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"Off-Label" use of antibiotics in critical patients

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Abstract

In intensive care units, the most prescribed drugs are antibiotics, as result of the high incidence of infections among patients admitted to these units. In medical practice, antibiotic resistance is a phenomenon with dramatic consequences, which has led to the development of new strategies to solve this public health problem, including the use of "off-label" drugs. Classification as an off-label prescription of a drug mainly refers to: unapproved therapeutic indication, formulation, dose (including dose interval), age or unapproved route of administration. The aim of this paper is to present the categories of appropriate "off-label" use of drugs with a detailed description of the principles of use in this regime of antibiotics as mono- or combo-therapy.

Keywords: "off-label" prescription, "off-label" criteria, "off-label" antibiotics

Most patients admitted to intensive care units receive antibiotics for curative or prophylactic purposes for surgery. Antibiotics are among the most prescribed medications in these intensive care units, as infections are frequently present in patients admitted to these medical departments. Severe forms of sepsis occur in approximately 30%, and death occurs in 25% of them, despite the support of maximal treatment [1.2].

On the other hand, the excessive use of antibiotics in medical practice has led to the emergence of numerous strains of bacteria resistant to commonly used antibacterial agents, bacteria that were previously sensitive to the action of the drugs from this group. The emergence of bacteria resistant to multiple antibiotics, multidrug resistant (MDR), for example, strains of *Staphylococcus spp., Proteus spp., Pseudomonas aeruginosa,* led to a call for following and developing new strategies to address this public health problem, including the "off-label" use. [3]

In medical practice, it has often been observed that some drugs prove to be effective for other indications, but not enough studies have been done to rigorously demonstrate the effectiveness for that use. The term "off-label" comes from the English (United States) term "product labeling", being defined as administration in a manner different from that recommended in the marketing authorization but which is more effective in treating a condition [4]. The "off-label" prescription of drugs refers to: unapproved indication, unapproved route of administration, unapproved formulation, unapproved dose, unapproved dosing interval or unapproved age range [4,5,6]. "Off-label" prescribing also includes drugs whose approval in the treatment of a disease has failed or is associated with unacceptable

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side effects or absolute contraindications [5]. ”Off-label” prescribing is controversial, but without this possibility, some patients may be deprived of the chance to be treated.

This paper presents the categories of appropriate ”off-label” use and the ”off-label” use principles of antibiotics and antibiotic combinations in patients admitted to intensive care units.

CATEGORIES OF APPROPRIATE ”OFF-LABEL” USE

The use of ”off-label” medicines should be based on reliable scientific evidence published in the medical literature. Only about 30% of ”off-label” prescriptions are supported by adequate scientific data [7]. Even if ”off-label” prescribing is not illegal and can sometimes be clinically appropriate, it raises some clinical, safety and ethical issues as there are not yet enough rigorous clinical trials, although there are some accurate rather-limited data on efficiency and safety in ”off-label” use. ”Off-label” use may be warranted if there is sufficient evidence (e.g., in vitro activity, pharmacodynamic data, and clinical design studies) to suggest a reasonable overall risk-benefit balance for a given clinical and epidemiological context [8].

A prescription is considered ”off-label” if it meets at least one of the following criteria:

- *Dose:* the prescribed dose exceeds the therapeutic dose mentioned in the package leaflet;
- *Age:* the prescribed drug was contraindicated for the patient”s age or there was no indication for the patient’s age;
- *Route:* the prescribed route of administration is different from that in the package leaflet;
- *Contraindication:* the prescribed drug is contraindicated in certain age groups and / or inadmissible due to lack of clinical trials;
- *Special drug access program:* The prescribed drug is approved for sale, but cannot be obtained by applying the special access program [9].

To date, three categories of ”off-label” use have been identified as appropriate:

- ”off-label” use justified by rigorous clinical and paraclinical evidence;
- use in the context of a formal research proposal;
- exceptional use, justified by individual clinical circumstances, following the meeting of a committee to analyze the patient’s case.

If the use does not fall into any of the categories mentioned above, the use of the drug is not considered appropriate [10].

Regarding the ”off-label” use of antibiotics, a single review was conducted in 2012, which assessed the frequency of use in both adult and pediatric patients, based on the analysis of relevant clinical trials in the PubMed and Scopus databases. Out of a total of 25 studies that met the inclusion criteria, 16 were prospective and 9 retrospective. The target population receiving antibiotics was the pediatric population (15 studies), adults receiving a specific antibiotic (7 studies), critically ill adults receiving 2 antibiotics (2 studies), and the general outpatient population (1 study). The percentage of ”off-label” antibiotic prescriptions among children ranged from 1% to 94%, while the variation was between 11% and 87% for all medicines. In the ”high dose” category, ampicillin and amoxicillin were the most prescribed as ”off-label” antibiotics, with ”off-label” prescriptions up to 96%. The prescription for ”off-label” antibiotics ranged from 19% to 43% in critically ill adult patients, while it ranged from 26% to 36% for all drugs (Figure 1). There were no data available on the most commonly prescribed antibiotics. Only one study reported that 23% of antibiotic prescriptions were ”off-label” in outpatient general care. This study has shown that the rate of ”off-label” prescribing in the population is high, especially in the pediatric age group [5].

PRINCIPLES OF ”OFF-LABEL” USE OF ANTIBIOTICS AND ANTIBIOTIC COMBINATIONS

Taking therapeutic decision should always be based on the best available evidence regarding the effects of a drug and the importance of the risk / benefit balance in its use [11]. The practitioner is free to choose how to treat a patient so that the end result is favorable, but often the contraindications or side effects can be a barrier that does not allow the use of drugs with a primary indication in the treatment of a disease [12].

A key element is to fully inform patients about the appropriateness of ”off-label” prescriptions, with their

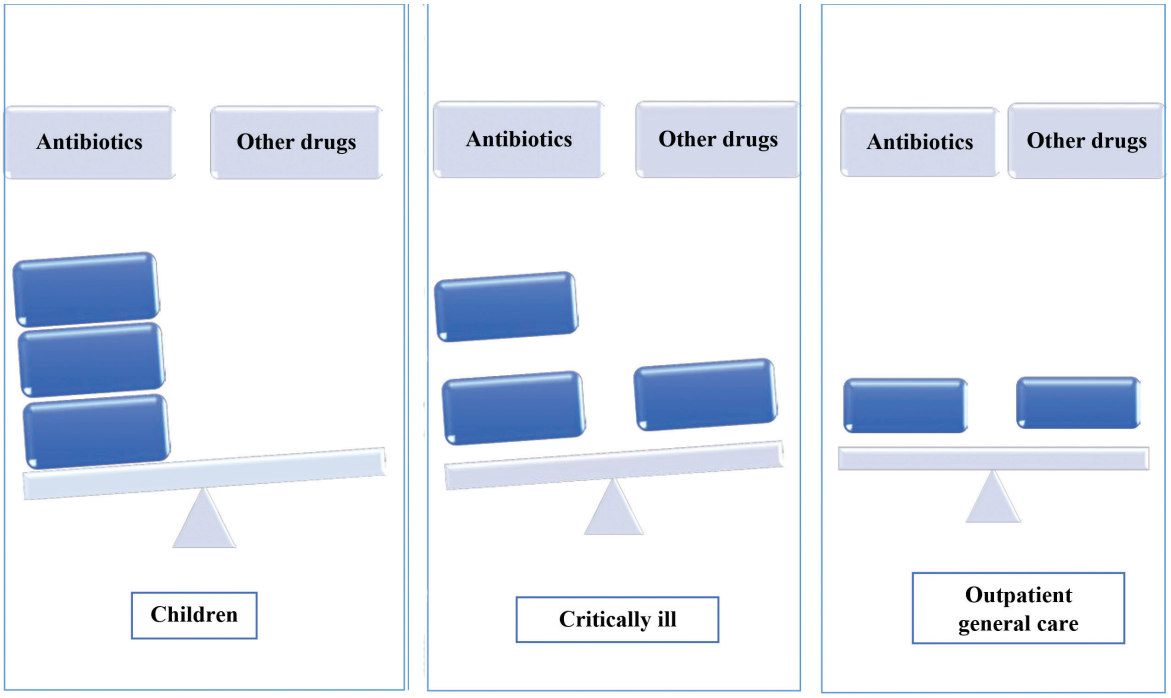

FIGURE 1. Frequency of using "off-label" therapy (after Tansarli et al., 2012)

signed consent. This is an essential element of good "off-label" use practice, given the safety risks involved in using an "off-label" product. In this regard, it is important that the prescribing physician will not be automatically responsible for the negative impact on the patient's health, especially if the "off label" use is mentioned in a professional guide or form.

Some key principles of an "off-label" prescribing recommendation have been established:

1. The presence of a serious or life-threatening condition;

2. The indicated first-line treatment has repeatedly failed or is not available, it is not tolerated, it is less optimal in certain situations, it is too expensive, costs are not reimbursable by the health insurance system;

3. There is no authorized treatment option for this clinical condition.

If "off-label" use is experimental as part of a study, then the patient (or parent / guardian for children and the indiscriminate) should be informed and should provide the signed agreement of consent to participate in the study. Physicians and patients should report side effects and results of "off-label" use. Thus, patients should be monitored to prevent any unwanted situation, requiring close collaboration between the physician and the patient or his family [7].

In addition, some conditions can be used for the "off-label" recommendations, resulting in a good final result from therapeutic point of view:

1. In the case of "off-label" administration of drugs to children, the prescriber must have well-determined skills and knowledge in the "off-label" prescribing of this age group (required to be a pediatrician), considering that this age group differs from adults in the etiology of diseases, pharmacokinetic and pharmacodynamic factors;

2. The "off-label" prescription must be adequate to meet the needs of the individual patient within the resources available at that time. For example, most drugs used in neonatology have not been tested for age and weight, and most doses have been extrapolated from adults and older children;

3. The "off-label" prescription must be rational and clinically appropriate. Therefore, the benefit / risk ratio must be analyzed very carefully, which must always be positive for each patient for whom the "off-label" administration is desired [13].

Any failure to comply the recommendations could lead to serious and sometimes fatal consequences.

Antibiotics are a major class of drugs prescribed worldwide, administered both empirically and for microbiologically proved infections in clinical practice. In addition, due to medical necessity and individuality of cases, sometimes physicians are required to prescribe drugs for ”off-label” indications [5,14]. The marketing authorization is granted for a specific indication or for a set of indications and doses, following rigorous testing, most often based on controlled recorded routes [6].

In the critical patient, admitted to an intensive care unit, the significance of this problem acquires a dramatic meaning as they present a high risk of mortality due to the acute suffered changes, as well as the invasive interventions to which they are most often subjected [4,15,16].

Given the lack of appropriate therapy for patients in intensive care units, the administration of ”off-label” medication in their case aims to reduce the gap between available treatments and optimal therapeutic outcomes [17].

CONCLUSIONS

”Off-label” prescribing of antibiotics is important for medical practice as innovation in basic care is promoted, enabling the development of new evidence-based practices.

Considering that we are in an era of accelerating bacterial resistance and diminishing antimicrobial resources, optimizing existing resources for antibiotic therapy is an increasingly important consideration for clinicians around the world.

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