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Hospital Medication Review: risk and network analysis

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Abstract

Objective: To assess the relationship between Drug Related Problems (DRP) and its respective drugs identified from a hospital medication review (MR). **Method:** This is a retrospective, cross-sectional observational study based in STROBE Statement. DRP records from study period (2019-2020) were collected from a hospital MR database and classified by Pharmaceutical Care Network Europe (PCNE) standards. Through an online form, a panel of experts (pharmacists and physicians) analyzed the clinical significance of DRP included, using the Hazard Scoring Matrix (HSM). Using Gephi software, two networks were built to visualize the relationship between DRPs and drugs from the following perspectives: (i) the hospital's pharmacists; and (ii) the panel of experts. **Results:** 1250 DRP related to 177 different drugs were included and compiled in 202 "DRP-drug" different combinations. According to the PCNE, 41.6% of DRP were classified as class C1 (drug selection), 20.3% as C5 (dispensing) and 13.8% as class C3 (dose selection). According to the expert panel, the "dose selection- antibiotic" combination was the one with the highest risk by HSM in the global and pharmacist analysis. To physicians, the combination "monitoring- vitamin K antagonist anticoagulants" was presented with the highest HSM. On the other hand, the "drug selection- antiulcer" combination, which was the most found in the database, was classified by the specialists with a low risk (HSM 6). **Conclusion:** The profile of "DRP- drug" combinations were different when compared results pre and post risk analysis. Thus, it was demonstrated that HSM can be a useful tool to improve DRP evaluation and to standardize MR services, guiding pharmacists to situations of greater clinical significance and increasing their effectiveness in improving health outcomes.

Key words: Medication Review; Risk Assessment; Medication Errors; Pharmacy Service, Hospital; Delphi Technique.

Revisão da farmacoterapia intra-hospitalar: análise de risco e de rede

Resumo

Objetivo: Analisar a relação entre os Problemas Relacionados a Medicamentos (PRM) e os medicamentos identificados no processo de revisão da farmacoterapia (RF) de um hospital universitário. **Método:** Trata-se de um estudo observacional retrospectivo e transversal. Os registros de PRM do período do estudo (2019-2020) foram coletados de um banco de dados de RF hospitalar e classificados conforme a *Pharmaceutical Care Network Europe* (PCNE). Em seguida, um painel de especialistas (farmacêuticos e médicos) analisou a significância clínica do PRM incluído, em formulário online, com base no *Hazard Scoring Matrix* (HSM). Utilizando o *software* Gephi foram construídas duas redes para visualização da relação entre os PRM e os medicamentos nas seguintes perspectivas: (i) dos farmacêuticos do hospital; e (ii) do painel de especialistas. **Resultados:** 1250 PRM relacionados a 177 medicamentos diferentes foram incluídos e compilados em 202 combinações diferentes de "PRM-medicamento". Pelo PCNE 41,6% dos PRM foram classificados como classe C1 (seleção do medicamento), 20,32% como C5 (dispensação) e 13,76% da classe C3 (seleção de dose). Pelo painel de especialistas, a combinação de "seleção de dose- antibiótico" foi a que apresentou maior risco na análise global e de farmacêuticos. Para os médicos, a combinação "monitoramento - anticoagulantes antagonistas de vitamina K" foi classificada com o maior risco. Em contrapartida, a combinação "seleção do medicamento- antiulcerosos", que foi a mais encontrada na base de dados foi classificada pelos especialistas com escore de risco baixo (HSM 6). **Conclusão:** A significância das combinações "PRM-medicamento" foi diferente quando comparados os resultados pré e pós análise de risco. Assim, demonstrou-se que o HSM pode ser uma ferramenta útil para melhorar a avaliação do PRM e padronizar os serviços de RF, orientando os farmacêuticos para situações de maior significância clínica e aumentando sua eficácia na melhoria dos resultados de saúde.

Palavras-chave: Revisão da Farmacoterapia; Análise de Risco; Erros de Medicação; Serviço de Farmácia Hospitalar; Método Delphi.

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Introduction

Over the last 30 years, the pharmaceutical profession has undergone significant changes related to its social responsibility, showing that bedside and patient-centered action is essential to guarantee the best and safest pharmacotherapy[1].

The most commonly applied medical intervention in health services is pharmacotherapy (the process of prescribing, dispensing and using medications), which is subjected to errors and problems[2]. It is estimated that there are 7,000 estimated deaths per year due to medication errors in the United States. In Brazil, some studies have suggested that assistance-related problems related are the fifth leading cause of death[3,4,5]. In addition to that, it is estimated that Drug-Related Problems (DRPs) or issues in pharmacotherapy are responsible for nearly 9% to 24% of the hospital admissions resulting from urgency care[6]. It is believed that approximately 70% of the problems in pharmacotherapy would be preventable with the clinical performance of a pharmacist[6].

Pharmacotherapy Review (PhR) is one of the clinical services provided by pharmacists, although it can also be in charge of physicians and nurses who have knowledge about the work process. It aims at increasing safety, ensuring effectiveness and improving medication use, as well as at reducing resource waste[7,8]. Pharmacists play a fundamental role in ensuring medication use quality, reducing the mortality and morbidity associated with medication errors and improving patients' clinical outcomes. Their actions to optimize pharmacotherapy also result in reduced hospitalization times and costs related to health services[9,10,11].

According to the *Pharmaceutical Care Network Europe* (PCNE), achieving positive outcomes with PR involves detecting DRPs and recommending interventions. This service is efficient in promoting patient safety and reducing the occurrence of adverse events, as long as the process is carried out with quality[12,13]. Standardization is important in determining the quality of a process and in reducing unnecessary variations. Health systems and institutions are integrated and, in this way, systematization generates results data, which can be compared and used to demonstrate the value of a service. In addition to that, the absence of a standard care process creates an environment that can result in gaps in the quality of the care provided[14]. In this sense, this study objective was to describe the DRPs identified from the records of the PR service of a public tertiary-level hospital and to analyze the most frequently observed DRP- Medication combinations.

Methods

This is a cross-sectional and observational study with retrospective data collection, carried out in a general, tertiary-level, public and teaching hospital. The study institution stands out as a university hospital center of considerable scope, with emphasis on teaching, research and extension. Its activities are aimed at meeting regional needs, although it also welcomes patients from other national and international locations on certain occasions. The institution plays an important role within the Unified Health System scope, being a reference in high-complexity assistance and advanced health care in areas such as Cardiology, Infectology, Medical Clinic and Hematology, among others.

The study was written in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) statement[15] guidelines and approved by the Research Ethics Committee under CAAE No. 49543321.6.0000.0096.

Description of the Pharmacotherapy Review (PHR) Process

PhR was a service performed by clinical pharmacists working in the Clinical Pharmacy Unit of the study hospital that aimed at guaranteeing pharmacotherapy effectiveness, safety and efficiency for hospitalized patients with resolution of all the DRPs identified.

Such service can be described through the DEPICT (Descriptive Elements of Pharmacist Interventions Characterization Tool)[16] components presented below: (i) Service target - Despite the objective focused on patient care, the PhR actions were targeted at the prescribing physician or Nursing team according to the need; (ii) Service *locus* - The actions were carried out in the hospital pharmacy structure or directly in the inpatient units of the study hospital; (iii) Intervention focus - No evaluation restrictions were established, with the PhR intended to assess all medications for all hospitalized patients; (iv) Data sources - Drug prescriptions, patient records, laboratory and complementary tests, interviews with the patient/caregiver and databases with clinical information were evaluated; (v) Variables evaluated- Based on the data sources previously described, medication choices, effectiveness and safety of the medications in use, treatment costs, accessibility and availability of medications and errors in prescription, dispensing and administration, in order to identify the DRPs; (vi) Pharmacist interventions - The PhR actions were focused on suggesting changes to drug prescriptions, monitoring results and requesting laboratory tests; (vii) Support materials - No materials that complement the actions were provided to the team; (viii) Timing and (ix) repetition of the actions - Carried out at any time in the pharmacist's routine and repeated based on new daily prescriptions, as long as there were pharmacotherapy-related demands; (x) Contact with the target - Contact with the target(s) was carried out individually or in a group at the time of case discussions; and (xi) Communication means with the target - Actions with the team are carried out in person, over the phone or by text messages.

Any problem related to at least one of the following factors was considered as a DRP: dose, selection, pharmaceutical form, therapy duration, prescription and dispensing process logistics, use or administration by the health professional or caregiver, intentional or unintentional patient behavior, in-hospital transfer or between health care levels, monitoring, or other unclassified ones. The DRPs identified during the PhR and the Pharmaceutical Interventions (PhIs) carried out with a focus on solving the DRPs were classified and recorded in a specific spreadsheet to monitor the activities performed in the Clinical Pharmacy Unit. It is worth noting that the pharmacist responsible for the PhR also considered presence of chemotherapy in the prescription, but the DRPs and PhIs related to this medication class were recorded in another sector of the hospital and were not evaluated in this study.

Data Collection and Organization

The data were collected in the monitoring spreadsheet of the PhR service of the aforementioned institution, organized with the aid of *Microsoft Office Excel* 365. Each DRP record contained the

following information: PhI number; pharmacist in charge; patient's name initials; patient registration at the institution; inpatient unit; DRP date; DPR description; medication involved; medication code; date, description of the pharmaceutical intervention (PhI); PhI acceptance or not; and observations.

Of the DRPs present in the database, those identified between 2019 and 2020 and related to any prescribed medication, whether present or not on the institution's list of essential medications, were included for analysis. Incomplete DPR records were excluded from the analysis, which precluded their clear interpretation.

The records were classified into nine different causes according to PCNE V9.1[12], namely: C1 - Drug selection; C2 - Medication pharmaceutical form selection; C3 - Medication dose selection; C4 - Treatment duration; C5 - Dispensing; C6 - Medication use process; C7 - Related to the patient; C8 - Related to patient transfer; and C9 - Others. The medications were classified according to the *Anatomical, Therapeutic and Chemical* (ATC) code proposed by the World Health Organization[17]. The ATC classification varied in level in some classes for convenience in grouping medications and to render assessment more feasible (for example: up to the fourth level for omeprazole - A02B and up to the third level for hyoscine - A03). The classification tables for DPRs according to PCNE and for medications are available for consultation in the supplementary materials and in the digital repository (https://osf.io/e8gch/?view_only=6f359498376544c6aadf0692a9c53feb).

Assessment of the Drug-Related Problems (DRPs)

The relationship between DRPs and medications was assessed from two perspectives: (i) the pharmacists' team that carried out the PhR, identified and registered the DRPs; and (ii) the experts' panel that evaluated the same DRPs according to severity and probability of occurrence.

For the first perspective, the frequency of DPR combinations with their respective medications was considered, observed in the hospital under study and recorded in the PhR service monitoring spreadsheet already mentioned.

For the second perspective, the Delphi[18] method was used, applied to a group of specialist made up of pharmacists (who did not participate in the first evaluation) and physicians, with at least three years of experience in caring for hospitalized adult patients. A total of 30 professionals (15 pharmacists and 15 physicians) were invited, with a minimum participation of 80% of specialists required to complete the evaluation.

The experts who accepted the invitation received a digital form with evaluation questions for each DRP and medication combination included. Each specialist had 30 days to answer the form and completed their assessment in a single round. From the submission day until the final response deadline, reminders were sent every seven days to the experts who had not yet carried out the assessment.

The DPR combinations with their respective medications were initially organized into pairs to ease understanding of the invited experts, using the following: "DRP as per the PCNE classification - Medication as per the ATC classification" (for example: "Selection - Antiulcers"). In the form, each specialist evaluated and classified each "DRP - Medication" combination regarding severity and probability of occurrence, following the scale description, as shown in Figure 1. These variables come from the *Health Care Failure Mode and Effect Analysis* (HFMEA) method used for proactive and interdisciplinary assessment of the quality of a work process in the health area, such as the PhR service performed by pharmacists[19]. The severity score is a measure of the potential effect of the failure mode, that is, what the impact would be on patients or patient care if this DRP were to occur. The probability score translates the chance of the DRP happening within a given period of time[19].

Figure 1. Severity and probability scale of the HFMEA (Health Care Failure Mode and Effect Analysis) method

	Severity Scale
Catastrophic (4)	Death, permanent major loss of function, suicide, rape, hemolytic reaction from transfusion, surgery or procedure on the wrong patient or body part
Major (3)	Permanent decrease in bodily function, disfigurement, surgical intervention, increased length of stay or level of care for 3 or more patients
Moderate (2)	Increased length of hospital stay or increased level of care for 1 or 2 patients
Minor (1)	No injury, no increase in length of stay or increase in level of care

	Probability scale
Frequent (4)	Likely to occur immediately or within a short period (can happen multiple times in a year)
Occasional (3)	Will probably occur (may happen several times in 1 to 2 years)
Uncommon (2)	Possible to occur (may happen sometime in 2 to 5 years)
Remote (1)	Unlikely to occur (may happen sometime in 5 to 30 years)

Source: Literal translation from DEROSIER *et al*, 2002[19].

From the measurements for both variables, the risk was estimated according to the *Hazard Scoring Matrix* (HSM) using the multiplication of the median of the severity and probability of the experts' answers. The HSM scale varies from 1 to 16 (Figure 2), where the higher the value, the greater the associated risk and clinical significance of the "DRP - Medication" combination. Priority was given to evaluating those most likely to present failures that could put the safety of people served by the health institution at risk.

Figure 2. Hazard Scoring Matrix (HSM) classification for the Health Care Failure Mode and Effect Analysis (HFMEA) method

Probability	**Severity**			
	Catastrophic	Major	Moderate	Minor
Frequent	16	12	8	4
Occasional	12	9	6	3
Uncommon	8	3	4	2
Remote	4	3	2	1

Source: Literal translation from DEROSIER *et al*, 2002. Note: The Hazard Scoring Matrix (HSM) is obtained by multiplying the probability and severity scores [e.g.: a Frequent (4) and Catastrophic (4) problem results in HSM 16].

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Construction Of The "DRP - Medications" Networks

Using the graph theory and the *Gephi*[20] software, two networks were built to visualize the relationship between DRPs and medications from the perspective of the pharmacists' team responsible for the PhR (Network 1), focusing on the observed frequency and the experts' panel (Network 2), focusing on clinical significance

In the networks, the nodes (circles), presented in different colors, represent the DRPs (blue) and the medications (orange). The size of the nodes was configured to be proportional to the number of times the medication or DRP appears in the records included in the analysis from the DRP database. The edges (lines), presented between the nodes, represent the relationship of the combinations between the DRPs and the medications. Thus, in Network 1, thickness of the edges was configured to represent the frequency of the association between each DRP and medication. In Network 2, thickness represented the multiplication of the combination frequency and the HSM median for the same combination. The algorithm used to distribute nodes in the networks was *Force Atlas 2*[20].

Statistical Analysis

The data collected and the evaluation by the experts' team were presented using descriptive statistics. The categorical variables were presented as relative and absolute frequencies, and the continuous variables as a central tendency and dispersion measures according to normality.

Results

The database used had 1,340 DRPs recorded. Of these, 90 records (6.7%) were excluded. The reasons for exclusion were as follows: A total of 23 incomplete records of the medication involved; 20 single interventions with a medication or class; 16 interventions not recorded or incomplete; 12 incomplete examination or condition specifications; six records with no medication involved in the DRP; four records without any description of the DRP involved; four records without patient record data; three records with DRP type with a single record; one duplicate record; and one with date outside the established study period.

Considering the 1,250 DRPs included, 255 were identified in 2019 and 995 in 2020. They involved 177 medications and 614 different patients, with a rate of two DRPs per patient. The medications were grouped into 46 therapeutic classes, with omeprazole, from the antiulcer class, as the most frequently used drug in the DRP records. Table 1 presents the 10 most frequently used medications among the DRP records in the period with representatives of the following groups: antiulcers, heparins, simple analgesics, lipid-lowering medications, antihypertensives, beta-blockers, corticosteroids, laxatives and opioid analgesics. More data on the medications and DRPs identified are available in the digital repository (https://osf.io/e8gch/?view_only=6f359498376544c6aadf0692a9c53feb).

Network 1 (Figure 3) presented a conformation with the DRP classes most found in the center. According to the PCNE classification, 41.6% of the DMRPs belonged to class C1 (Drug selection), 20.32% to class C5 (Prescription and dispensing logistics), 13.76% to class C3 (Dose selection), 8.72% to class C2 (Pharmaceutical form), 8.64% to class C6 (Medication use process), 3.52% to class C4 (Treatment duration), 1.68% to class C8 (Related to the patient transfer), 1.68% to class C9 (Others) and 0.08% to class C7 (Related to the patient).

The panel was made up of 12 physicians specialized in the Intensive Medicine, Medical Clinic, Oncology, Infectology and Cardiology areas. The 12 pharmacists who agreed to participate were specialists in Clinical Pharmacy and worked in intensive care units, cardiology and medical clinic. Thus, an overall response rate of 80% was obtained for both professional classes.

The panel analyzed 202 DRP - Medication combinations. In the overall analysis, the maximum score achieved was 14, referring to the antibiotics dose (C3) DRP, as can be seen in Table 2. In addition to that, antibiotics ranked 1st, 2nd and 7th with different DRPs among those at highest risk. In the combinations that reached the maximum risk score as per HSM (greater than 12), the medications that stood out were antibiotics and vitamin K antagonist anticoagulants.

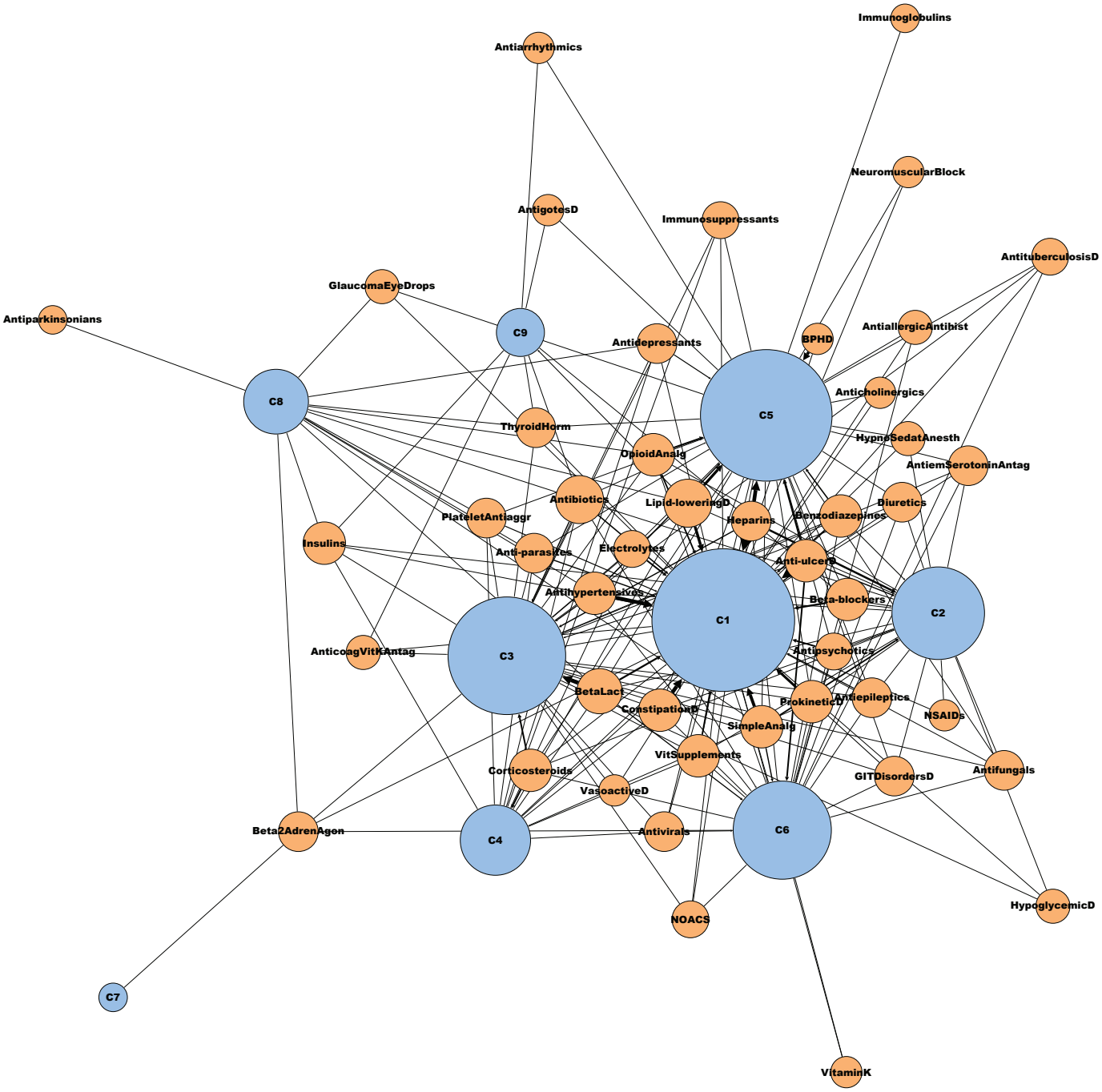
By the pharmacists' panel, the antibiotics dose combination DRP (C3) was classified as with the highest risk, whereas by the physicians' panel it was the monitoring vitamin K antagonists DRP (C9). It is noted that, among the medications involved in DRPs with the highest risk as assessed by the physicians are benzodiazepines, antiplatelet agents and new oral anticoagulants (NOACs). These did not appear among the top 12 with the highest risk classified by the pharmacists (Tables 3 and 4).

Table 1. The ten medications most frequently involved in the Drug-Related Problems (DRPs) recorded (Paraná, Brazil).

Ranking	Number of DRPs (%)	Medication	ATC class	Name on the network
1	106 (8.48)	Omeprazole	A02BC	Antiulcers
2	99 (7.84)	Enoxaparin	B01AB	Heparins
3	63 (4.88)	Dipyrone	N02BB	SimpAnal
4	50 (4.00)	Atorvastatin	C10AA	Lipid-lowering medications
5	29 (2.32)	Enalapril	C09AA	Antihypertensives
6	28 (2.24)	Carvedilol	C07AG	Betabloc
7	26 (2.08)	Ranitidine	A02BA	Antiulcers
8	26 (2.08)	Dexamethasone	H02AB	Corticosteroids
9	25 (2.00)	Bisacodyl	A06AB	ConstDr
10	24 (1.92)	Morphine	N02AA	OpAnalg

Key: DRPs- Drug-Related Problems. ATC- Anatomical Therapeutic Chemical Classification System; SimpAnal- Simple Analgesics; Betabloc- Beta-blockers; ConstDr- Drugs for constipation; OpAnalg- Opioid analgesics.

Figure 3. Network 1- Combinations (DRP- Medication) with weight of the associations (edges) proportional to the number of the pharmaceutical interventions base (Paraná, Brazil)



Note: The nodes (circles) represent the DRPs (blue) and the medications (orange). The node sizes were configured to be proportional to the number of times the medication or DRP appears in the records included in the analysis. The edges (lines), presented between the nodes, represent the relationship of the combinations between DRPs and medications, and the edges' thickness was configured to represent the frequency of the association between DRPs and medications in the database. Key: PRM- Drug-Related Problems; C1- Drug selection; C2- Pharmaceutical form selection; C3- Dose selection; C4- Treatment duration; C5- Dispensing; C6- Use process; C7- Related to the patient; C8- Patient transfer; C9- Other problems; NeuromuscularBlock- Neuromuscular Blockers; BPHD- Benign prostatic hyperplasia drugs; HypnoSedatAnesth- Hypnotics sedatives anesthesics; OpioidAnalg- Opioid analgesics; PlateletAntiaggr- Platelet antiaggregants; Beta-blockers; BetaLact- Beta-Lactams; ConstipationD- Constipation drugs; SimpleAnalg- Simple analgesics; NSAIDs- Non-steroidal anti-inflammatory drugs; NOACs- New Oral Anticoagulants.

Table 2. Global ranking of the 12 DRP- Medication combinations with the highest risk indicated by the experts' panel (pharmacists and physician) (Paraná, Brazil).

Ranking	PCNE classification	Therapeutic class	Severity, Med (IQR)	Probability, Med (IQR)	HSM
1º	C3	Antibiotics	4 (3-4)	3,5 (2-4)	14
2º	C1	Antibiotics	3,5 (3-4)	3,5 (3-4)	12,25
3º	C9	Vitamin K Antagonist Anticoagulants	4 (3-4)	3 (3-4)	12
4º	C3	Heparins	4 (4-4)	3 (2-4)	12
5º	C3	Insulins	4 (3-4)	3 (2-4)	12
6º	C3	Benzodiazepines	4 (3-4)	3 (2-3)	12
7º	C4	Vitamin K Antagonist Anticoagulants	4 (3-4)	3 (2-4)	12
8º	C1	Vitamin K Antagonist Anticoagulants	4 (3-4)	3 (2-4)	12
9º	C1	Heparins	4 (3-4)	3 (2-3,25)	12
10º	C3	Vitamin K Antagonist Anticoagulants	4 (3-4)	3 (2-3,25)	12
11º	C3	Antiplatelet Agents	4 (3-4)	3 (1,75-3)	12
12º	C3	Antifungals	4 (3-4)	3 (2-4)	12

Key: HSM- Hazard Scoring Matrix; Med- Median; IQR- Interquartile Range; PCNE- Classification of the drug-related problems according to Pharmaceutical Care Network Europe V9.1; C1- Drug selection; C3- Dose selection; C4- Treatment duration; C9- Other problems.

Table 3. Ranking of the 12 DRP- Medication combinations with the highest risk indicated by the pharmacists' panel (Paraná, Brazil)

Ranking	PCNE classification	Therapeutic class	Severity, Med (IQR)	Probability, Med (IQR)	HSM
1º	C3	Non-Beta Lactam Antibiotics	4 (3,75-4)	4 (2,75-4)	16
2º	C4	Non-Beta Lactam Antibiotics	4 (3-4)	3,5 (2,75-4)	14
3º	C4	Beta Lactam Antibiotics	3,5 (3-4)	4 (2,75-4)	14
4º	C9	Vitamin K Antagonist Anticoagulants	4 (3-4)	3 (3-4)	12
5º	C1	Non-Beta Lactam Antibiotics	4 (3-4)	3 (2,75-4)	12
6º	C3	Heparins	4 (3,75-4)	3 (2-4)	12
7º	C3	Insulins	4 (3,75-4)	3 (2-4)	12
8º	C1	Beta Lactam Antibiotics	4 (3-4)	3 (2-4)	12
9º	C1	Vitamin K Antagonist Anticoagulants	4 (3-4)	3 (2-4)	12
10º	C3	Vitamin K Antagonist Anticoagulants	4 (4-4)	3 (2-3)	12
11º	C3	Beta Lactam Antibiotics	4 (3,75-4)	3 (3-4)	12
12º	C6	Non-Beta Lactam Antibiotics	4 (3-4)	3 (2-4)	12

Key: HSM- Hazard Scoring Matrix; Med- Median; IQR- Interquartile Range; PCNE- Classification of the drug-related problems according to Pharmaceutical Care Network Europe V9.1; C1- Drug selection; C3- Dose selection; C4- Treatment duration; C6- Use process; C9- Other problems.

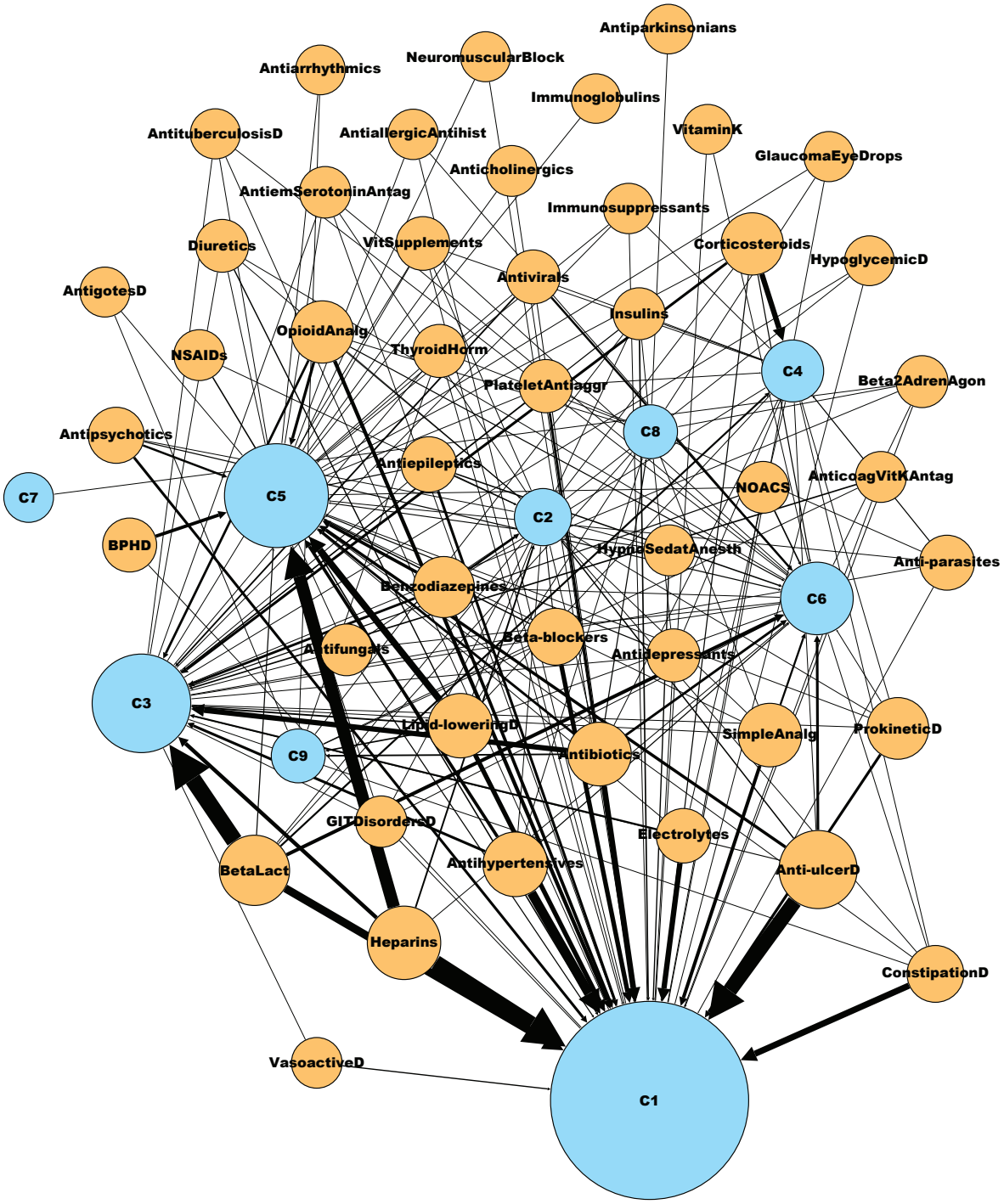
Table 4. Ranking of the 12 DRP- Medication combinations with the highest risk indicated by the physicians' panel (Paraná, Brazil)

Ranking	PCNE classification	Therapeutic class	Severity, Med (IQR)	Probability, Med (IQR)	HSM
1º	C9	Vitamin K Antagonist Anticoagulants	4 (3,75-4)	3,5 (3-4)	14
2º	C1	Non-Beta Lactam Antibiotics	3 (3-4)	4 (3-4)	12
3º	C3	Heparins	4 (4-4)	3 (2-4)	12
4º	C3	Insulins	4 (3-4)	3 (2,75-3,25)	12
5º	C3	Benzodiazepines	4 (3-4)	3 (2,75-3)	12
6º	C1	Insulins	4 (3-4)	3 (2-3,25)	12
7º	C1	Beta Lactam Antibiotics	3 (2-4)	4 (3-4)	12
8º	C1	Antiplatelet Agents	3 (2-3)	4 (2-4)	12
9º	C4	Non-Beta Lactam Antibiotics	3,5 (3-4)	3 (2-4)	10,5
10º	C4	Beta Lactam Antibiotics	3,5 (2,75-4)	3 (2-4)	10,5
11º	C6	NOACs	3,5 (2,75-4)	3 (1,75-3)	10,5
12º	C1	Vitamin K Antagonist Anticoagulants	4 (3,75-4)	2,5 (2-4)	10

Key: HSM- Hazard Scoring Matrix; Med- Median; IQR- Interquartile Range; PCNE- Classification of the drug-related problems according to Pharmaceutical Care Network Europe V9.1; C1- Drug selection; C3- Dose selection; C4- Treatment duration; C6- Use process; C9- Other problems; NOACs- New Oral Anticoagulants

Network 2, which received the HSM weight in the relationships between DRPs and medications, proved to have a different configuration from the first (Figure 4). The DRP classes and medications with the highest risk (severity and probability weight) were in the lower region of the network, highlighting the combinations with the thinnest lines. At the top we find the medications with the lowest associated risk and with less frequent DRPs.

Figure 4. Network 2- Combinations (DRP- Medication) with weight of the associations (edges) proportional to the HSM value obtained by the experts' panel (Paraná, Brazil).



Note: The nodes (circles) represent the DRPs (blue) and the medications (orange). The node sizes were configured to be proportional to the number of times the medication or DRP appears in the records included in the analysis. The edges (lines) presented between the nodes represent the relationship of the combinations between the DRPs and the medications, with the edges' thickness proportional to the median HSM value obtained in the experts' panel for the same combination. Key: PRM- Drug-Related Problems; C1- Drug selection; C2- Pharmaceutical form selection; C3 - Dose selection; C4- Treatment duration; C5- Dispensing; C6- Use process; C7- Related to the patient; C8- Patient transfer; C9- Other problems; NeuromuscularBlock- Neuromuscular Blockers; BPHD - Benign prostatic hyperplasia drugs; HypnoSedatAnesth - Hypnotics sedatives anesthesics; OpioidAnalg - Opioid analgesics; PlateletAntiaggr - Platelet antiaggregants; Beta-blockers; BetaLact- Beta-Lactams; ConstipationD- Constipation drugs; SimpleAnalg- Simple analgesics; NSAIDs- Non-steroidal anti-inflammatory drugs; NOACs- New Oral Anticoagulants.

Discussion

Standardizing care in health units contributes benefits both to patients and to the assistance team. Oftentimes with limited time and resources, health institutions are unable to analyze all processes in detail as a way of making decisions for workforce allocation. Thus, building networks can be a useful tool to visualize general events of interest for study.

The most prevalent "DRP - Medication" combinations in the PhR database were different from those with the highest risk for the patients according to the experts' panel. A tool capable of evidencing DRPs with greater clinical impact (higher risk) can improve the quality of PhR performed by pharmacists, increasing the potential for improving health results.

The two antiulcer medications selected at the institution (omeprazole and ranitidine) were among those most involved in DRPs. However, they were classified as low risk by HSM. Based on this result, the study team recommended updating the gastric ulcer prophylaxis protocol at institutional level and widely disseminating it to all professionals involved, aiming to reduce observation of this DRP. Indicating this therapy as gastric ulcer prophylaxis is recognized as beneficial; however, its indication has been considered inappropriate in most cases. The consumption reduction rates after implementing an institutional protocol were significant in another study carried out with adult patients. The authors pointed out that the time and impact on working hours for this PhI are considered minimal, making this review potentially cost-effective[21]. The economic impact of the PhIs related to antiulcer medications was shown in another prospective interventional study conducted with adult patients in wards and intensive care units. The PhR with PhI for discontinuation of these medications yielded cost savings of 18,000 dollars per month, resulting in an annual reduction of approximately 216,000 dollars[22]. Even in a population more vulnerable to gastrointestinal bleeding, such as patients with chronic kidney disease, the prevalence of inappropriate use of these classes is high. In a pre- and post-intervention trial with pharmacists in Nephrology units, there were relative reductions of 44% and 67% in inappropriate use and costs, respectively. As found in our institution, omeprazole and ranitidine were among the main agents for acid suppression therapy. Safety in omeprazole use in the population with nephropathies should be guaranteed, as well as the risks minimized, as the medication is related to acute kidney injury caused by tubulointerstitial nephritis, especially in the aged population[23,24].

The enoxaparin anticoagulant, the second most involved in DRPs during the period, was highlighted in the global ranking of combinations with the highest risk. Prescribing these drugs is a major challenge for care teams. Thrombotic events and bleeding are related to cardiovascular diseases, which represent the main cause of death and hospitalization at the global level[25]. Although not present on the list of most prevalent DRPs, warfarin was the anticoagulant with the highest risk according to the experts' panel. Such reason can be justified due to the complexity of the therapeutic regimen, with variable pharmacodynamics depending on variation in elimination rates, consumption of food options rich in vitamin K, drug interactions and adherence. Through PhR, the International Normalized Ratio (INR) is monitored so that anticoagulation is achieved with minimized bleeding risk. A cohort study shown that pharmaceutical consultations resulted in achieving target INR values in five days when compared to the standard treatment, 88% vs 38% ($p<0.001$). In addition to that, INR values above 4, considered outside the therapeutic target and predisposing to bleeding, were reduced from 27% to 2% ($p<0.001$)[26].

Switching from warfarin to NOACs is an alternative if it is impossible to use it or there are failures in monitoring with warfarin. The process called transition or bridge between anticoagulants requires care to prevent adverse events. In this context, pharmacist-led stewardship services for conversions between warfarin and NOACs has shown beneficial effects. Factors such as kidney or liver dysfunctions, major interactions with NOACs, weight, pregnancy or lactation and socioeconomic status were taken into consideration when performing PhIs suggesting a transition between anticoagulants. In addition, lower hospital readmission rates or demand for care due to causes such as bleeding and thrombotic events were observed in patients transitioned from the warfarin therapeutic regimen to NOACs[27].

According to tables 2, 3 and 4, inappropriate use of antimicrobials was related to greater severity and this DRP was observed with high frequency in the clinical practice. Treating an infection presupposes appropriate choice of a medication to eradicate the agent and prevent resistance. In turn, this arises when the infectious agents are exposed to large antimicrobials amounts, increasing the risk of spreading diseases and reducing the chance of controlling already established infections[28]. Drug selection, dose and treatment duration were the highest risk DRP - Medication combinations as assessed by the experts' panel.

While the pharmacists listed dose and treatment duration as the main risk factors, the medical professionals considered antibiotic selection as the main aggravating factor. This fact can be justified by the role of the pharmaceutical professional in evaluating medications that require dose adjustments according to decline in renal function, therefore considered a safety DRP. In addition, choice of the dose may not have been considered with the same relevance by the medical professionals due to the concern about eradicating the agent, preceding the toxicity risk of these medications, therefore indicating the effectiveness DRP as the main aspect to be prevented. A study by Gruenberg, which compared the reasoning behind choosing the pharmacists' and physicians' antimicrobial regimes, presented similar notes to the current study, as both professionals understand that choice of the antimicrobials is a relevant stage but take different information into account when defining the treatment[29]. Another research study presented significant results for reducing total hospitalization and antimicrobial medication costs, data that meet the concern presented by the experts' panel in relation to antibiotics[30]. Both studies indicate the benefit of the pharmacists' participation in the antimicrobial use process.

Comparing the combinations rankings with higher risks, it is observed that, among the physicians, the attention was focused on medications that altered blood hemostasis. According to the PCNE classification, the main problems raised were choice of the medication, dose and failures in the use process. It is also worth highlighting the DRPs involving benzodiazepines, as they were absent from the pharmacists' list and present in the physicians' assessment. According to studies by Fick and Jovevski, which deal with the inappropriate medication use in older adults, the decision on the benzodiazepine dose to be used was considered a determining factor for future complications[31,32]. In the same research studies, other drugs considered inappropriate for older adults were discontinued or had their doses reduced after PhIs performed in emergency care. Muscle relaxants, hypnotics, benzodiazepines and alpha-adrenergic receptor blockers stood out among the agents involved in the PhIs[31,32]. The current study suggested the prescribers' concern about the safety and risk of bleeding and excessive sedation inherent to these medications, which would be life-threatening conditions.

Although responsible for monitoring adverse reactions, the pharmacists did not indicate the DRP with benzodiazepines among the main risk combinations. One reason would be lack of training of these professionals to assess sedation levels and their absence from bedside care in many cases, leaving the assessment hostage to data in the literature. For the pharmacists, the DRPs with antimicrobial agents were the most relevant, possibly due to their greater participation in management of infectious diseases at the institution and their expertise in relation to the analysis of pharmacokinetic and pharmacodynamic parameters used in optimizing therapeutic regimes. Taking into account the data herein presented, according to criticality, monitoring of DRPs involving anticoagulants and antimicrobials should be prioritized in PhR processes.

In a general context, the methodology used in the current study presents Network 1, built only with data from the institution's DRPs as an illustration of how the institution's pharmacists see the DRPs (Figure 3). Network 2, which used the same "MRP - Medication" combinations, but applied the HSM weight in building the network, illustrates how the experts in the field see the same DRPs (Figure 4). When comparing both networks, we verified that the HSM weight modifies the network, showing that there is a difference between the institution's pharmacists and the specialists consulted in relation to the same DRP - Medication combinations. Unfortunately, there are no previous studies that have carried out the same assessment in the same context, rendering comparative discussions impossible. However, it is possible to reinforce that the combination of methods applied in this study allows insights into the need for continuous team training to carry out pharmaceutical services with a focus on situations of greater clinical relevance (for example: spending more energy evaluating antibiotics and vitamin K antagonists than antiulcers such as omeprazole).

One of the study limitations was that the period used for the DRP records was largely in 2020, the year in which the COVID-19 pandemic began in Brazil and around the world. This may not completely reflect the reality of the health institution outside the health emergency period. The experts' panel heterogeneous composition may have influenced the results, as professionals from different specialties may have different perspectives on the same DRP. Another barrier was the large number of "DRP - Medication" combinations offered to the experts for evaluation, which caused some participants to submit feedback related to lack of time to complete the answers and possible inaccuracy in interpreting the information evaluated. Length of the form also made it impossible for the experts to complete more rounds, which precluded consensus analyses carried out based on the agreement between the experts' answers.

Conclusion

The results from the DRP and medication analyses using both methods applied were divergent, which could be evidenced with the network construction tool. These findings suggest that the HSM risk use analysis can support identifying DRPs of greater clinical significance, having the potential to guide prioritization of the pharmacotherapy review service and increase its effectiveness.

It is believed that the risk analysis employed in this study can be useful to identify, prioritize and reduce failure modes in the drug prescription, dispensing and administration processes and to change the organizational culture from reactive to preventive approaches.

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Collaborators

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Declaration of conflict of interests

The authors declare that there is no conflict of interest in relation to this article.

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