

# Analysis of clinical pharmacist interventions in the COVID-19 units of a French university hospital

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## ABSTRACT

**Objectives** The objectives were to compare clinical pharmacist interventions between two care groups: COVID-19-positive and COVID-19-negative patients, and to identify drugs that require particular attention, especially those involved in COVID-19 management.

**Methods** A prospective cohort study was conducted on patients with positive and negative COVID-19 statuses admitted to Lille University Hospital over 1 month. Pharmaceutical analysis instigated interventions to rectify drug-related errors. For each pharmaceutical intervention (PI), the anatomical therapeutic chemical classification of the drug and the outcome of such an intervention were specified.

**Results** The study included 438 patients. Prescription analysis led to 188 PIs performed on 118 patients (64 COVID-19-positive patients and 54 COVID-19-negative patients). Most drug-related problems were incorrect dosage representing 36.7% (69/188) of all interventions: 27.9% (29/104) for the COVID-19-positive group and 47.6% (40/84) for the COVID-19-negative group. The most frequent PI in 34% (64/188) of cases was terminating a drug: 27.9% (29/104) for the COVID-19-positive group and 47.6% (40/84) for the COVID-19-negative group. The main drug classes involved were antithrombotic agents (20.7%, 39/188), antibacterials for systemic use (13.8%, 26/188) and drugs for gastric acid-related disorders (6.4%, 12/188). Study population was limited to a single centre over 1 month.

**Conclusion** No difference in PI was noted between the two groups. The presence of pharmacists led to a reduction in drug-related prescription problems, especially for antithrombotic and antibacterial drugs for both groups. Clinical pharmacy commitment in such a pandemic is therefore important.

## INTRODUCTION

A pandemic of COVID-19 caused by a new coronavirus of SARS-CoV-2 broke out in China in December 2019 and in France in February 2020.

Manifestations of the disease can range from asymptomatic infection, mild upper respiratory tract disease, severe viral pneumonia with respiratory failure and even death.<sup>1</sup> Population demographics and prevalence of comorbidities are different between countries, but published studies have shown a high frequency of hypertension, diabetes<sup>2</sup> and coronary heart disease.<sup>3</sup> Obesity was especially high for patients admitted to intensive care for SARS-CoV-2.<sup>4</sup>

Multiple organs such as lungs, kidneys, liver, heart and brain<sup>5</sup> are affected by the SARS-CoV-2

virus. Drug management is thus complex and based on symptomatic treatments such as oxygen, anticoagulation<sup>6</sup> and antibiotics to the infection itself or to a secondary bacterial infection. Several clinical studies are currently in progress to evaluate the efficacy and safety of specific drugs in adult patients.<sup>7</sup> The therapeutic management of COVID-19 is added to the patient's home treatments and can lead to adverse drug events or drug–drug interactions, especially with some drugs being assessed in clinical trials.<sup>8</sup> All hospital prescriptions benefit from pharmaceutical analysis, which is one of the tasks of hospital pharmacists<sup>9</sup> whose presence in care units helps to reduce the rate of drug errors and optimise drug management.<sup>10–12</sup>

A building at Lille University Hospital was reorganised to absorb the substantial influx of non-critical patients with suspected COVID-19 or infection. This reorganisation was combined with the requisition of physicians of every specialty. To guarantee the continuity of patient care, a team of clinical pharmacists was deployed in these COVID-19 units. The role of hospital pharmacists in the pandemic context remains unclear.<sup>13</sup>

The first objective of this study was to compare clinical pharmacist interventions in two care groups: COVID-19-positive and COVID-19-negative patients. The second objective was to identify drugs that require particular monitoring, especially drugs involved in COVID-19 management (antibacterial, antithrombotic and specific drugs).

## METHODS

### Study design and patients

This single-centre prospective cohort study was performed at the Lille University Hospital. All patients admitted consecutively between 24 March and 24 April 2020 to COVID-19 units and who had benefited from pharmaceutical analysis were enrolled in the study. Patients who had not benefited from pharmaceutical analysis were excluded from the study. Some prescriptions could not be analysed by the pharmacists because patients remained in COVID-19 care units outside the pharmacists' working hours or patients were quickly transferred to other clinical departments (ie, intensive care units). COVID-19-infected or suspected patients were admitted to COVID-19 care units if they presented signs of COVID-19 infection (cough, fever, breathing difficulties, digestive problems and asthenia). They stayed in COVID-19 units until the negative result of the airway and/or faecal real-time reverse transcriptase (PCR) sampling.



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When COVID-19 status was not known, patients were excluded from the study. The medication routine (prescription, analysis, delivery and administration) was identical to that of the hospital centre.

Protocols using drugs specific to the management of COVID-19 were created in our computerised physician order entry (CPOE) and electronic health record (EHR) software. Physicians could be trained to prescribe these protocols.

Pharmaceutical analyses were performed from Monday to Friday by clinical pharmacists trained and prepared for the task. Pharmacists did the pharmaceutical analysis and pharmaceutical intervention (PI) in their facilities and interacted with physicians by written message or phone call.

Transfers of patients from COVID-19 units to other wards in our hospital were considered as a single admission. All readmissions during the study period are mentioned.

Data collected included demographic information (age, gender and Body Mass Index (BMI)), comorbidities (hypertension, obesity and diabetes).

The number of home medications before admission was traced from the databases of patients' medical history and controls.

For each patient hospitalised, medical prescriptions were analysed daily throughout their stay (COVID-19 units and other wards) by three clinical pharmacists. Our CPOE and EHR software make use of all patient data: medical history, haemodynamic and physiological functions (capillary glycaemia, heart and respiratory rates, blood pressure and diuresis), biology (kidney function, liver function, blood chemistry, blood counts, coagulation tests and microbiology data). All prescription analyses were performed as defined by the French Society of Clinical Pharmacy (SFPC).<sup>14</sup> In particular, all drug dosages, indications, contraindications, drug interactions and possible side effects were verified and confirmed in accordance with the medical criteria set out previously. When the trained pharmacists detected an opportunity to improve care, a PI was launched for physicians by written message via our software or phone call.

All PIs were recorded according to the PI classification tool proposed by the SFPC that itemises the nature of the drug-related problem and the PI, the therapeutic classification following the Anatomical Therapeutic Chemical (ATC) Classification System (ATC code) and the outcome of the PI (online supplemental data).<sup>15</sup>

### Data collection

Trained pharmacists reviewed and collected data on an ad hoc Excel datasheet for all consecutive patients from their admission until 24 April 2020. The study was registered with the French National Data Protection Commission (*Commission Nationale de l'Informatique et des Libertés*). The declaration number to the register of treatments is DEC20-381.

### Statistical analysis

Quantitative variables such as age, BMI, number of comorbidities and number of home medications were expressed as medians (quartile 1–quartile 3), if not stated otherwise.

For comparisons of both groups (positive and negative COVID-19), the Student's t-test was applied after assessing the normality of data distribution by the Shapiro-Wilk test ( $p > 0.05$ ). If non-parametric, the Mann-Whitney test was used. Categorical variables are presented as numbers and proportions and were compared using  $\chi^2$  test and Fisher exact test ( $p$  values = 0.05). All analyses were performed using XLSTAT V.3.03 software (Addinsoft, Paris, France).

**Table 1** Baseline demographic and clinical characteristics of both groups\*

	COVID-19-positive status (N=222)	COVID-19-negative status (N=216)
Characteristics		
Age (years)	68.0 (56–78)	69.0 (53.8–81.3)
20–39, n (%)	16 (7.2)	24 (11.1)
40–49, n (%)	18 (8.1)	18 (8.3)
50–59, n (%)	38 (17.7)	21 (9.7)
60–69, n (%)	47 (21.2)	42 (19.4)
70–79, n (%)	51 (23.0)	43 (19.9)
80–89, n (%)	40 (18.0)	50 (23.1)
≥90, n (%)	12 (5.4)	14 (6.5)
Female gender, n (%)	85 (38.3)	102 (47.2)
BMI (kg/m <sup>2</sup> )†	27.6 (24.0–31.6)	26.1 (22.4–31.2)
Comorbidities, n (%)		
Hypertension	113 (50.9)	108 (50.0)
Obesity (BMI≥30)	48 (21.6)	51 (23.6)
Morbid obesity (BMI≥35)	20 (9.0)	21 (9.7)
Diabetes	45 (20.3)	50 (23.1)
Number of home medications	4.0 (1.0–7.3)	6.0(3.0–10.0)
Age intervals (years)		
20–39	0.5 (0.0–1.0)	1.5 (0.0–6.0)
40–49	1.0 (0.0–2.0)	3.0 (2.0–7.0)
50–59	3.0 (0.3–6.0)	4.0 (1.0–6.0)
60–69	3.0 (1.0–7.8)	8.0 (4.0–11.0)
70–79	5.0 (2.0–8.0)	10.0 (6.0–12.0)
80–89	6.0 (4.0–8.5)	7.0 (5.0–9.0)
≥90	8.0 (6.0–8.3)	6.0 (5.0–7.8)

\*Data presented as medians (quartile 1–quartile 3).

†Data available for 306 patients.

BMI, Body Mass Index.

## RESULTS

### Patients' characteristics

A total of 456 patients were hospitalised in COVID-19 units during this study period. For 18 patients, the pharmaceutical analysis was not performed because of premature discharge or transfer to another ward without any clinical pharmacist consultation. Overall, 438 patients were included in our analysis.

Mainly men (57.3%, 251/438) over 60 years (68.2%, 299/438) were included in our study (table 1). COVID-19 infection was confirmed in 222 patients (50.7%). Men accounted for 61.7% (137/222) and 52.3% (114/216) of the COVID-19-positive and COVID-19-negative groups, respectively. Most were overweight, with a BMI median of 27.0 (24.0–31.6) and 26.1 (22.4–31.2) kg/m<sup>2</sup> in the COVID-19-positive and COVID-19-negative groups.

Table 1 shows that impaired metabolic health, including hypertension, dyslipidaemia and diabetes, was prevalent in the cohort study. Hypertension was the most common cardiovascular disease, affecting more than 50% (221/438) of patients in both groups: 113 and 108 patients in the COVID-19-positive and COVID-19-negative groups, respectively. Obesity was also present in more than 20% of cases in both groups (99/438).

The number of home medications was significantly different in both groups: 4.0 (1.0–7.3) for the positive group and 6.0 (3.0–10.0) for the negative group ( $p < 0.0001$ ).

### Pharmaceutical activity and drug-related problems

A total of 188 PIs were performed on the medication prescriptions of 118 patients: 64 and 54 patients for positive and

**Table 2** Drug-Related problems and PIs for patients with COVID-19-positive and COVID-19-negative statuses

PIs	Addition		Stop		Substitution		Biological/drug follow-up		Optimal administration		Dosage adaptation		Total	
	+	-	+	-	+	-	+	-	+	-	+	-	+	-
COVID-19 status														
Non-conformity to guidelines			19	17	6	1					2		27	18
Drug follow-up							2	3					2	3
Indication not treated (forgetting a drug)	16	10											16	10
Underdosage			1		1						11	16	12	17
Overdosage			5	3			1				12	19	17	23
Drug without indication			6	2									6	2
Side effect			1	1	2		1						3	2
Inappropriate administration				1	1				18	5		1	18	8
Drug–drug interactions							2		1	1			3	1
Total	16	10	32	24	8	3	4	5	19	6	25	36	104	84

PI, pharmaceutical intervention.

negative groups, respectively ( $p=0.236$ ), resulting in an average PI rate of 1.6 PIs/patient.

Physicians' acceptance rate of PIs for COVID-19-positive patients was 88.5% (92/104), and that for COVID-19-negative patients was 90.5% (76/84).

Table 2 presents drug-related problems and PIs for patients with COVID-19-positive and COVID-19-negative status, respectively.

Most PIs focused on antithrombotic agents (ATC B01) with a total of 21.8% (41/188) in both groups. Dosage errors (related to obesity) represented 56.1% (23/41) of PIs on antithrombotics: 11 and 12 PIs for positive and negative groups, respectively (table 3). The second most drug-related problem was non-conformity to guidelines (duplicate medication and non-adjustment of heparin to renal function) and concerned 24.4% (10/41) of PIs on antithrombotics: six and four PIs for positive and negative groups, respectively. In 14.6% of cases (6/41), PIs led to the addition of an antithrombotic agent when anticoagulation was necessary but not prescribed.

During hospitalisation, the therapeutic care of patients with general anti-infective agents for systemic use (ATC J) represented 17.6% (33/188) of PIs in both groups. There were no significant differences between the positive (23/33) and negative groups (10/33) ( $p=0.090$ , figure 1). In 78.8% of cases (26/33), PIs were performed for antibacterial agents, especially penicillins (17/33 for both groups) and macrolides (5/33 for both groups). For these drugs, switching from intravenous to oral administration under certain conditions such as treatment duration of >3 days, a reduction in C reactive protein was proposed in 30.3% (10/33 for both groups): seven and three PIs for positive and negative groups. Dosage error (prescription of spiramycin at 3 000 000 IU in intravenous infusion) and non-conformity to guidelines (coprescription of piperacillin/tazobactam and amoxicillin/clavulanic acid) were also reported, leading to dosage adaptations and modified treatment, respectively. For one patient, a therapeutic follow-up of itraconazole plasma concentrations was proposed; this revealed underdosage.

During our study, no PIs were performed on specific drugs used for COVID-19 such as remdesivir.

Nineteen per cent (35/188) of all PIs concerned ATC A drugs. No significant differences in PIs were observed between the two groups: 71.4% (25/35) and 28.6% (10/35) for positive and negative groups, respectively ( $p=0.747$ ). Non-conformity to guidelines (20.0%, 7/35) and overdosage (20.0%, 7/35) were the most prevalent. The ATC A drugs most involved were proton pump inhibitors (PPIs) and antidiabetic medications. PIs on PPIs

(31.4%, 11/35) were carried out for both groups: six and five for positive and negative groups, respectively, and most of these PIs resulted in reduced dosages (45.5%, 16/35). In one case, a drug (lansoprazole) was no longer prescribed. Antidiabetic medications, especially oral antidiabetic agents, accounted for more than 25.7% (9/35) of PIs: 4/9 and 5/9 for positive and negative groups, respectively.

The rate of PIs was significantly different in the two groups for the respiratory system (ATC R) (4 and 14 PIs for positive and negative groups, respectively;  $p=0.009$ ). PIs resulted in stopping Long-acting beta-2 agonist nebulisation (salbutamol, terbutaline and ipratropium) when not adapted to the patient ( $SpO_2 \geq 96\%$  in ambient air) in 27.8% (5/18) of cases: one and four PIs for the positive and negative groups, respectively. PIs on ATC R led to modifications of inadequate doses of inhaled drugs in 38.9% (7/18) of cases: one and six PIs for positive and negative groups, respectively. In one case, a PI was performed because of a redundant prescription of the same drug class (LABA+inhaled corticosteroids (ICSs)). Clinical pharmacists also helped three patients to understand the appropriate use of inhaling devices when transferred to pneumology wards. Globally, most PIs focused on overdosing and underdosing (33.3%, 6/18 PIs) and resulted in dose adjustment. Treatment termination was recommended for 33.3% (6/18 PIs).

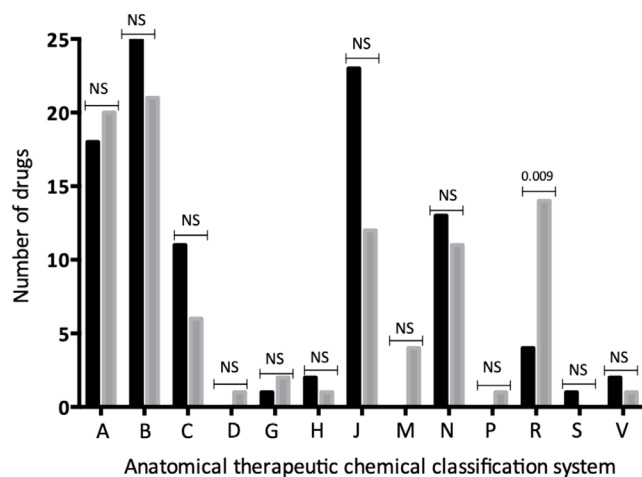
PIs related to non-conformity to guidelines represented 21.2% (22/104) and 21.4% (18/84) of total PIs for positive and negative groups, respectively (table 3). These PIs included eight drug-related errors (20%, 8/40) resulting from acute kidney injuries (AKIs) in both groups, which led to stopping the drug (metformin, ACE, allopurinol and spironolactone in three cases, two cases and one case, respectively). In all, three PIs focused on dosage adaptations in chronic kidney disease (heparin and oral anticoagulant for the positive group and oseltamivir for the negative group).

## DISCUSSION

To our knowledge, this prospective study is the first to assess hospital pharmacy interventions in reducing drug-prescribing errors during the coronavirus pandemic. In this monocentric cohort of 438 patients who underwent the COVID-19 test, it should be noted that for about 50% of patients, the PCR test was positive. More than a quarter of all patients presented a drug-related problem that required a PI. This rate is above that in Howard *et al's* review (3.7%)<sup>16</sup> and can be explained by the fact that patients with this infection were considered as emergencies

**Table 3** Classes of drugs and drug-related problems

Drug	Drug-related problem										Total (n=188)
	Non-conformity to guidelines	Drug follow-up	Indication without drug therapy	Underdosage	Overdosage	Drug without indication	Side effect	Inappropriate administration	Drug interaction		
Alimentary tract and metabolism	2	4	4	1	5	1	1			35	
A02 Drugs for acid-related disorders	2	4	4	1	5	1	1				
A03 Drugs for Functional Gastrointestinal Disorders	1										
A06 Drugs for Constipation	5	3	3		3	1	1				
A10 Drugs Used in Diabetes											
A11 Vitamins		1	1						1		
A12 Mineral Supplements		4	4		2						
Blood and blood-forming organs	10	6	6	11	12					43	
B01 Antithrombotic agents		2	2								
B03 Antianemic preparations									1		
C01 Cardiac therapy	1	1	1							16	
C02 Antihypertensives	1										
C03 Diuretics	1	1	1								
C07 Beta blocking agents					2						
C08 Calcium channel blockers	1								1		
C09 Agents acting on the renin-angiotensin system	3			1		1			1		
C10 Lipid-modifying agents		1	1							1	
D07 Corticosteroids, dermatological preparations		1	1								
D04 Urologicals				2					1	3	
Genitourinary system and sex hormones											
H01 Pituitary and hypothalamic hormones	1									3	
H03 Thyroid therapy									1		
J01 Antibacterials for systemic use	4			5	6	1			10	33	
J02 Antimycotics for systemic use		1									
J05 Antivirals for systemic use				1	3	1				7	
M02 Topical products for joint and muscular pain						1					
M03 Muscle relaxants				1							
M04 Antigout preparations	3	1	1								
N02 Analgesics	3				3				4	24	
N03 Antiepileptics		1	1						3		
N05 Psycholeptics		1	1						4		
N06 Psychoanaesthetics	2			1							
P01 Antiprotozoals				1						1	
R03 Drugs for obstructive airway diseases	5	3	4	4	3	2			1	18	
S01					1					1	
All other therapeutic products (oxygen)	3			29	40	8	5	26	4	3	
Total	45	5	26	29	40	8	5	26	4		



**Figure 1** Distribution of drugs according to anatomical, therapeutic and chemical classification system. NS, not significant.

and were treated by physicians who were specialists but not specialised in this disease.

In this monocentric prospective study, patients were mainly older men with pre-existing hypertension (50.4%, 221/438), obesity (22.6%, 99/438) and diabetes (21.7%, 95/438). These comorbidities were also identified in the large US study by Richardson *et al*, which included 5700 US patients, but at higher rates than in our study (56.6%, 41.7% and 33.8% for hypertension, obesity and diabetes, respectively).<sup>2</sup> Chronic respiratory diseases were highly prevalent in our cohort, especially chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea, just as in other studies.<sup>17 18</sup>

Our comorbid patients were polymedicated at home: the number of home medications was 4.0 (1.0–7.3) and 6.0 (3.0–10.0) for COVID-19-positive and COVID-19-negative patients, respectively ( $p < 0.0001$ ), which is lower than that in the study by Beuscart *et al*.<sup>19</sup>

As suggested by Li *et al*, clinical pharmacists have been extremely important in ensuring patient safety during the coronavirus pandemic.<sup>13</sup> Innovative pharmacy services were proposed by this Chinese team, especially for community pharmacists. In our hospital, the clinical pharmacy team was reorganised to ensure the drug-related management of COVID-19 infected or suspected patients, followed by PIs if necessary.

The proportion of accepted PIs was very high in our study, with an average of 89.5% (168/188 PIs) in both groups. This rate was higher than those identified in published studies<sup>20</sup> but lower when compared with Leape *et al*.<sup>10</sup>

During the 1-month study period, the major prescribing errors were related to antithrombotic agents (ATC B), that is, 21.8% (41/188) of all PIs. These PIs were important due to the high risk of thromboembolic complications in patients with COVID-19.<sup>6 21 22</sup> Thus, certain PIs focused on the addition of anticoagulant agents when non-prescribed in four COVID-19-positive patients (one PI was not accepted by the physician and one was not followed because of the patient's discharge). In more than a quarter of cases, dosage error was observed and PIs led to treatment modification.

For ATC A (alimentary tract and metabolism), clinical pharmacists mainly participated in optimising the appropriate use of PPIs in both groups. Indeed, PPIs are often overprescribed or overdosed, and most PIs were recommended in reducing dosages (41.6%, 5/12).<sup>23</sup> Long-term use of PPIs has been associated with

numerous adverse events, for example, pneumonia, dementia and chronic kidney disease.<sup>24–26</sup> Oral antidiabetic agents were largely prescribed during the study, leading to drug-error prescriptions. In fact, in three cases, metformin prescriptions were stopped by pharmacists due to AKI and were discontinued for another patient during high-level oxygen therapy.

Despite the lack of data to support their use, anti-infective agents (ATC J) were the cornerstone for treatment in suspected or confirmed respiratory coinfections, and pharmacists paid particular attention to prescriptions of broad-spectrum empirical anti-infective agents.<sup>27</sup>

In vitro, remdesivir is a substrate for the cytochromes CYP2C8, CYP2D6 and CYP3A4, P-glycoprotein transporters and an inhibitor of CYP3A4. We were particularly vigilant in our analyses of these potential interactions. However, any specific PI was performed.

SARS-CoV-2-infected patients with chronic respiratory diseases (asthma or COPD) require effective treatment relying on nebulisation by bronchodilators, oxygen and/or the use of drug-inhaling devices. In the positive group, 4 PIs were performed, while in the negative group, 14 PIs were performed. Most PIs concerned nebulised short-acting and inhaled long-acting bronchodilators: redundant prescriptions of the same class (two LABA+ICS), dosage errors and confusion among prescribed items.

A substantial proportion of PIs focused on dose adjustment or interruption of treatment for kidney injury, especially during AKI. More than 2% (3/118 patients) of the study patients were concerned by these PIs. For AKI in overall COVID-19-positive patients, the rate of PIs was 1.0% (1/104 PIs), which is very low, but this rate is to be considered in view of a very low incidence (2%) in the meta-analysis of AKI in hospitalised patients with COVID-19.<sup>28</sup> Unfortunately, the rate of AKI in this study is not available.

All general care units dedicated to treat patients with COVID-19 required the mobilisation of several physicians and interns to manage a huge influx of patients. In this context, hospital pharmacists helped to harmonise medical practices. Indeed, new protocols, in particular for preventive anticoagulation in obese patients, were implemented during our study.<sup>29</sup> Clinical pharmacists were able to assist prescribers in implementing this protocol.

## Limitations

This study has several limitations. The study population was limited to a single centre with a limited sample size which nevertheless is representative of the Northwest European population. The study period lasted only 1 month between March and April, but enabled us to examine the first peak of the COVID-19 epidemic.

## What this paper adds

### What is already known on this subject

- Management of COVID-19-positive patients is particularly complex, given the use of various drugs with a risk of drug interaction.
- The presence of pharmacists led to a significant reduction in prescription problems.

### What this study adds

- Drug-related problems and pharmaceutical interventions (PIs) concerned particularly antithrombotic and antibacterial drugs.
- No difference in PI was found relative to patient care pathways.
- The implementation of clinical pharmacy during a pandemic period is important.

Another limitation is that home medications were traced from patients' medical records because of the absence of medication reconciliation on admission. This does not provide an exhaustive list of home medications and probably underestimates their number, especially for older patients.<sup>30</sup>

## CONCLUSION

This study indicated no relative difference in PIs between COVID-19-positive and COVID-19-negative patients. The presence of pharmacists led to a significant reduction in drug-related prescription problems, especially for antithrombotic and antibacterial drugs in both groups.

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**Supplementary data : Pharmaceutical intervention classification tool proposed by SFPC** <sup>15</sup>

### **1. Drug related problem**

- Non conformity to guidelines or contra-indication
- Untreated indication
- Subtherapeutic dosage
- Supratherapeutic dosage
- Drug interaction
- Adverse drug reaction
- Improper administration
- Failure to receive drug
- Drug monitoring

### **3. Drug classification (ATC)**

- A Alimentary tract & metabolism
- B Blood & blood forming organs
- C Cardiovascular system
- D Dermatological
- G Genito urinary system & sex hormones
- H Systemic hormonal preparations
- J Anti-infective for systemic use
- L Anti-neoplastic & immunomodulating agents
- M Musculo-skeletal system
- N Nervous system
- P Antiparasitic products
- R Respiratory system
- S Sensory organs
- V Various

### **2. Intervention**

- Addition of a new drug
- Drug discontinuation
- Drug switch
- Change of administration route
- Drug monitoring
- Administration modalities optimization
- Dose adjustment

### **4. Intervention follow-up**

- Accepted
- Non accepted
- Non assessable