Magna Scientia Uceva (2022) 2:2, 149- 156
ISSN:2805-6884 e-ISSN:2805-6701
https://doi.org/10.54502/msuceva.v2n2a1

Reflection Research Article

Medicine

Avoiding pitfalls in antibiotic therapy: the antibiotic stewardship approach

Enfoque de administración de antibióticos: Evitando las trampas en la terapia con antibióticos

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First draft submitted:
18-08-2022
Accepted for publication:
11-09-2022
Published on line:
13-12-2022

Key words:

ABS interventions; antibiotic policies; clinical practice; dosing regimen; ICU; Multi Drug Resistance (MDR); severe side effects.

Palabras clave:

Intervenciones ABS; políticas de antibióticos; práctica clínica; régimen de dosificación; Resistencia a múltiples fármacos (RMF); UCI.

Citation:

Huppertz Thyssen M.H. Rodríguez Saavedra C. Avoiding pitfalls in antibiotic therapy: the antibiotic stewardship approach. *Magna Scientia UCEVA* 2022;2:2 149-156. *https://doi.org/10.54502/msuceva.v2n2a1*

Abstract

The aim of this reflection is to determine the effectiveness and safety of ABS interventions. A strong correlation between antibiotic overuse and the growing worldwide resistance, but also with individual side effects is well established and should open the door to a more personalized approach to anti-infective therapies. Antibiotic resistance is a global public health challenge and is recognized as a global threat to human health by national healthcare agencies, governments, medical societies and the World Health Organization (WHO). The anticipated clinical scenario of Pan- Drug – Resistant (PDR) bacteria is accelerated by antibiotic overuse. In fact, multi- drug – resistance (MDR) is already the cause of severe infections, complications, longer hospital stay and increased mortality in most of the countries. Herein, the techniques of an Antibiotic Stewardship Approach and their stepwise implementation are summarized and highlighted. There is often a general lack of understanding on how to choose the right antibiotic at the right time and in the right dose. This article discusses general principles like the best choice and use of different antibiotic classes, a better use of beta- lactams according to principles of pharmacokinetics, avoidance or limitation of unnecessary combination therapies, shorter courses of therapy without any disadvantage in infection control and the value of PCT monitoring. We hope to contribute to the promotion and implementation of these important therapeutical principles, aiming at the reduction of unnecessary or wrong antibiotic therapies and, so, at the decrease of side effects, mortality and further resistance.

Resumen

El objetivo de esta reflexión es determinar la efectividad y seguridad de las intervenciones ABS. Está bien establecida una fuerte correlación entre el uso excesivo de antibióticos y la creciente resistencia mundial, pero también con los efectos secundarios individuales, y debería abrir la puerta a un enfoque más personalizado de las terapias antiinfecciosas. La resistencia a los antibióticos es un desafío de salud pública mundial y las agencias nacionales de atención médica, los gobiernos, las sociedades médicas y la Organización Mundial de la Salud (OMS) la reconocen como una amenaza mundial para la salud humana. El escenario clínico anticipado de bacterias Pan-Resistentes a Medicamentos (PDR) se acelera por el uso excesivo de antibióticos. De hecho, la multirresistencia (MDR) ya es causa de infecciones graves, complicaciones, estancias hospitalarias más prolongadas y aumento de la mortalidad en la mayoría de los países. En este documento, se resumen y destacan las técnicas de un enfoque de administración de antibióticos y su implementación gradual. A menudo hay una falta general de comprensión sobre cómo elegir el antibiótico correcto en el momento correcto y en la dosis correcta. Este artículo discute principios generales como la mejor elección y uso de diferentes clases de antibióticos, un mejor uso de betalactámicos de acuerdo con los principios de farmacocinética, evitar o limitar terapias combinadas innecesarias, ciclos de terapia más cortos sin ninguna desventaja en el control de infecciones y el valor de seguimiento del PCT. Esperamos contribuir a la promoción e implementación de estos importantes principios terapéuticos, con el objetivo de reducir las terapias antibióticas innecesarias o incorrectas y, por lo tanto, la disminución de los efectos secundarios, la mortalidad y la resistencia adicional.

Introduction

Worldwide, increasing resistance against antibiotics is a big clinical issue in our daily work, especially in the ICU. Multi Drug Resistance is not limited to India and the Middle East anymore, but it is emerging in Europe, especially in south-eastern countries. There is not only a problem of Multi- Drug - Resistant (MDR) bacteria with Extended- Spectrum- Beta- Lactamases (ESBL) but meanwhile of Extended- Drug -Resistant Bacteria (XDR) with carbapenemases – up to 66.9% of infection isolates in Greece. [1] Pan-Drug-Resistant- Bacteria (PDR) with resistance against any known antibiotic exist [2]. This development had already been foreseen by Sir Alexander Fleming in 1945 [3]. The fact that there has been very little development of antibiotics with new mechanisms of action due to a lack of economic incentives during the last 15 years, worsens the situation.

Antibiotic stewardship

A strong correlation between antibiotic overuse and the growing resistance is well established, in accordance with the saying "the more you use it, the quicker you lose it." As 2/3 of nosocomial infections are endogenous, we select MDR/XDR bacteria by antibiotics and spread it on other patients by a lack of hand hygiene. With the rise of Carbapenem- Resistant Enterobactericeae, the increasing use of second- line treatment options will induce new resistances. International and German studies show that 20- 50% of antibiotic therapies in hospitals are inappropriate. In up to 20% of antibiotic therapies severe side effects like Clostridium difficile infections (CDI) occur [4,5].

To impede the spread of resistance, many interventions were started in the past 10 years, summarized as "Antibiotic Stewardship Programs." ABS aim to "preserve the miracle of antibiotics"[6], reduce the side effects of antibiotic therapies, as well as morbidity and mortality, shorten antibiotic therapies, hospital stay and minimize costs. The figure 1 shows the plainest definition of this approach.

General structures and interventions of Antibiotic Stewardship (ABS)

To reach its goals, ABS implements structures and interventions summarized by the keywords: research; education and enablement; restriction and pre-approval (antibiotic policies, SOPs); surveillance. Between 2007 and 2018, several editorials and guidelines have been published [7-11].

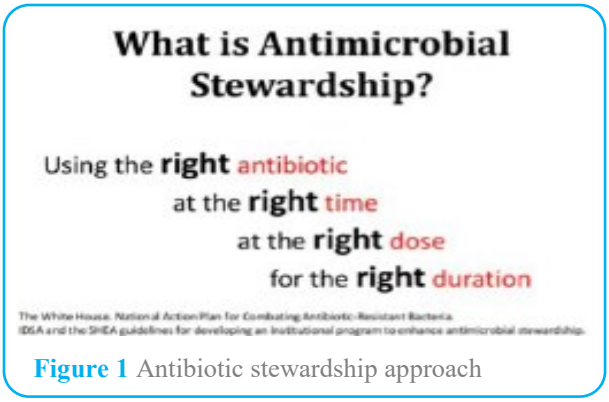

Figure 1 Antibiotic stewardship approach

Select a team

ABS expert, physician, clinical pharmacist, clinical microbiologist, approval and support of hospital administration, go to the bedside, perform multidisciplinary rounds and councils.

Obtain baseline information on antimicrobial use

Consider the following baselines: *i*) institutional pathogen spectrum and *ii*) institutional susceptibilities.

Density of use

Monitor RDD (Recommended Daily Doses)/100 patient days.

Implementation of antibiotic prescribing policies

Standard operating procedures for the environment, according to the specific pathogen spectrum and susceptibilities. Implement standard length of therapy and write down the stop date when start the process implementation.

Restriction and pre-approval; Monitoring

Adherence to SOP (Point Prevalence Analysis).

Audit and feedback; Education/ Enablement

Appropriate use.

ABS time out on day 3

Stop? Change? Continue? How long? Cultures?

De-escalation

Clinical improvement/ results of culture.

Surveillance of nosocomial infections, benchmarking of NI and density of antibiotic use

Consider to carry out the benchmarking with comparable hospitals (national programs). It is of special interest to initiate an ABS approach in the ICU due to the high density of antibiotic use. Detailed descriptions of ABS implementation in the ICU have been published [12-14].

Implementing an antibiotic stewardship program is effective and save

A meta- analysis of 32 trials investigating the effect of antibiotic stewardship, shows a significant reduction of MDR gram-negative bacteria, MRSA und CDI [15]. Thus, there is evidence for decision makers that the implementation of ABS interventions reduces the medical and economic burden of infections with antibiotic-resistant bacteria and CDI in hospital inpatients. In a 2017 Cochrane database review of 58 RCTs and 163 NRS, the authors found an increasing compliance to prescribing policies, a decreasing of unnecessary antibiotic use, a shorter duration of treatment (-1.95 d in 14 RCT), a reduced length of hospital stay (-1.12 d in 15 RCT) and reduced incidences of CDI, MRSA, MDR gram-negatives. All these findings were statistically significant. There is a high-quality evidence (28 RCT, 15827 patients) that implementing the afore-mentioned interventions will reduce antibiotic use without adversely affecting mortality [16].

The ABS approach in daily routine. Pitfalls to avoid

No prolonged perioperative prophylaxis

Perioperative antibiotic prophylaxis (POP) is always "single shot only". Some (low- quality) evidence suggesting benefits of a prolonged POP exists only in cardiac surgery. For any other clean or clean-contaminated procedure there is evidence and the firm recommendation not to give additional prophylactic antimicrobial doses after closing the surgical incision, also if the patient has a drain in place [17]. Antibiotics should be given repeatedly only during surgery, in accordance with the duration of the procedure and the half-life- time of the substance. Broad- spectrum antibiotics should never be used for POP. Though this is clear and simple, we know it is one of most frequent inappropriate uses of antibiotics in clinical practice [4,5]. It is useful to implement a written policy (SOP) with the surgical partners and to monitor the adherence.

Time-dependence of beta- Lactams, prolonged infusions

The PK- PD issues are relevant for the clinical use of beta- lactams in critically ill patients. Efficacy is related to fT> MIC. 100% fT > MIC of the dosage interval is the optimal exposure in critically ill patients [18]. Several meta-analyses between 2015-2018 have addressed the question whether the difference between classical bolus infusion, prolonged infusion (>3hrs) or continuous infusion is of clinical relevance. A recent high quality- evidence (22 RCT, 1876 patients) meta- analysis by Vardakas et al. [19] demonstrated that prolonged or continuous infusion of Piperacillin- Tazobactam and Meropenem provides significantly better survival than bolus infusions (RR 0.70; 95%CI 0.56- 0.87). For cephalosporins, statistical significance was not reached. There is no evidence whether prolonged or continuous infusion is better. The difference in survival was more significant in gram-negative than in gram-positive infections, in MDR than in highly susceptible bacteria and when APACHE score was > 22. Thus, for severe infections, low susceptibility and on the ICU, prolonged infusions of Pip-Taz and Meropenem after a loading bolus are recommended. The use of continuous infusions leads to problems of drug- stability and incompatibility. Therapeutic Drug Monitoring (TDM) should be available as you risk the antibiotic serum level being lower than MIC all the time (fT > MIC=0) (see figure 2).

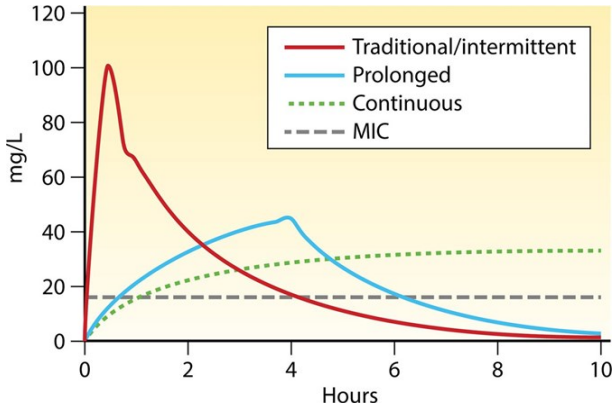

Figure 2 Prolonged /continuous Beta Lactam infusion

Individualized dosing may be the key in the critically ill: TDM

It has been shown that critically ill patients may suffer from inadequate antibiotic exposure because of physiological changes as altered fluid status, augmented renal clearance, extracorporeal circulation, and impaired renal / hepatic function [20]. The European Committee on Antimicrobial Susceptibility Testing has recently (1.1.2019) changed its definition of "I" in the antibiogram from "intermediary" to "susceptible, increased exposure". These theoretical approaches are relevant to the problem of "hit hard" and "get to the point" of antibiotic therapy. TDM is well established for Vancomycin (AUC/MIC is decisive) and aminoglycosides (Cmax/MIC is decisive), with measurement of through- and peak- levels to establish low toxicity and efficacy, but not yet extensively available for Pip-Taz and Meropenem. Yet, it may be useful in the critically ill or in morbidly obese patients [21, 22] (see figure 3).

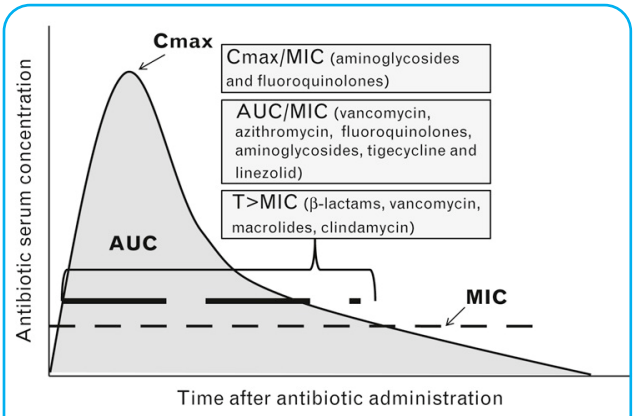

Figure 3 Antibiotic concentration at the site of infection

From figure 3, can be noted that a microorganism is categorized as "susceptible, increased exposure" when there is a high likelihood of therapeutic success due to an increasing agent exposure by adjusting the dosing regimen or by its concentration at the site of infection.

The role of fluoroquinolones (FQ)

As FQ have a big intracellular volume of distribution they are less susceptible to ICU- related changes in the volume of distribution than the hydrophilic beta-lactams. This seems ideal to address the afore-mentioned problems. But FQ are clearly related to the increasing incidence of MRSA and ESBL, as they are excreted with the sweat on the skin and contribute to inducing bacterial resistance. Furthermore, Ciprofloxacin shows low activity against *S. aureus* and there is an increasing resistance of *E.coli* in Europe (ECDC). Finally, many warnings about side effects have been issued between 2016 and 2018, so that they may no longer be considered as first choice substances [23-26].

Class 3 cephalosporins and the correlation to CDI and ESBL incidence

In many countries Ceftriaxone is used as first-line therapy for moderate-severe CAP despite its poor activity against *S. aureus*. The density of use of class 3 cephalosporins correlates strongly with the incidence of ESBL and CDI. There is recent evidence that this might be an explicit problem of Ceftriaxone because of a 50% not-metabolized hepatobiliary excretion with very high bowel concentrations. This leads to selection of resistant bacteria. Cefotaxime proved to be better in a clinical trial [27] and in microbial research [28] and may also be preferable with respect to the afore-mentioned problems of individual dosing range and fT>MIC (3x1g -6x 2g/d).

Shorten antibiotic therapy courses

A lot of high-quality evidence demonstrates that shortening antibiotic therapy courses is a safe and useful ABS intervention, even in gram negative sepsis [29-33]. Nevertheless, there are exceptions like osteomyelitis, spondylodiscitis, endocarditis or *S. aureus* bacteremia (see table 1).

Table 1 Infections for which short course therapy has been shown to be equivalent in efficacy to longer therapy

Disease	Treatment, Days	
	Short	Long
Community acquire pneumonia	3-5	7-10
Nosocomial pneumonia	≤ 8	10-15
Pyelonephritis	5-7	10-14
Intraabdominal infection	4	10
Acute exacerbation of chronic bronchitis and COPD	≤ 5	≥ 7
Acute bacterial sinusitis	5	10
Cellulitis	5-6	10
Chronic osteomyelitis	42	84

Combination treatment: De-escalate

Even the 2016 surviving sepsis campaign guidelines [34] state early narrowing of antibiotic therapy, once the patient improves or the pathogen is identified. A prospective observational study [35] and a systematic review of 2 RCT and 12 cohort studies [36] found that de-escalation of empirical therapy in the ICU leads to lower mortality and was a protective intervention. Even in uncomplicated *S. aureus* bacteremia (MSSA and MRSA) the ARREST trial [37] did not detect any benefit (but more adverse effects) of adjunctive rifampicin, as long as there was no non-removable foreign body with the risk of biofilm. Investigating bloodstream infections with carbapenemase- producing Enterobactericeae the increment (retrospective cohort) study suggest that only critically ill patients with a high mortality score enjoyed improved survival from combination therapy [38].

PCT

Subject to controversial data and discussions for many years, PCT is no “magic bullet”. But there is recent evidence from a meta-analysis (26 RCT, 3336 patients PCT guided therapy, 3372 patients control), that PCT- guidance may not only be safe to shorten antibiotic therapies in critically ill patients [39], but currently decreases mortality rate [40]. The current Surviving Sepsis Guidelines (2021) recommends PCT for the indication of antibiotic therapy guidance, along with clinical signs, but not for the diagnosis of sepsis/septic shock [41].

Conclusion

An Antibiotic Stewardship Approach is mandatory to maintain antibiotic effectiveness and to face the worldwide increasing multi-drug resistance of bacteria. In this reflection, we highlighted the evidence that ABS interventions are safe, useful and effective. In order to deal adequately with the scenario, it is necessary to create an interdisciplinary team, to consent and implement local guidelines and to perform surveillance, audits and feedback. Implement an antibiotic time out on day 3 for any therapy and define the length of therapy right from the start. It is highly recommended to use penicillin- derivates first line, but for example, in *Pseudomonas* infections, BLI is not always necessary. Avoid carbapenems whenever possible to prevent the further spread of capapenemases. The use of FQ should be second line only due to extensive increase in CDI and ESBL as well as several warnings and restrictions. With regard to CDI cefotaxime might be better than ceftriaxone due to different excretion kinetics. To improve pharmacokinetics (get to the point) there is sufficient evidence to use prolonged infusions for piperacillin-tazobactam and meropenem. therapeutic drug monitoring (TDM) is mandatory for vacomycin and aminoglykosides and may be useful for β-Lactams in selected critically ill patients. De-escalate as soon as possible according to microbiological results and clinical improvement. Combination therapy should be performed only in septic shock and under special conditions and should not be a routine approach. It is safe to shorten antibiotic therapies for nearly all indications. Finally, PCT guidance can safely shorten antibiotic therapies and even reduce side effects and mortality.

Consent for publication

The authors read and approved the final manuscript.

Competing interest

The authors declare no conflict of interest. This document only reflects their point of views and not that of the institution to which they belong.

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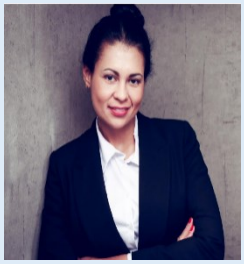

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