (which might prevent the clinician from ordering a specific test) or are seen as "unreliable" [10], perpetuating the prescription of unnecessary or excessively large spectrum antibiotics in the absence of positive cultures or in the presence of negative ones.

The caveat of using biomarkers (C-reactive protein and procalcitonin, for example) for sepsis diagnosis in the ICU is that such methods have very low specificity and might be elevated in non-infectious prior conditions, like severe hypoxemia, cardiogenic shock, surgery, trauma [11] or graft dysfunction in transplanted patients [12].

Such technologies are not always available in low-resource settings, but there is room for improvement when using traditional culture methods. Many pre-analytical factors, such as previous disinfection of collection site, collecting adequate blood volume, and using continuous monitoring blood culture systems, impact on blood culture results [13]; using a dedicated phlebotomy team for blood culture collection reduced the contamination rates [14].

Additionally, a great challenge when diagnosing lower respiratory tract infections is to distinguish colonization from infection. Using quantitative or semi-quantitative methods and standardizing sputum, tracheal aspirate or bronchoalveolar lavage specimens collection could aid in making this distinction and ultimately prevent unnecessary antimicrobial prescription.

Another important issue is the difficulty in communication between microbiology professionals and those involved directly with patient care. In a survey by Villanueva et al. [15], in HIC hospitals, blood culture results were more frequently (98%) notified to the treating clinician within 24 h of positive results, compared to only 22% of LMIC hospitals. Improving the communication between microbiologists and caregivers is a low-cost intervention that might impact on time to diagnosis and ultimately time to treatment.

In summary, optimizing patient surveillance in order to shorten time to diagnosis, improving diagnostic methods through rapid testing and strengthening the communication between microbiologists and attending physicians is key to reduce time to diagnosis in order to provide timely treatment.

2. Choice of empirical treatment and the importance of local epidemiological data

It is well known that antibiotics must be started as soon as possible when sepsis is suspected or confirmed, ideally within the first hour [16], which depends on not delaying sepsis diagnosis, and also on choosing the adequate empirical drug for treatment ("right first time"). This poses a great challenge in LMICs where rates of multidrug resistant (MDR) infections are on the rise, even for community-acquired infections. In this sense, rapid antimicrobial susceptibility tests might aid on tailoring therapy within the first hours of treatment.

Choosing the right empirical treatment implies on not missing the causative pathogen and, at the same time, preventing the use of potentially toxic and unnecessarily broad-spectrum drugs. As reported form the 90 s, knowing the local epidemiology of antimicrobial resistance is critical, particularly in urgent settings such as septic shock. Nevertheless, surveillance of MDR microorganisms is suboptimal in LMICs. Ouedraogo et al. [17] highlighted that in many West African countries the reporting of MDR organisms is deficient and prevalence rates are unknown. Adequate and centralized reporting systems are an important tool in AMS, as they provide valuable insight on resistance rates and ultimately might guide appropriate empirical therapy options.

Lim et al. [9] have recently proposed surveillance strategies for MDR microorganisms in LMIC. In their study, several MDR surveillance strategies were used in LMICs; most relied on microbiological data obtained from laboratories and did not follow a case-based approach, suggesting that there is room for improvement on surveillance and reporting. Using protocols based on local microbiological data is associated with an increase in adequate antimicrobial administration [18]; therefore, AMS programs must alight the importance of collecting adequate surveillance data and make it available for caregivers, as well as provide training for medical staff in order to tailor empirical therapy to the local epidemiology.

3. Adequate dosing regimens and selective pressure

The fear of antibiotic-associated complications, such as nephrotoxicity, often leads to prescribing under-dosed antibiotics or omitting loading doses, particularly regarding those that are widely recognized for common and serious side effects. A survey on use of polymyxins found that a large proportion of doctors omit loading doses for colistin and often prescribe underdoses [19]. A study on vancomycin use in an emergency department in the United States [20] found that only 22.1% of vancomycin doses were correct; more than 70% were under the recommended, indeed. Similarly, aminoglycoside prescription was not in accordance to current guidelines in 66% of prescriptions from an Australian hospital [21].

Although complications of overdosing antimicrobial regimens are widely known, it is likely that the risks of under-dosing are frequently overlooked. Rather than preventing complications, under-dosing provides selective pressure that facilitates the emergence MDR microorganisms [11]. Providing adequate antimicrobial regimens, in the pharmacokinetic-pharmacodynamic (PK/PD) sense, is a greater challenge in severe infections, when vasopressors or mechanical ventilation are required. We reported that standard doses might be insufficient for patients with increased volume of distribution (fluid resuscitation), increased cardiac output (early phases of shock) or who underwent mechanical ventilation or other organ support techniques [11]. A landmark multinational study [22] aiming to examine beta-lactam plasma concentrations in critical patients found that 20% of patients did not even achieve free drug concentrations above MIC for 50% of the dosing interval; large variations were seen across units, highlighting the need for personalized dosing regimens.

In this sense, the development of objective tools aiming to improve adequate dosing prescription is increasingly important. A pre-post intervention study evaluating the impact of dose calculators found significant reductions in dose errors for gentamycin and vancomycin [23]; Bayesian distribution of software aimed at monitoring concentration levels using peak and trough concentrations are being increasingly used in hospitals worldwide and are strongly recommended for monitoring vancomycin levels in severe *Staphylococcus* aureus infections [24], for example. Nevertheless, serum level concentration tests are not widely available, most software is costly and its acquisition is rarely seen as a priority for hospitals in LMICs. The development of more affordable open-source software will facilitate doctors from LMICs to have access to dose calculators; nevertheless, continuous education must highlight the importance of adequate dosing regimens and provide training regarding upcoming software.

4. Antimicrobial options

Increased rates of MDR infections have been reported worldwide [25]; LMICs are not only challenged with a lower availability of antibiotic options, they also experience higher rates of MDR organisms and often have suboptimal surveillance. In Brazil, for example, there has been an increase in MDR *Pseudomonas aeruginosa* over the past years [26], as well as for meticillin-resistant *Staphylococcus aureus* [27], Vancomycin-Resistant *Enterococci* [28] and carbapenemase-producing *Enterobacterales* [29]. In Serbia, increasing rates of multidrug resistant

Klebsiella pneumoniae, Acinetobacter baumannii and *Pseudomonas aeruginosa* have been observed [30]. A study on antimicrobial resistance in West African countries [17] found alarming rates of multidrug resistant organisms; for example, the prevalence of Extended-spectrum beta--lactamase producing *Escherichia coli* was up to 66%, and the prevalence of carbapenemase-producing microorganisms was around 36% in reference hospitals in Nigeria.

Despite alarming rates of MDR infections, access to new antimicrobials is scarce in LMICs. This poses a challenge for all care practitioners in low-resource settings, particularly in critical care units and emergency departments where time to therapy is a bigger issue. Alternative combined regimens for MDR infections often rely on nephrotoxic drugs, such as polymyxins, in a context where multiple events contribute to renal injury.

In settings where MDR infections are highly prevalent, particularly polymyxin-resistant Gram-negative bacteria and vancomycin-resistant Gram-positive bacteria, acquisition of new beta-lactams/beta-lactamase inhibitors (BLBLI) and cephalosporins must be seen as a priority: patients with MDR infections treated with BLBLI demonstrate increased survival and lower renal injury rates in infections by KPC-producing Enterobacterales and MDR *Pseudomonas aeruginosa* [31]. In settings where these new therapies are not available for all patients with MDR infections, AMS programs aiming to prioritize patients who will benefit the most from such therapies are warranted.

5. De-escalation

De-escalation consists replacing a broad-spectrum empirical therapy for a narrow-spectrum therapy followed by its discontinuation; it might also include reducing the number of antimicrobials in a combination therapy [32]. One of the goals of AMS is to reduce using broad-spectrum drugs whenever possible, reducing selective pressure and ultimately the rates of MDR microorganisms. De-escalation to narrow-spectrum drugs is often feared by physicians working with critical care patients due to patient severity; there is a common sense that if a patient is improving with an empirical drug, it might not be safe to de-escalate. The lack of trust in microbiological methods in low-resource settings [10], as mentioned previously, contributes to unnecessary maintaining broad-spectrum drugs in the presence of negative cultures.

De-escalation might be possible in more than one third of patients with ventilator-acquired pneumonia (VAP) and it has been associated with higher survival rates in several studies [33–35]; obtaining respiratory samples before antimicrobial therapy initiation is key to make de-escalation possible [34]. Knowledge of the local epidemiology and prevalence of resistance and using rapid antimicrobial susceptibility tests aid in de-escalation.

In some groups of patients who have severe underlying conditions, such as hematological and transplanted patients, de-escalation might be challenging considering the need for very broad-spectrum empirical therapies; additionally, the presence of neutropenia discourages physicians to narrow antimicrobial spectrum [36]. Clinical biomarkers such as C-reactive protein (CRP) or procalcitonin (PCT) might indicate when it is safe to de-escalate in lung transplant patients [37] presenting an episode of acute respiratory failure where it would be difficult early differentiation between graft dysfunction or pneumonia.

Continuous medical education on antimicrobial therapy, improved communication between microbiologists and attending physicians plus optimizing surveillance can contribute to empower front line physicians to provide safe de-escalation.

6. Shortening treatment duration

Recent studies indicate that shortening treatment duration of infections in critical care patients is safe for most patients. Treating ventilator-associated pneumonia for a reduced period (8 vs. 15 days) did not affect clinical outcomes [38]; additionally, a review on duration of treatment for sepsis found that regimens during up to 7 days might be as safe as those that take up to two weeks [39].

Nevertheless, providing shorter antimicrobial courses should not be applied in a “one size fits all” approach and must be done in a case-by-case fashion. Changes in baseline CRP and PCT [40] and clinical parameters are helpful when deciding when to de-escalate. Resolution of hypoxemia, fever and white cell count was present in 74.7%, 73.3% and 53.3%, respectively among intubated patients with pneumonia within three days of therapy, being early signs of recovery; in contrast, resolution of radiological opacities, and clearance of secretions lasted a median of 14 and 6 days until resolution, being late events ant they should not preclude a short duration of treatment [33] in pneumonia. In our experience in the real-world, these are common triggers for “escalation”, often inappropriate. In order to optimize clinical improvement, it is critical to choose adequate-spectrum, bactericidal empirical therapy and not delay its administration [41]. Also, improvement of urinalysis can be used as a tool to deem a regimen as effective and help therapy simplification.

Guidelines on antimicrobial treatment might provide important tools on when to decide for a shortened duration of treatment, combining source control, use of biomarkers (when available), antimicrobial susceptibility and severity of infection. Additionally, further studies on shortening treatment duration, both observational and clinical trials, will be useful for establishing a more objective and tailored approach for this matter.

7. The importance of diversity

Cycling has been reported as potential tool to prevent emergence of resistance. However, the experience reported by the authors indicate that heterogeneity of antibiotic prescription, ensuring diversity, are associated with lower incidence rate of MDR microorganisms [42], including *Enterococcus faecium, Staphylococcus aureus, Klebsiella* species, *Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species (ESKAPE) [43], suggesting that patient-specific regimens might impact on MDR rates. This highlights the need for a more personalized approach to antimicrobial therapy. In this sense, AMS programs should have a key role in promoting antimicrobial diversity in patient prescription, ensuring larger heterogeneity. Low diversity, with a predominant use of an antibiotic class is facilitating the emergence of resistance. Predominance of carbapenems have been associated with carbapenem-resistant *Acinetobacter baumannii,* whereas ESBL has emerged with predominant use of third-generation cephalosporines [42].

8. AMS programs and the importance of continuing education

AMS is resource-demanding and depends on a very intricate health system structure that encompasses infection prevention and control (IPC) – which for once depends, among other factors, on the physical capacity of health facilities –, laboratory resources, infection surveillance and epidemiology, medical and nursing education, antibiotic availability and post-prescription surveillance. All these factors, much less available in LMICs, impact on stewardship and these differences must not be neglected.

Hospitals in LMICs have less formal AMS and IPC programs, less available antibiotic options and smaller distance between hospital beds, where single-patient rooms are less commonly reported, impacting on infection prevention and posing a challenge for separating patients with MDR infections from those admitted for other reasons [15]. Additionally, in most LMIC hospitals, the majority of professionals involved in AMS are not infectious diseases (ID) specialists [15], highlighting the need for antibiotic prescription to be seen as a core competence of any physician involved directly with patient care. However, in LMICs, where this is even more important – due to a lower availability of ID specialists – it is likely that doctors and pharmacists are even less prepared to deal

with issues related to antibiotic prescription: a survey in four African countries indicated that around half of healthcare students were not familiar to the term "antimicrobial stewardship" and had no access to up-to-date information on antibiotics [44]. In another survey, conducted in East Africa, 82.3% of final year medical and pharmacy students knew when to start antimicrobial therapy, but a third of them did not know how to choose the appropriate antimicrobial regimen [45].

Although the lack of ID specialists in AMS programs is partly explained by the unavailability of such professionals in some settings, considering that a large proportion of healthcare professionals are not aware of the importance of AMS, it is likely that the importance of incorporating pharmacists and ID specialists or clinical microbiologists for infection control and surveillance is underestimated by hospital managers [15]. In this sense, stewardship is often seen as a strategy aimed at reducing antibiotic costs rather than improving patients' outcomes, when actually AMS is better defined as "the right drug at the right time and the right dose for the right bug for the right duration" [1].

Taken together, these findings indicate that healthcare education in resource-limited settings must account for the limited availability of ID specialists and therefore should encompass AMS as a core competence in providing patient care. This gap in medical training regarding antimicrobial therapy poses a bigger problem in the ICU, where the proportion of infections caused by MDR organisms is higher [1] and there is a smaller window of opportunity when providing the adequate antimicrobial regimen at the appropriate time, particularly in patients with septic shock. Although more than 3/4 of patients in the ICU receive antibiotics [46], prescriptions and dosage regiments are often inadequate [22].

Therefore, antimicrobial therapy training must be incorporate as a core competence for internists, hospitalists, critical care and emergency medicine doctors, who must be empowered and trained to take decisions on antimicrobial treatment in the adequate time. Considering the dynamic nature of local antimicrobial resistance and prevalence patterns of infection, it is important that such competences are continuously updated. Hospitals must encourage and provide longitudinal training on AMS to hospital physicians, and in this sense, formal AMS and IPC programs might provide and facilitate continuous education on antimicrobial therapy. In this sense, a consensus on the competences of generic antimicrobial prescribing and stewardship was developed by the European Society of Clinical Microbiology and Infectious Diseases [47].

9. AMS in the post-COVID era

The SARS-CoV-2 pandemic posed a great challenge in providing adequate AMS due to a combination of excessive workload, overcrowded ICUs, an unprecedented number of patients requiring invasive ventilator support for long periods (with the subsequent high rates of hospital-associated infections) [48] and difficult diagnostic testing.

Validation of diagnostic tests with clinical outcomes as primary endpoints are an unmet clinical need. The clinicians' fear of suboptimal outcome if a pathogen is missing requires microbiological strategies with short turnaround times. Blood cultures and adequate microbiologic specimens from the infectious site (eg. respiratory secretions in a subject with pneumonia) obtained near the infection onset should be obtained. Rapid diagnostic, without culture steps, for susceptibility becomes a major challenge. In samples with common microbial colonization, such as intubated patients, quantitation becomes a useful tool to discriminate from true infection in the real-world. C-reactive protein, procalcitonin and other biomarkers can assist decisions [49].

Rapid molecular tests need to be incorporated to the early pathogen detection and detailed information has been recently reported [6]. Available evidence from severe infections can be translated to internal medicine wards with milder infections, and further research is required on elderly, multimorbidity and chronic organ failure patients.

In a recent publication [50], 77.2% of institutions in low and middle income countries had active AMS programs. Remarkably, infectious diseases specialists shortage in this setting due to limited resource settings is common. Therefore, the role of the internist in driving efforts in LMIC is remarkable, assuming tasks of leadership and clinical training in antibiotic optimization in the post-COVID19 era.

Table 1
Challenges when providing AMS in hospital settings and possible strategies .

Challenges	Proposed strategies
Gaps in healthcare education	Addressing antimicrobial stewardship as a core competence of intensive care education, focusing on appropriate antibiotic choice and duration
Longer time to treatment	Improving communication between microbiologists and intensive care professionals; acquiring more rapid diagnostic tools when feasible
Frequent inadequate dosing	Providing continuous education on antimicrobial prescription; using dose calculators and drug concentration measurements
Less availability on diagnostic tools	Discussing the importance of incorporating new technologies when possible; improving communication between microbiology professionals and treating clinicians
Less availability on treatment options	Reserve large-spectrum drugs for specific clinical scenarios and use narrow-spectrum antibiotics whenever possible; discussing incorporating new antibiotics in settings where scarce options are available for MDR infections
Gaps in reporting and surveillance	Establishing centralized surveillance programs and using electronic health records to automate reporting
Longer than necessary duration of treatment	Updating current guidelines considering recent studies on shortening duration of antimicrobial treatment; guidelines should provide objective information regarding treatment duration and specific criteria for longer or shorter antimicrobial courses

ID, infectious diseases; AMS, antimicrobial stewardship; IPC, infection prevention and control; ICU, intensive care unit; MDR, multidrug resistant .

10. Conclusions

Although new technologies, such as better rapid diagnostic tests and new antibiotics, are facilitating the management of hospitalized patients with severe infections, these are not widely available and many challenges remain in both high and low income settings. We provide a summary of the most important challenges when providing adequate AMS in hospital settings (and possible strategies) in Table 1.

Adequate antimicrobial prescription for hospitalized patients depends on adequate diagnosis of true infection, identification of etiological agent, early initiation of potent and appropriate therapy, dose optimization, appropriate duration and adequacy to local guidelines, ensuring diversity in prescriptions whenever possible. This depends on continuous medical education, knowledge of local surveillance and epidemiology and availability of diagnostic methods and therapeutic options, all of which are less available in low-resource settings, providing particular challenges to those physicians based in LMICs. Although most literature on this subject is produced in HICs, we believe a tailored approach for resource-limited settings is warranted, focusing on healthcare education and raising awareness on this matter.

Further studies on de-escalation and shortening duration of therapy, as well as the continuous development of rapid tests and biomarkers, will provide more objective tools that might aid in prescribing tailored antimicrobial therapy.

Disclosure

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