

# The Reduction in Duration of Antibiotic Therapy as a Key Element of Antibiotic Stewardship Programs

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## Abstract

The incidence and mortality rates of severe infections are still very high. Moreover, the growing threat of bacterial resistance and the progressive reduction of research into new antibiotics, overshadow the future of the fight against infections. We need to preserve the effectiveness of available antibiotics. This can only be achieved if we minimize the development of bacterial resistance. We have sufficient evidence to show that reducing the duration of antibiotic treatment can minimize the potential development of bacterial resistance, without worsening the prognosis of infections. So, we think that the proposal to shorten the antibiotic treatment should become a key element of our antibiotic stewardship programs.

**Keywords:** Antibiotic optimization; Antibiotic de-escalation; Duration of antibiotic treatment; Antimicrobial stewardship programs

## Opinion

### The progressive loss of antibiotic therapy efficacy

Infection control has always seemed like something within our reach, but the truth is that the incidence and mortality rates associated with infections are still very high. Sepsis plays a part in one of two or three hospital deaths [1] and the mortality rates of severe infections are as high as 50% [2,3]. The management of infectious diseases is always complex and the design of effective treatments is very difficult in many situations and for many physicians. Such is the case that there are many published studies that demonstrate how consulting an expert reduces infection-associated mortality rates [4,5]. However, this problem has become more complicated over the past few years as a consequence of antibiotic resistance, the progressive reduction of efficacy margins of available antibiotics and the lower availability of new antibiotics [6]. It is an alarming situation, that must be addressed with more institutional, and therefore, bureaucratic, political and social conviction.

### What can we do? On the way to a new antibiotic policy

To ease this problem, one of the most important options, as far as healthcare professionals are concerned, is the optimization of antibiotic therapy. The development of an active antibiotic policy in healthcare centers, directed by a group of experts, that promotes an improvement of efficacy and a reduction of antibiotic resistance, is quite probably the main challenge an Infectious Disease specialist faces today [7-9].

Achieving a reduction of antibiotic exposure still remains the main objective of any antibiotic policy. There is a well-known relationship between the overall amount of antibiotic exposure and the development of bacterial resistance. It's a complex issue, but until now the main element of antibiotic policies in our hospitals was the reduction of exposure to better antibiotics (which were also the most expensive). This was carried out by restricting the access to their prescription and limiting their indications. This policy did not really consider the patient's prognosis and was frequently posed in dichotomous terms, focused on indication at the start of treatment. It never demonstrated any improvement other than economic savings, and it could theoretically cause a negative impact on antibiotic efficacy and severe infection prognosis. These new and expensive antibiotics that we try to restrict

and protect against bacterial resistance, are also the most effective against severe infections when used as initial empirical treatment, at high doses or prolonged perfusions, and/or in combination therapy [10-26]. So insisting on their restriction in empiric therapy could be useless...and dangerous [27].

Therefore it's imperative to find a way to minimize exposure to antibiotics that does not compromise efficacy.

On the other hand, and in a different way than restrictive methods, the institutional attempt to use pedagogical consults as the only tool to achieve an adequate empiric antibiotic treatment for all infectious syndromes could also be useless and inefficient. Training activities are always needed, but have severe limitations to be applied in clinical practice.

### Antibiotic de-escalation and reduction in duration as a means to reduce antibiotic exposure

We must be realistic and look for interventions and measures that are easier to transmit and easier for physicians to adopt. The scientific community is now accepting that a way of reducing antibiotic use is by adjusting the treatment after the third day, taking into account the antibiogram and the patient's clinical evolution. Early treatment suspension is also an option when the treatment has proven to be quickly effective, the patient has no severe immunodepression or difficult-to-treat microorganisms, bacterial reservoirs or biological sanctuaries with difficult access to antibiotics [7,8,28].

This would mean a new paradigm in antibiotic therapy: intensive initial treatments with better options, focused on attaining optimal

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efficacy and better prognosis. When the patient has improved and we have microbiological results, those antibiotics can be switched for others with less ecological impact or costs and we can finally interrupt the treatment, earlier than we would have until now [28,29].

These types of proposals are easier to accept by physicians that tend to hesitate to replace certain antibiotics, in which they trust, for others when treating a critical patient. Even though they accept their advantages in terms of ecological impact and costs, they feel these antibiotics are less safe [30]. It's easier to accept this proposal to replace, or even suspend, an antibiotic that has already proven its efficacy, the patient's situation has improved and there are no longer doubts about the patient's prognosis.

The only thing that's left if to find the arguments that can confirm that these exposure-reducing strategies (de-escalation and shortening of duration) are safe and do not compromise antibiotic therapy efficacy.

### **Scientific arguments that support de-escalation and shortening of antibiotic therapy duration proposals**

Fortunately, the number of published studies that try to answer these questions has increased over the past year. They allow us to affirm the following aspects, with significant scientific evidence and for the type of patients previously mentioned (without immunosuppression, difficult bacterial infections, antibiotic sanctuaries...):

1) The action and effect of antibiotics occur promptly, must be clinically visible after no longer than 3-4 days and must reach their maximum efficacy after no longer than 5-8 days, depending on the case. There are studies that demonstrate how fast bacteria disappear from the site of infection when they are sensitive to the antibiotics employed [31], as well as how fast inflammatory biomarkers decrease with an effective antibiotic treatment [32]. And last but not least, there are many clinical trials that demonstrate that the same clinical results can be achieved with both shortened and standard therapy strategies. There is no evidence that demonstrates that reducing the duration of antibiotic therapy, even as short as 3 days, leads to worse clinical results. It has been seen that when the evolution of inflammatory biomarkers, such as procalcitonin, is taken into account, antibiotic therapy suspension is safe, no matter how early on the suspension occurs [33-37]. There is additional data that suggests that when the values of these biomarkers, especially procalcitonin, aren't elevated, treatment restraint or suspension is safe [38].

2) We refer to de-escalation as the switch from a broad-spectrum antibiotic to a narrower spectrum agent or the reduction in the number of initially prescribed antibiotics [39-42]. It has proven to be a safe strategy and does not compromise efficacy, when compared to the sustained standard broad-spectrum empirical treatment [43,44]. When we adjust the antibiotic treatment based on the antibiogram, we're really just articulating the need for a pathogen-directed treatment. It's a concept that seems easy enough to transmit, assume and even demand. In order to conduct this treatment adjustment, a culture sample must be taken before empirical antibiotic treatment is initiated. This is an area we must continue to improve. However, de-escalation can also be an option when microbiology results are not available, as long as the patient's clinical condition has quickly improved, the inflammatory biomarkers have decreased significantly, and the variables mentioned before have been controlled. After all, de-escalation strategies support the idea that most of the antibiotic effect occurs during the first 3-5 days of treatment [32,45-48].

3) Unlike clinical efficacy, the induction of resistances to antibiotics is slower and increases over the time of exposure. The longer we maintain antibiotic treatment, the higher the possibility of encouraging and selecting antibiotic-resistant bacteria [49-56]. The other mechanism that causes an increase of resistance is the exposure to subtherapeutic concentrations of antibiotics [49-51,54-56]. This depends on pharmacodynamics, antibiotic activity, and the doses or strategies that are used. This was already described by Fleming shortly after discovering penicillin (Nobel lecture, 1945). We now have studies [49-56], both in vitro and in patients, during and after treatment, that search for changes in colonizing flora, and that show that these changes are associated with specific drugs, strategies and treatment duration. Finally, these publications support the idea that treatments that generate subtherapeutic concentrations at the site of infection and are maintained for longer periods of time have a higher potential for inducing resistance.

### **Can these ideas be put into practice?**

These ideas are establishing a new paradigm of antibiotic therapy that consists of strong and short treatments. They have proven that we can improve antibiotic efficacy against severe infections. To do so, we must incorporate antibiotics with high antibacterial activity into empirical treatments and optimize their dosage to reach target concentrations at the site of infection [28]. These are what are now referred to as "front loading strategies" and "pharmacokinetic/pharmacodynamic (PK/PD) goals". Moreover, as well as increasing efficacy, this strategy reduces the emergence of bacterial resistance during treatment.

However, it is practically impossible to completely avoid the selection of resistant mutants. This selection can be observed after the first 3-4 days of exposure and becomes more intense as long as treatment persists [49-51]. Because of this, the reduction of duration of antibiotic therapy could be an important option to approach the bacterial resistance threat [53].

When we try to put these ideas into practice, the first step would probably be to reduce the duration of antibiotic therapy. This option is the easiest to include in our hospital's antibiotic policy [29]. In our experience, this proposal is accepted by at least 2/3 of healthcare professionals at our hospital and it causes a quick and significant reduction of antibiotic exposure [57]. Physicians who actively participate in antibiotic stewardship programs have the responsibility of knowing, applying and spreading the knowledge that has been collected over the past few years on this subject.

### **Proposals Summary about the short-course of antibiotherapy**

At present, we have enough scientific bases to support the following proposals:

A previous and important safety measure to consider is that the short-course of antibiotic therapy must not be applied to the following: patients with severe immunodepression, with severe infections and/or infections produced by multidrug-resistant bacteria (MRSA, multidrug-resistant *Pseudomonas* spp or *Acinetobacter* spp), patients with a delay in surgical source control, with a prosthetic infection or with infections where antibiotic access is limited. Patients who haven't received an adequate initial treatment (poor design of antibiotherapy or by the presence of large inoculate, or particularly resistant or persistent bacteria) or who don't improve quickly must also be excluded. In these cases, the shortening of therapy must be considered with caution due to lack of evidence.

Safety of therapy shortening has mostly been studied in respiratory diseases (excluding empyema and pulmonary abscess). We can conclude that:

- Community-acquired pneumonia can be treated with only 2-3 days after clinical improvement, and 5 days could be enough (as included in clinical guidelines) [58-66].
- Acute Chronic Obstructive Pulmonary Disease (CPOD) exacerbations can be treated for 5 days [46,67,68].
- Ventilator-associated pneumonia (and bacterial tracheitis) should be treated for no longer than 8 days (as established in Cochrane Library recommendations) [69-73].
- ORL infections should be treated for no longer than 5-7 days (including strep throat if a cephalosporin is used instead of penicillin) [74,75].

When it comes to other infectious diseases, we have less scientific evidence, but we can affirm that the following proposals are safe:

- Non-necrotizing skin infections: 5-10 days [76,77]
- Intraabdominal infections: 3-7 days [78-80]
- Uncomplicated UTI: 1-3 days [81,82]
- Complicated, non-severe UTI: no longer than 7 days [83,84]
- Complicated, severe UTI: we should maintain the standard 2 week treatment because there is no data that supports treatment duration reduction. However, when fluorquinolones and carbapenems are used, we can reduce the duration to 7-10 days [85]. Any other treatments should still be administered for 10-15 days [86-88].
- Acute bacterial meningitis (caused by meningococcus or Haemophilus influenza) could be treated correctly for 7 days [89,90]. If it were caused by pneumococcus, there is less evidence about duration reduction, and it should probably be treated for 10-14 days [91]. Likewise, *Listeria monocytogenes*, *Streptococcus agalactiae* and gram-negative bacilli still may require 3 weeks of treatment.
- Septic Arthritis: For children, if the clinical response is good and the C-reactive protein level normalizes shortly, a treatment of 10 days is sufficient [92].
- Some experiences or reports, with very few patients, suggest that shorter treatments in patients with Bacteremia (7 days) [93,94] or some kind of Endocarditis (14 days) [95-97] could be as effective as standard treatments.

There are also reviews [72,98,99], guidelines [66,80], meta-analysis and systematic reviews [64,65,91,94] that show that the shortening of antibiotic therapy is a safe practice.

Finally, studies have shown that interventions to reduce the duration in antibiotic therapy are effective and lead to significant clinical benefits [57,100-102].

## Conclusions

We have enough scientific evidence to affirm that we can safely shorten the duration of antibiotic therapy in a wide range of infections

and patients. If we accomplish this, we'll be contributing to a reduction of bacterial resistance.

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