








LETTER TO THE EDITOR

PRAT tool: a harmonization of antimicrobial stewardship program interventions

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Abstract

Objective: The Antimicrobial Stewardship Program (ASP) in hospitals aims to promote the rational use of antimicrobials, providing better results to patients (increasing effectiveness and decreasing the risk of adverse events), hospital epidemiology (impact on levels of microbial resistance), and enable cost-effectiveness studies. Therefore, a tool (called PRAT– antimicrobial therapy-related problem) is suggested in this paper. This unvalidated tool is the initial step towards organizing the antimicrobial therapy-related interventions to improve the use of this drug class, mainly by suggesting a harmonized registry process of ASP interventions.

Methods: Therefore, this work presents the PRAT tool, developed based on the 10 years' experience of ASP at Pequeno Príncipe Hospital, inspired by the classification for drug-related problems of the Pharmaceutical Care Network Europe and according to a collaborative work using the Delphi technique. **Results:** This tool allows the identification and exact description of the antimicrobial therapy-related problem in 17 domains and 67 subcategories. Based on this identification, it suggests how to classify this problem (effectiveness, safety and need/indication) and what interventions can be conducted. **Conclusion:** This tool has the potential to establish a profile of antimicrobial-related problems, allowing prioritization to be visualized through the most (and least) interventions made in a given period, and might be useful in improving the quality of care through settings, by means of targeted educational interventions. Furthermore, if there is a harmonization of terminology for the classification of antimicrobial therapy-related problems, other hospitals can adopt it, and so the tool can improve research and comparison between institutions (benchmarking).

Keywords: Anti-infective agents; Hospitals; Drug therapy.

How to cite

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The concept of the Antimicrobial Stewardship Program (ASP) was first introduced by John E. McGowan Jr and Dale N. Gerding in the USA, and was then included in 1997 in the guidelines of the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) for the prevention of antimicrobial resistance in hospitals. ASP refers to a program or series of coordinated interventions

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designed to improve and measure the appropriate use of antimicrobial agents in a health institution, promoting cost savings, optimizing therapeutic results and reducing antimicrobial resistance¹⁻³.

However, an additional step is required for ASP: without one harmonized classification system of antimicrobial-related problems, it will be difficult to measure the attributable clinical and economic benefits of such programs. This classification has the potential to define a profile of the real antimicrobial therapy-related problem of health institutions.

Harmonization implies making different people, plans and situations suitable for each other, so they can work together more easily⁴. From this semantic standpoint, harmonization was one of the main legacies of the Centers for Disease Control (CDC) and Clinical and Laboratory Standards Institute (CLSI)⁵. In 1977, CDC, CLSI and other entities defined the Certified Reference Materials (CRMs) and Reference Measurement Procedures (RMPs) for laboratorial investigations of infectious diseases. Without CRMs and RMPs, there would not be standards for appropriate diagnosis and treatment of infectious diseases, which is the foundation for the ASP: "correct drug for the correct bug"^{6,7}.

All countries have generally come to the consensus that ASP can promote the better use of antimicrobial agents^{8,9}. Van Dijk et al.⁹ suggested that accurate descriptions of interventions, implementation strategies and inclusion of behavioral aspects should be priorities to improve the scientific evidence in antimicrobial program.

Furthermore, structured and standardized classification systems that are considered comprehensive and easy to apply to pharmacotherapeutic problems, with little time spent in daily clinical practice are rare¹⁰.

It is necessary that this classification is comprehensive and easy to apply, given the reduced time that professionals have for registration activity, and, preferably, does not compromise the daily clinical practice¹⁰.

A standardized classification with high acceptance among ASP professionals and researchers would increase knowledge about the process and the results⁸. To our knowledge, there are no specific classifications for problems and interventions with antimicrobials, therefore, our objective is to present a tool that classifies these problems, which was developed based on the long experience of the ASP of Pequeno Príncipe Hospital (HPP) and which has the potential to be used by other institutions that adopt an antimicrobial management program.

Accumulating experience in the observation and detailed description of a series of antimicrobial therapy-related problems, associated with the consolidation of the ASP, and creation of a field of action (Antimicrobial Stewardship) of the Multiprofessional Residence in Child and Adolescent Health, the ASP-HPP team improved the harmaceutical Care Network Europe (PCNE)¹⁰ classification locally by describing subcategories with specific problems with antimicrobials, detected daily and over more than 10 years of service experience.

A collaborative work with key staff from the hospital allowed a stepwise development of the tool and is described as below using a pragmatic approach:

- 1) An initial evaluation of the most common interventions and antimicrobial-related problems found in ASP practice.
- 2) More than 5 years of discussions to define and set the tool, involving five pharmacists, an infectious disease physician and an Infection Control Team.
- 3) Validation of the tool is ongoing, and a large database with more than 10,000 interventions is being cleaned and will be soon analyzed.

The PRAT (antimicrobial-related problem) tool is presented in Table 1. This tool has two drivers: a) identification of the general problem domain and its specific problem related to the use of an antimicrobial; b) and their respective conduct (intervention) to improve drug therapy for infections.

Table 1. Systematization of codes for pharmacotherapeutic interventions associated with antimicrobials

Code	Primary domain of the problem identified	Subcode	PRAT Description	Suggested intervention	Classification of the problem
1	Prescribed dose	1.1	Subdose based on literature and/or protocol	To increase dose	E
		1.2	Subdose according to the ATM serum level	To increase dose	E
		1.3	Subdose based on creatinine clearance or edema/obesity	To increase dose	E
		1.4	Overdose based on literature and/or protocol	To decrease dose	S
		1.5	Overdose according to the ATM serum level	To decrease dose	S
		1.6	Overdose based on creatinine clearance or edema/obesity	To decrease dose	S
2	Frequency	2.1	Increased frequency (shortest interval)	To decrease frequency (to increase the interval)	S
		2.2	Decreased frequency (longest interval)	To increase frequency (to decrease the interval)	E
3	Route of administration	3.1	Not appropriate route of administration for the clinical condition	To replace route	E or S
		3.2	Loss of venous access or patient with criteria to start antibiotic switch therapy	To perform switch therapy (from IV to Oral)	E or S
		3.3	Loss of venous access or patient with criteria to start antifungal switch therapy	To perform switch therapy (from IV to Oral)	E or S
4	Dose form	4.1	Not appropriate dosage form for the route of administration	To replace dosage form	E or S
		4.2	Intolerance due to medication palatability	To change dosage form/to administer with food/ other	E or S
5	Unnecessary medication	5.1	Patient without infection and using ATM (empirical initial use)		N/I
		5.2	Extended time of antibiotic therapy		N/I
		5.3	Extended antibiotic prophylaxis	To suspend ATM	N/I
		5.4	Patient with unnecessary ATM association based on culture or clinic results		N/I
6	<i>Inadequate pharmacotherapy</i>	6.1	Microorganism resistant to the ATM according to antibiogram	To replace ATM	E
		6.2	Empirical therapy not consistent with epidemiology or laboratory/images results	To replace ATM	E or N/I
		6.3	Patient with previous allergy to the ATM	To replace ATM	S
		6.4	ATM off label use with adverse event/adverse reaction occurrence	To replace ATM	S
		6.5	Subtherapeutic serum dosage maintained after ATM dose adjustment	To replace ATM	E
		6.6	Microorganism unresponsive to ATM or patient with no clinical response	To increase dose or replace ATM	E
		6.7	ATM without tissue penetration into the infectious site	To increase dose or replace ATM	E
		6.8	ATM with <u>narrow-spectrum</u> activity for the patient's clinical condition or culture result	To perform ATM escalation	N/I
		6.9	ATM with <u>broad-spectrum</u> activity for the patient's clinical condition or culture result	To perform ATM de-escalation	N/I
		6.10	Worsening of kidney or liver function using ATM	To replace ATM	S
		6.11	Therapy not consistent with the institutional protocol	To replace ATM	N/I

Table 1. Continued...

Code	Primary domain of the problem identified	Subcode	PRAT Description	Suggested intervention	Classification of the problem
7	Insufficient pharmacotherapy	7.1	Patient with previous allergy to the ATM	To start or combine antibiotic	N/I
		7.2	Patient with <u>no</u> coverage for Gram-negative bacteria and with clinical or laboratory indication	To start or combine antibiotic	N/I
		7.3	Patient with <u>no</u> coverage for viruses or fungi or parasite and with clinical or laboratory indication	To start or combine antiviral/ antifungal/ antiparasitic	N/I
		7.4	Patient with <u>no</u> surgical prophylactic ATM	To start antibiotic prophylaxis	N/I
		7.5	Patient with immunodeficiency or other justified clinical condition without prophylactic ATM	To start antibiotic prophylaxis	N/I
		7.6	Early suspension of ATM (without clinical or microbiological cure)	Extend therapy	E
		7.7	Patient without cover for anaerobic bacteria and with clinical or laboratory indication	Start or combine ATM	N/I
8	Dilution	8.1	Volume of the infusion solution not prescribed (NS 0.9% or D5NS)	To guide prescription of ATM volume of dilution	S
		8.2	Increased volume of dilution	To decrease volume of dilution	S
		8.3	Decreased volume of dilution	To increase volume of dilution	S
		8.4	Dilution without stability for the proposed infusion time	To guide diluent change	E
		8.5	Inadequate diluent for the clinical condition	To change diluent	S
9	Infusion time/rate	9.1	Extended infusion time	To decrease infusion time	E
		9.2	Decreased infusion time	To increase infusion time	S
		9.3	Absence of infusion time prescription	To prescribe infusion time	S
10	Therapeutic ineffectiveness	10.1	Use of ATM without effect in a patient with confirmatory examinations of infection to which the microorganism is susceptible	To replace ATM	N/I
11	Interaction drug-drug or drug-food interaction	11.1	Risk of decreased ATM effectiveness	To change the schedule or replace ATM	E
		11.2	Increased risk of ATM reaction or toxicity	To change the schedule or replace ATM	S
12	Physical-chemical incompatibility	12.1	ATM incompatible with diluent or medication	To change schedule or diluent or access route	E
		12.2	Insufficient venous access number for pharmacotherapy	To change venous access	E
13	Drug administration	13.1	Patient does not receive ATM due to prescription or administration problems	To request ATM prescription or to request ATM dose	E
		13.2	Loss of stability due to delay in ATM administration	To change ATM and guide the team	E
		13.3	Delay in administration time according to protocol	To investigate the cause and report	E
		13.4	Inadequate scheduling of dialysable medication	To investigate the cause and report	E
		14.1	Lack of renal and/or liver or other system functions follow-up	To request examination	S
14	Laboratory or imaging tests to monitor the therapeutic response	14.2	Absence/need for hemogram, hemoculture and/or cultures	To request examination	S or E
		14.3	Lack of ATM serum level	To request examination (serum dosage)	S or E
		14.4	Absence of rapid diagnostic tests	To discuss the request for the examination with the doctor	S
		14.5	Absence of imaging tests and graphic methods	To discuss the request for the examination with the doctor	S or E

Table 1. Continued...

Code	Primary domain of the problem identified	Subcode	PRAT Description	Suggested intervention	Classification of the problem
15	Device	15.1	Infected catheter without possibility of lock therapy	To consider catheter removal	S
		15.2	Infected catheter with possibility of lock therapy	To start lock therapy according to the protocol	N/I
		15.3	Absence of prophylaxis in patients with long-term catheter according to the protocol	To start taurolidine	N/I
		15.4	Device obstruction	To remove device or clearance measures	N/I
16	Doctor's prescription	16.1	Typing error (dose, unit, route)	To correct dose prescription	S or E
		16.2	ATM prescription duplication	To suspend one of the prescribed ATMs	S
		16.3	Absence of dose prescription or medical prescription	To prescribe dose	E
17	Adverse reaction	17.1	Risk of adverse reaction to ATM (eg: leakage, allergy, kidney damage)	To start premedication and/or hydration	S
		17.2	Reaction with oral ATB predicted or not in package insert and clinically significant	To transition ATM oral to IV or replace ATM	S
		17.3	Reaction with oral ATM predicted or not in package insert and clinically significant	To suspend or replace ATM IV	S

Note: ATM, antimicrobial; IV, intravenous; N/A, not applicable; PRAT, antimicrobial therapy related problem. * Impact refers to a didactic classification to attribute whether the pharmacotherapeutic intervention was related to the ATM use (or not) necessity/indication (N/I), the ATM effectiveness (E) or the ATM safety (S), which means, whether the PRAT caused or could cause an adverse event to the patient.

This tool has 17 categories and 67 subcategories as demonstrated in Table 1. The categories are called the primary domain of the identified problem and are as follows: prescribed dose; frequency, route of administration; dose form, unnecessary or inappropriate medication; inadequate pharmacotherapy; insufficient pharmacotherapy; dilution, infusion time/rate; therapeutic ineffectiveness; interaction drug-drug or drug-food interaction; physical-chemical incompatibility; drug administration; laboratory or imaging tests to monitor the therapeutic response or toxicity; device, doctor's prescription (items related to the process); and adverse reaction.

The 67 subcategories are the description of the PRAT, that is, they are all the specific and possible problems encountered with antimicrobials described in detail. These subcategories can have the consequence of not reaching the desired therapeutic objective (compromising effectiveness) or the appearance of undesirable effects (compromising safety) or even unnecessary or not indicated use (need / indication).

In order to characterize the problems addressed in the tool, in the PRAT table it classification of the problems is suggested, allowing the interventions to be prioritized in a future step. The problem can compromise the following aspects:

- **Effectiveness:** problems that will affect the therapeutic effect of the treatment, such as underdose (subcode 1.1, 1.2 or 1.3)
- **Safety:** refers to the potential for adverse reaction or toxicity, such as overdose interventions (subcode 1.4, 1.5 or 1.6)
- **Need/indication:** this relates to whether the patient needs the antimicrobial or not or whether or not the use is indicated, according to clinical and laboratory parameters, such as, for example, prolonged antibiotic therapy time (subcode 5.2) or a patient without coverage to determine the microorganism (subcodes 7.1, 7.2 and 7.3).

In addition, the PRAT table also presents the respective proposals for pharmacotherapeutic interventions that are recommended for each specific problem. These proposed interventions

(related to 17 domains and 67 subcategories) are according to identified PRAT and are performed to improve the patient's clinical results.

A key point in the design, evaluation and implementation of the proposed pharmacotherapeutic intervention is the acceptability by the healthcare team (mainly medical and nursing staff). Thus, it is essential that, based on the identification of the PRAT and its respective intervention, the degree of acceptability of this conduct (intervention) carried out by the ASP team is measured, being classified as "accepted", "not accepted with justification" and "not accepted without justification".

Furthermore, this classification system has some considerations and follows these examples:

- I. Pharmacotherapeutic counseling is not addressed by our tool, because it is different from pharmacotherapeutic intervention. The intervention is a recommendation initiated in response to a drug-related problem in an individual patient at any stage of the medication process, whilst the counseling is performed prior to the occurrence of PRAT, in order to prevent this problem.
- II. Intervention is not a group of activities, however the professional acts to improve the use of antimicrobial agents or infectious diseases diagnosis and monitoring for every single patient.
- III. Different from that previously suggested by other authors¹¹, from our PRAT system perspective, an intervention is not a formulary restriction, but is a specific and punctual action during the process of using the antimicrobial, such as the suggestion to interrupt or replace the antimicrobial due to the wrong choice of the same for a specific infection in a patient. Therefore, the ASP intervention is unique for each patient.
- IV. In addition, the identification of the intervention alone is not sufficient. Our tool is more specific in describing the problem than in the format described by other authors, who focus on reporting interventions without presenting their causes. For example, the PRAT system promotes that the antimicrobial de-escalation is a reduction in the antimicrobial therapy spectrum, in which the problem is the choice of an empirically expanded spectrum therapy, after the identification of the antimicrobial-resistance profile (subcode 6.9).
- V. The acceptability of interventions is an important aspect to consider in the phases of development, evaluation and implementation of pharmacotherapeutic interventions. Successful implementation depends on the acceptance rate by the care team. If an intervention is considered logical and based on clinical, technical and scientific precepts and, therefore, acceptable, it will be more likely to adhere to treatment recommendations and benefit from the best clinical results. In addition, acceptability helps the ASP team to make decisions about the form, content and delivery of the proposed intervention components.

As this is the first tool attempting to unify the interventions performed by ASP, many positive aspects would be enhanced, as described below:

- I. ASP reports usually focus on "inappropriate dose"¹². Such information is a reduced way of sharing knowledge. ASP professionals want to know the underlying situation that resulted in an incorrect dose and the intervention for it. For example: reduced renal clearance (the problem) and reduction in the dose of antibiotics with elimination mainly at the renal level (the intervention) is a more informative process that might increase critical thinking and local decision-making (subcode 1.6). Using this tool, the impact of ASP interventions on relevant outcomes will be less heterogeneous, so it will contribute with appropriate group comparisons.
- II. The use of this classification system optimizes the evaluation of pharmacotherapeutic interventions and the acquisition of antimicrobial-related problem in a structured way, favoring the continuity of care through the promotion of mutual information. Moreover, this data can be used for epidemiological data and increases the ASP' vigilance regarding patient needs related to medications.

The tool is not without limitations:

- I. Despite our experience of its use, the PRAT was not validated. We strongly believe that making this publicly available will promote discussions and development about harmonizing ASP interventions.
- II. Not all PRAT presented by this tool might be considered by different ASPs, so each institution should adapt and make the best use of this tool to register the problems and interventions.
- III. Understanding the description of the PRAT is not simple, requiring some time for the incorporation and appropriation of this new practice. A suggestion to reduce this limitation is to implement local software and electronic medical records in order to create epidemiological data

A single antimicrobial-related problem system will promote less heterogeneous reports, benchmarking and innovation, as ASP practitioners will understand what interventions should be prioritized and to what extent they affect clinical and economic outcomes. Through this tool, the economic impact of the pharmacotherapeutic intervention can be measured in the near future.

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Authors' contributions

All authors of this manuscript participated directly in the planning, execution and writing of this study, in which each author had the following contribution: **MR** contributed to conceptualization, project administration, methodology, data curation, visualization, supervision and writing – review and editing; **LO** contributed to conceptualization, visualization, methodology, writing original draft and writing review e editing; **HB** contributed to conceptualization, project administration, methodology, data curation, visualization and supervision; **HPN** contributed to conceptualization, methodology, visualization and writing review e editing; **DS** contributed to conceptualization, methodology and visualization; **MF** contributed to methodology, writing original draft and writing review e editing; **FM** contributed to conceptualization, project administration, supervision, validation,, data curation, and writing – review and editing.