Official journal of the Spanish Society of Chemotherapy

Current strategies for infectious diseases management

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Timing in antibiotic therapy: when and how to start, de-escalate and stop antibiotic therapy. Proposals from a stablished antimicrobial stewardship program

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Revista Española de Quimioterapia
doi:10.37201/req/s03.22.2022

ABSTRACT

The current morbimortality of serious infections is unacceptable and there is a need to promote the increase in the efficacy of empirical and targeted antibiotherapy. This could be achieved by initiatives coming from ASP teams aimed at promoting increased efficacy of antibiotic therapy .In the optimization of the antibiotic therapy there are several critical points in which an adequate timing could achieve benefits in the survival of patients with severe infections: prompt initiation of empirical treatment; de-escalation performance, appropriate targeted treatment; and finally, curtail antibiotic duration.

Keywords: antimicrobial stewardship program, de-escalate, timing, empirical treatment, targeted treatment

INTRODUCTION

The implementing and promotion of the Antimicrobial Stewardship Programs (ASP) [1] during the last decade into the hospitals is a successful history without any doubt. It improved the control of the infections by the clinicians in a new dialectic context which includes experts in Pharmacy and Microbiology in the generation of fully operative expert teams that are able to provide effective clinical interventions in real time to patients with serious infections or produced by difficult-to-treat bacteria. These interventions also include the safe reduction of antibiotic exposition (de-escalation or reduction of the duration of antibiotic therapy). In addition, have improved registration, control and awareness of the challenges of managing these infections, and established a new educational training in these areas. And with the dissemination of all these measures, an evident improvement in the diagnosis, management and treatment of infectious diseases has been achieved.

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Nonetheless, it has not been possible to demonstrate a clear improvement in the general prognosis of severe infections [2,3], or in the prevention of the appearance and development of the multidrug-resistant (MDR) bacteria [4,5], which are the two main reasons for the creation and dissemination of the ASP.

In general, the ASPs have not changed the primary objective of the old antibiotic policies, which was to restrict the use of antimicrobials (with focus on the new antimicrobials), with the intention of reducing the selective pressure they exert on the development of microbial resistance to antibiotics. With this type of interventions, it has been possible to reduce costs and improve efficiency on a transient and sectorial basis and, eventually, it has been possible to reduce infections by multidrug-resistant bacteria. But they have not substantially improved the prognosis of serious infections [6].

In order to improve the management of the current high morbidity and mortality due to the serious infections, it may be necessary to modify this emphasis on the overuse of antibiotics. Perhaps, it will be necessary to admit with more determination that we need to increase the efficacy of antibiotic therapy in this stage, based on non-restrictive prescribing of new antibiotics and strategies at the time of diagnosis.

The key points for improving the efficacy of the antibiotic therapy. In our opinion the ASP teams could promote initiatives capable of reducing morbimortality associated with serious infections, as:

1. Early and more precise detection of patients with sepsis/severe infections, poor prognosis and high-risk for MDR bacteria colonization in every/all different care setting. This will require the implementation of optimized programs and strategies for Sepsis detection, ideally using new artificial intelligence technologies and computerized programs.

2. Early and more precise microbiological diagnosis, which would enable faster, deeper and better dissemination of

individualized microbiological diagnosis and a more operational knowledge of the local pathogenic flora. This would require the incorporation of technical and strategic innovations in microbiological diagnosis.

3. Improved efficacy of antibiotherapy in both, empirical and targeted treatments; and also the promotion of De-escalation performance and shortening the antibiotic treatment duration [7], which have proven to minimize the development of MDR bacteria. This would require optimized management of new antibiotics agents and new antimicrobial strategies (from antibiotic combination to supplementation with new pharmacological and non-pharmacological products, immunotherapy, phagotherapy, bacterial genetic modification, etc.).

The critical importance of "timing" in these initiatives:

Although in this Review we focus on the importance of timing in the design of the antibiotic strategy, the impact of early diagnosis of Sepsis/Severe Infection and Microbiological Diagnosis is no less important. Therefore, we encourage that all these aspects must always be part of any strategy implemented by the ASP teams in order to attempt a reduction in the morbimortality of Infections.

In the optimization of the antibiotic therapy there are several critical points in which an adequate timing could achieve benefits in the survival of patients with severe infections. On a direct way: 1) In empirical treatment, and 2) In Targeted Treatment and indirectly, in the choice of the moment for 3) De-escalation performance and 4) to curtail antibiotic duration.

TIMING IN EMPIRICAL TREATMENT

When the severity of the patient with suspected infection is greater, it is essential to start antibiotic treatment immediately. There are many studies correlating delayed initiation of empirical treatment with decreased survival. This is a continuous variable, that allows the formulation of a basic principle in empirical antibiotherapy, which is "the earlier it is started, the greater the survival achieved" [8]. Based on the available data, severe infections should be treated within the first hours after diagnosis, and never later than 3-4 h.

This is so important that ASP teams should establish surveillance programs to monitor delays in the initiation of antibiotic therapy in patients with severe infections. The measurement of time from patient admission to the hospital to intravenous antibiotic administration ('door-to-needle time') is a good indicator of promptness or delay of appropriate empirical treatment, and also includes an assessment of the capability of our health system in the early detection and management of sepsis/severe infection. Thus, these indicators would be an achievable and useful tool for improvement of antibiotic management.

The current criteria for Sepsis have a high specificity in the diagnosis of severe infection. But their sensitivity is lower, and there are many patients with severe infections who do not meet these criteria [9,10]. To improve our ability to detect severe infections accelerating or anticipating the initiation of empirical antibiotherapy, with focus again in the most vulnerable patients, new criteria must be adopted. These new criteria, although not sufficiently standardized, has proven to have a good predictive capacity [9,10]. For example, the presence of a systemic inflammatory response syndrome (SIRS), high risk of progression and severity (for instance, a Charlson> 3) and high inflammatory markers (such as CRP > 200 mg/L or Procalcitonin > 5-10 ng/mL) can predict severe infection with high probability [9]. Other criteria such as Age > 65 years, vascular catheters, clinical suspicion of endocarditis, NEWS score, predictive models of bacteremia [10] may contribute in this direction, to facilitate an prompt initiation of empirical antibiotherapy.

Moreover, it would be possible to improve this timeliness if primary care would assume and participate in improving the screening of severe infections in outpatients.

When evaluating these strategies, early initiation of empirical antibiotic therapy in severe infections is a necessary and essential criterion to qualify the treatment as adequate. The other necessary condition is that the choice of antibiotic(s) is appropriate; that is, the antibiotic(s) must be effective (active) against the microorganism causing the infection in each particular patient. Without these two conditions, empirical antibiotic therapy can never be considered adequate. Early and Active is the only choice. Active but Late is associated with worse clinical outcomes, similar to those achieved with Early but Inactive or even Late and Inactive treatment [11,12].

As delay reduces the effectiveness of antibiotherapy, so does the prescription of antibiotics that are not active against the pathogens causing the infection [13]. Surprisingly, in our current clinical practice, the rate of prescribing empirical antibiotic therapy that is inactive or ineffective is very high (up to 20 and 30%) [13–18]. And the rate would be even worse assuming this new strategic concept that appears in recent leading publications: that in severe infections caused by multidrug-resistant bacteria, two active antibiotics improve the survival rate over that achieved with monotherapy [16,19–21]. Furthermore, in the choice of empirical antimicrobials we should to consider several other factors: first of all, the ability of eradicate the infection and its ecological impact, the appropriateness of PK/PD properties to the site of infection, the bacterial inoculum size and the degree of microbial resistance, vulnerability or risk of progression of the patient, and severity of infectious process. Therefore, the optimal empirical antibiotic therapy is considered to be that initiated early, with the highest erradicatory capacity and with the appropriate PK/PD profile, precisely tailored to each individual patient.

For our ASP team, the follow-up of adequate use of empirical treatment has become an important indicator of the use of antimicrobials. And to improve it we have implemented real-time audit programs for all bacteremia and multidrug-resistant isolates in other cultures.

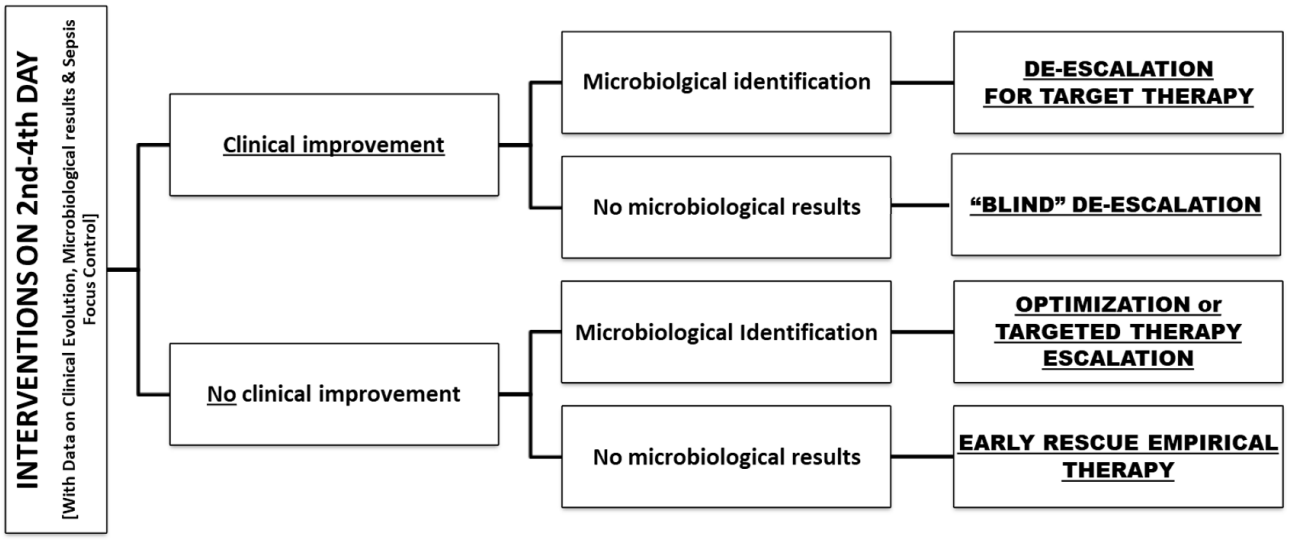

Figure 1 | **Possible Interventions on the 2nd-4th day of antibiotic treatment**

In addition, we adapted our antibiotherapy guidelines, in a timely manner, to the local microbiological map and to the rest of the needs that we have mentioned before.

TARGETED TREATMENT, ACCURACY IN ANTIBIOTHERAPY

The choice of the empirical treatment is only the first step of a complex process of infection management that will require our attention. Then there are still multiple opportunities to further optimize it, to adjust it accurately to the individual characteristics of every infectious process and of each patient.

In antibiotic therapy optimization, the assessment of clinical evolution and the microbiological results are of special relevance, and can already be evaluated typically on the 'third day', between 24 and 72 hours from the start of treatment. And we have here, at this moment, the best opportunity to assess the effectiveness of empirical treatment. The effectiveness of antibiotic treatments is shown very quickly (hours and, therefore, the absence of significant improvement on the third day of treatment (based on the general clinical evolution, the septic focus control, the vital signs, inflammatory biomarkers and other data from complementary tests) is a good predictor of ineffectiveness and poor progression and, consequently, a good reason to reconsider and re-design it uses at that time. The results of microbiological tests (from cultures of clinical specimens and screening of multi-R colonization) allow identification of the etiologic agent causing the infection and, therefore, accuracy of antibiotic treatment (ensuring de-escalation to targeted therapy). The availability of rapid microbiological tests (that are able to provide results within hours) will allow us to reduce that initial period of 'etiological uncertainty' that has an important impact on the prognosis, and therefore contributes to the to the improvement of the clinical outcomes.

The evaluation of antibiotic therapy on the third day is based, accordingly, on clinical evolution data and microbiological results, and should be performed between 24 h and 72 h [9].

Depending on the obtained findings, and with the septic focus successfully controlled (in the event that this requires interventions other than antibiotherapy, such as surgery or the removal of infected prosthetic material, the optimization of antibiotherapy may lead to one of these four options, which may overlap (Figure 1).

De-escalation is a key strategy for antibiotherapy optimization. Generally, defined as the reduction of the initial antimicrobial spectrum based on microbiological results, either by switching from a broad-spectrum antimicrobial to a narrow one, or from combination therapy to monotherapy. In other words, it is no more than the choice of the most appropriate treatment against the identified pathogen, in a phase in which, clinical improvement achieved after an antibiotic 'intensive or induction' phase, would lead to a certain 'maintenance phase', less demanding, in which the reduction or simplification of the antibiotic coverage or potency is possible without negative impact on prognosis, and with ecological advantages (by reducing the duration of exposure to antibiotics and regimens with a critical ecological impact).

Rapid diagnostic microbiological tests and MDR pathogens colonization screenings would allow us to de-escalate from 24-72 h, provided that clinical improvement in the patient has been achieved and empirical antibiotic coverage turns out to be unnecessary [9].

In the absence of microbiological results, de-escalation, in

cases where the clinical evolution is favorable, should be considered [9,22]. It is based on the idea that most of the overall efficacy of antibiotherapy is achieved in the first days of treatment, and once a significant clinical improvement has been observed, a practically complete extinction of pathogenic bacterial inoculum has been done, and microbial regrowth and recurrence of symptoms would not occur in patients without severe immunosuppression, uncontrolled septic foci or prosthetic material with ineradicable inoculums. And this is more likely to be true the more active or effective the chosen of initial empiric antibiotherapy was. In addition, the absence of growth of MDR bacteria in cultures (from clinical samples or in colonization screenings) reduces the need to maintain coverage against them.

For our ASP team, it is a priority to promote and monitor that all patients with severe infections should be assessed for the efficacy of antibiotherapy (based on clinical course and inflammation biomarkers) and microbiological results) between 24 and 72 h after the antibiotic therapy is initiated, allowing an optimization or accuracy of antibiotherapy (Escalation or New empirical rescue therapy, De-escalation -with or without microbiological results, Stopping, if the suspicion of infection disappears).

And this requires economic investments (in the improvement of the healthcare management of severe infections and microbiological diagnosis).

ANTIBIOTIC TREATMENT DURATION

Antibiotic efficacy concerns clinical efficacy (Resolution of symptoms), and could be measured by Time to microbiological eradication (or sterilization of positive microbiological cultures), which under experimental or controlled conditions, would be between 2 and 9 days (according to 'in vitro' studies, microbiological monitoring studies in patients and biological estimates), depending on the bacterial species (e.g., *Escherichia coli 2*-4 days; *Staphylococcus aureus* 4-9 days), the pharmacological or pharmacodynamic properties of Antibiotics (there is a 'Pharmacodynamic Hierarchy' that classifies them according to their activity and eradicatory capacity, and generally places the new antibiotics in the best positions), and the management of these antibiotics (At appropriate doses and based on optimized PK/PD parameters, the time to eradication is reduced; synergistic combination of antibiotics -active against the same bacteria- also decreases time to eradication).

Most of the beneficial effect of appropriate antibiotherapy accumulates in the first 5-7 days. And if the initial antibiotherapy is appropriately optimized, even in the first 2-5 days.

This approach is based on multiple published studies which show us, for example, In vitro, the maximum bactericidal effect is completed on the 7th day (ciprofloxacin vs. BGN) [23]. Biological estimates consider that the time to eradication of *E. coli* is 2-4 days, and of *S. aureus* 4-9 days (compared to 6 months for *Mycobacterium tuberculosis*). Computational biology in experimental models has established that microbiological eradication can be achieved in 3.9 days (with intensified initial treatment -front loading-) and 8.7 days (with standard treatment) [24]. In vivo, rapid eradication of the causal pathogen of severe pneumonia (in BAS cultures) can be observed in most patients [25].

Clinical and microbiological biomarkers of infection and inflammation generally improve in 3-5 days when antibiotherapy is effective [26,27]. There are studies showing significant differences in efficacy, that is, in the time until eradication, between various antibiotics when the comparison is established in those first 2-3 'critical' days of antibiotherapy (meropenem vs. piperacillin/tazobactam [28]; daptomycin vs. vancomycin [29]. In other studies, differences in efficacy are established based on the reduction of the symptom period (moxifloxacin vs levofloxacin) [30].

In the last 20 years, numerous clinical studies were published demonstrating the similar efficacy and safety of 3- to 8-day vs more prolonged (> 10-14 days) antibiotic treatments [31].

On the other hand, the negative ecological impact of antibiotherapy begins after the first few days. Disruption of the ecological balance and overgrowth of MDR flora can occur within the first 2-4 days of treatment, but is significantly delayed with intensive initial antibiotherapy -front loading-, especially if concentration levels of the antibiotic in the septic focus are above the mutations preventive concentration [31–34]. However, when antibiotic therapy is not capable of eradicating the pathogenic microbial inoculum, its prolongation over time greatly increases its ability to select and promote the emergence of resistance. In such a way that the longer the duration of the treatment, the more intense antibiotic activity is required to avoid the emergence of mutations during the treatment [35]. This last point challenges the appropriateness of De-escalation (which reduces antibiotic spectrum when the opposite might be necessary to avoid the emergence of resistance in that scenario. But, in practical terms, the best way to minimize the selection and emergence of resistant microorganisms during antibiotic treatment involves employing a front-loading strategy (early and intensive antibiotherapy, with the maximum achievable eradicatory capacity) and shortening the duration of treatment [36].

Overall, we could assume that practically all common bacterial infections, including severe cases, could be treated successfully for 5-8 days [31,33]. With the exception of certain conditions where the safety of shortening of the duration is not well demonstrated [31,33]:

a) Absence of a rapid and significant clinical response to initial treatment.

b) Major Immunosuppressed patients (neutropenic, cancer under chemotherapy, etc...).

c) Involving infections that affect tissues or structures difficult to access for antibiotics and that cannot be 'withdrawn':

I. Devitalized or abscessified tissues (No control of the septic focus).

II. Bone (osteomyelitis), endocardium (endocarditis), vitreous humor (endophthalmitis)...

III. Prosthetic material, catheters, biofilms…

d) In infections produced by particularly drug-resistant, persistent or latent/quiescent bacteria:

I. *M. tuberculosis* and other infections of slow chronopathology.

II. *S. aureus* (especially MRSA).

III. Non-fermenting gran-negative bacilli, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, etc.

Finally, to implement all these ideas, the ASP team needs to design specific programs and initiatives that place them in the healthcare surveillance and intervention programs, in the development of the local microbiological map and the local Antibiotherapy Guidelines, and in the educational programs. These should be diffused throughout the hospital, starting with the critical areas and extending to the outpatient setting.

CONCLUSIONS

Assuming that the current morbimortality of serious infections is unacceptable, and if we want to contribute to minimize it, we should work on a reorganization of the ASPs that, mainly but not exclusively, promotes an increase in the efficacy of antibiotic therapy and a reduction of its negative ecological impact through improvement of the design of empirical and targeted antibiotherapy (to maximize its efficacy). Numerous studies indicate that improvements can be made in both directions with earlier, more accurate and optimized treatments against the specific infection-causing bacteria in the particular patient, and with the highest possible eradication capacity. The timing of antibiotherapy would be of decisive importance in this design. A very important part of the current and future efficacy of antibiotherapy of severe infections involves the search for earlier antibiotherapies (empirical, targeted and rescue), which should be de-escalated when possible and at the optimum time, and stopped after the shortest time possible with proven efficacy and safety.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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