Drug-Associated Nephrotic Syndrome: A Global Pharmacovigilance Perspective

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Abstract

Introduction: Nephrotic syndrome is a rare clinical manifestation, with an estimated incidence of 3 cases per 100 000 population per year, which can be triggered by medications contributing to the development of its histopathological forms. The literature references various drugs such as antibiotics, allopurinol, pamidronate, sirolimus, among others. Pharmacovigilance studies enable the evaluation of the safety of these medications in large populations, identifying drugs most strongly associated with the phenotype under investigation.

Methods: This study involved the detection of notifications related to the development of nephrotic syndrome in VigiBase, and assessed the available data based on frequency, disproportionality, and their nephrotoxic role.

Results: During the selected period and among 37 145 123 available notifications, 7211 notifications related to drug-associated nephrotic syndrome were filtered using the appropriate MedDRA term. These predominantly affected male consumers aged 45-64 years, with the majority of notifications originating from the USA. Medications classified under ATC class L- antineoplastic and immunomodulating agents, were most frequently involved, and with penicillamine showing the highest association with this phenotype (ROR 231.28), followed by inotersen (ROR 24.49) and sunitinib (ROR 20.31), among others. These notifications had a mortality of 4.2%, with proton pump inhibitors being frequently implicated.

Conclusion: This study assessed VigiBase for the primary medications involved in the development of nephrotic syndrome, both in terms of frequency and associative strength. Clinician involvement is crucial in increasing notifications of adverse drug reactions. Understanding the main agents involved in various renal phenotypes helps improve prescription practices and ensures greater patient safety.

Keywords: Drug-Related Side Effects and Adverse Reactions; Nephrotic Syndrome/chemically induced; Pharmacovigilance

INTRODUCTION

The nephrotic syndrome is a clinical syndrome defined by significant proteinuria, responsible for hypoalbuminemia with consequent dyslipidemia, edema, and other complications.[1] Its incidence is estimated to be around 3 cases per 100 000/person-year, making it a rare but significant condition.[2]

Medications, a known cause of renal disease, account for approximately 20% of community and hospital-acquired acute kidney injury episodes,[3,4] with these figures potentially being much higher among the elderly or in intensive care units.[5]

Medications can cause damage in any renal compartment, from the glomerulus to the tubulointerstitium, resulting in various renal manifestations such as acute kidney injury, proteinuria, or nephrolithiasis.[6–8]

Although medications are a known cause of renal disease, drug-induced tubulointerstitial disease is the most frequently reported condition, with glomerular involvement being less described. However, recent studies have deepened our understanding of the pathogenesis of drug-induced glomerular disease, mainly affecting podocytes, endothelial cells, and mesangial cells, considering four main mechanisms of glomerular toxicity: i) cytotoxic injury or alteration of ionic charges of the filtration barrier, ii) immune-mediated injury, iii) toxicity related to xenobiotic accumulation, and iv) glomerulosclerosis.[9]

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The consequences of these lesions are diverse, ranging from minimal change disease,[10,11] to focal segmental glomerulosclerosis[11] resulting in the development of nephrotic syndrome, with or without association with other renal manifestations such as uremia manifested by acute kidney injury.

Several medications described sporadically in the literature have been associated with the development of some of these lesions, including gemcitabine, interferon, antibiotics, allopurinol, pamidronate, sirolimus, hydralazine, penicillamine, among others.[12]

Pharmacovigilance is essential for medication safety, allowing early identification of adverse reactions through continuous patient safety monitoring,[13] with pharmacoepidemiology being responsible for assessing the risks associated with medication use, as well as monitoring its effectiveness.[14] Thus, the evaluation of pharmacovigilance databases aimed at studying the consequences associated with medication use becomes a crucial endeavor, assessing notifications of adverse drug reactions identified in clinical practice. These studies enable the recognition of the affected consumer typology (age, sex), the geographic area of the reaction (country), the main drug classes involved, the most reported active ingredients, the degree of association between a specific drug and the studied phenotype, besides knowing the outcome of the reported adverse reaction.[15] All data is aggregated within each notification obtained, reported by the notifier at the time of reporting to each country's pharmacovigilance system. However, the conclusions drawn from pharmacovigilance studies, including associations or their strength, require validation through clinical studies.

The authors' main objective was to evaluate the WHO's VigiBase, one of the largest databases for collecting spontaneous adverse reaction reports, fully anonymized, to assess the medications most frequently reported in association with the development of nephrotic syndrome. It is noteworthy that Portugal has been contributing data to VigiBase since 1993. To the authors' knowledge, this is one of the first studies to evaluate this database to achieve this objective.

MATERIAL AND METHODS

Our study was conducted after approval from VigiBase to collect data and after approval from the ethics committee for their processing. We gathered data from VigiBase, an extensive database that aggregates spontaneous ADR reports from multiple countries worldwide, ensuring complete data anonymity. The data covers the period from 1968 to 2022. To ensure accuracy, we implemented rigorous procedures to eliminate duplicate notifications and assigned a unique identification number to each report for precise referencing. To achieve this, all notifications with repeated identification numbers were excluded, ensuring the absence of duplicate notifications. This dataset includes up-to-date information and offers comprehensive details for each notification, including anonymized patient information, notifier details, reaction severity, implicated drug, and a detailed description of the reported ADR.

The notifications were gathered following the selection of appropriate Medical Dictionary for Regulatory Activities (MedDRA) term at the Preferred Terms level.[16] Each drug was identified by its active ingredient, adhering to WHODrug nomenclature standards. Additionally, drugs were categorized into pharmacological groups based on the WHO's Anatomical Therapeutic Chemical (ATC) classification system. This approach facilitated a systematic analysis of the data based on specific pharmacological classifications.

In our study, disproportionality analysis utilized both the Information Component (IC) and the Reporting Odds Ratio (ROR). The IC compares the observed frequency of a specific adverse reaction associated with a medication against the expected frequency in the general population. A positive IC suggests that the adverse reaction is reported more often than expected, implying a potential association. By adjusting for expected frequencies, the IC minimizes random variations and reduces false positives, highlighting statistically significant associations.

The IC method filters out spurious data, excluding chance associations and thereby reducing false positives. The IC_{025}, representing the lower limit of the 95% confidence interval (with a positive value required by the Uppsala Monitoring Centre to statistically confirm the detection of a signal[17]), indicates the level of certainty that an observed medication-adverse reaction association is not random. This index compares the expected and observed values for a drug-adverse reaction pair, helping, with its positive value, to reduce the identification of false positives for new signals, in case the adverse reaction has a low expected frequency in the database, which would result in a high ROR.

For the main drugs identified either by frequency or their association with this phenotype, provided they had an $IC_{025} > 0$, the authors conducted a second assessment using both the ROR and evaluation through a bibliographic score developed by investigational team. The ROR is an index used in case-non-case studies that evaluates the strength of disproportionality, with an ROR value of 1 indicating no signal, meaning in this context that the ADR is reported equally with the drug under evaluation and any other drug.[18] For a signal to be present, an ROR > 1 is required for a specific drug-reaction pair.

For the development of this bibliographic score, each medication was evaluated using five distinct bibliographic sources — two databases,[19,20] one website,[21] and two reference books.[22,23] These sources were chosen for their bibliographic relevance and extensive literature on adverse drug reactions. This score was not validated and was used exclusively as a surrogate for the evidence of references regarding the

nephrotoxicity of each medication. Quantitative classification of drugs was based on the frequency of mentions across these sources to determine their nephrotoxic potential. A bibliographic score (BS) was systematically assigned to each drug, ranging from 0 (non-nephrotoxic) to 5 (nephrotoxic). Drugs were categorized as non-nephrotoxic with a BS of 0, potentially nephrotoxic with a BS of 1 to 2, and fully recognized as nephrotoxic with a BS of 3 or higher.

RESULTS

From the data collected between 1968 and 2023, WHO accumulated a total of 37 145 123 notifications, of which 7211 notifications were identified expressing an alleged nephrotic syndrome associated with medication use. These notifications implicated a total of 1943 medications or medication combinations during the evaluated period and have been increasing since the first 2 cases reported in 1968 at an average annual rate of 12.96%. A significant portion of the notifications originated from the United States (38.1%) and Japan (13.0%), with physicians being the primary reporting agents (49.8%) (see Table 1).

Table 1. Main Countries and Qualification of Reporting Agents

Countries	Number of notifications	Percentage	Reporter qualification	Number of notifications	Percentage
USA	2796	38.2	Physician	3626	49.5
Japan	939	12.8	Other Health Professional	871	11.9
France	533	7.3	Consumer/Non Health Professional	726	9.9
Germany	512	7.0	Pharmacist	360	4.9
UK	497	6.8	Lawyer	61	0.8
			Unknown	1567	33

UK – United Kingdom of Great Britain and Northern Ireland; USA – United States of America

Most affected consumers were male (50.4%), with the most reported age range being between 45 and 64 years, with 1760 notifications (24.4%), and the average age was 48.79 ± 23.39 years. From the perspective of the clinical manifestation presented by consumers, expressed by the main MedDRA terms, the main terms co-reported with nephrotic syndrome were acute kidney injury, which was the most frequent with 616 (8.4%) notifications, followed by peripheral edema with 479 (6.5%), and worsening of hypertension with 388(5.3%) notifications (see Table 2).

Table 2. Main MedDRA Terms Co-Reported in Association with Nephrotic Syndrome (top-10)

Co-Reported MedDRA Terms	Number of notifications	Percentage
Acute kidney injury	616	8.4
Edema peripheral	479	6.5
Hypertension	388	5.3
Edema	385	5.3
Renal failure	356	4.9
Renal impairment	286	3.9
Glomerulonephritis	258	3.5
Chronic kidney disease	252	3.4
Albuminuria	243	3.3
Weight increased	243	3.3

MedDRA – Medical Dictionary for Regulatory Activities

The medications classified as 'Antineoplastic and Immunomodulating Agents' (ATC L) were the most represented in the Anatomical Therapeutic Chemical (ATC) classification system, with 2433 notifications involved (33.2%), followed by 'Antiinfectives for systemic use' (ATC J) with 2096 (28.6%) notifications (see Table 3).

Table 3. Main ATC Classes Involved in Drug-Associated Nephrotic Syndrome

ATC Class	Number of Notifications	Percentage of Notifications
ATC: L Antineoplastic and immunomodulating Agents	2433	33.2
ATC: J Antiinfectives for systemic use	2095	28.6
ATC: S Sensory organs	1412	19.3
ATC: M Musculo-skeletal system	1322	18.1
ATC: A Alimentary tract and metabolism	1181	16.1
ATC: D Dermatologicals	1038	14.2
ATC: C Cardiovascular system	832	11.4
ATC: R Respiratory system	661	9.0
ATC: N Nervous system	561	7.7
ATC: G Genito-urinary system and sex hormones	547	7.5
ATC: H Systemic hormonal preparations, excl. sex hormones and insulins	376	5.1
ATC: V Various	278	3.8
ATC: B Blood and blood forming organs	262	3.6
ATC: P Antiparasitic products, insecticides and repellents	65	0.9

ATC- Anatomical Therapeutics Class

Among the most reported active ingredients, the COVID-19 vaccine was the most reported as a suspected medication, involving 954 notifications (13%), followed by bevacizumab with 307 (4.2%) and penicillamine with 167 (2.3%) notifications (see Table 4).

Table 4. Active Ingredients Most Frequently Reported in Association with Drug-Associated Nephrotic Syndrome (top-10)

Active Ingredient	Number of Notifications	Percentage of Notifications
COVID-19 vaccine	954	13.0
Bevacizumab	307	4.2
Penicillamine	167	2.3
Sunitinib	161	2.2
Diclofenac	154	2.1
Ibuprofen	150	2.0
Ciclosporin	150	2.0
Mycophenolic acid	144	2.0
Tacrolimus	142	1.9
Lansoprazole	134	1.8
Omeprazole	130	1.8

Among the medications with a significant disproportionality analysis, there are 37 medications with IC_{025}>0 (see Table 5). Among these, we highlight penicillamine with a strong association with the phenotype with an IC_{025} of 6.8, followed by sunitinib with an IC_{025} of 4.0 and bevacizumab with 3.9. Sirolimus, ciclosporin, and mycophenolic acid, widely used medications in Nephrology, follow with an IC_{025} of 3.4, 3.2, and 3.0, respectively.

Table 5. Medications with a disproportionality index IC_{025}>0 (top-10)

Active Ingredient	IC_{025}
Penicillamine	6.8
Sunitinib	4.0
Bevacizumab	3.9
Sirolimus	3.4
Ciclosporin	3.2
Mycophenolic acid	3.0
Pazopanib	2.9
Lithium	2.8
Dasatinib	2.0
Inotersen	2.0
Omeprazole	2.0

Penicillamine was the medication with the highest disproportionality index, with an ROR of 231.28 and an IC_{025} of 6.8, making it the active ingredient most strongly associated with the development of nephrotic syndrome.

Among immunosuppressive medications, by far the most relevant (in number) among those that showed the greatest disproportionality, we highlight sunitinib as the one with the strongest association with nephrotic syndrome (ROR 20.31; IC_{025} 4.0), bevacizumab (ROR 18.1; IC_{025} 3.9), sirolimus (ROR 16.25, IC_{025} 3.4), ciclosporin (ROR 11.36; IC_{025} 3.2), and pazopanib (ROR 10.52; IC_{025} 2.9). Next were the medications used in the treatment of nervous system diseases, with Inotersen showing the highest association (ROR 24.49; IC_{025} 2.0), followed by lithium (ROR 9.58; IC_{025} 2.8) and riluzole (ROR 9.37; IC_{025} 0.5).

Finally, medications used in musculoskeletal diseases also showed several examples of significant association with the development of nephrotic syndrome, as occurred with penicillamine showing the strongest ROR of all notified medications associated with the development of nephrotic syndrome (ROR 231.28, IC_{025} 6.8), diclofenac (ROR 4.41, IC_{025} 1.8), celecoxib (ROR 3.58, IC_{025} 1.4), or naproxen (ROR 3.18, IC_{025} 1.3) (see Table 6).

Table 6. Disproportionality Analysis for Nephrotic Syndrome According to the Bibliographic Score

Active Ingredient	ATC Class	Number of Notifications	IC_{025}	ROR	BS
Sirolimus	L	44	3.4	16.25	4
Bevacizumab	L	303	3.9	18.10	3
Naproxen	M	79	1.3	3.18	3
Celecoxib	M	62	1.4	3.18	3
Penicillamine	M	167	6.8	231.28	3
Sutinib	L	161	4.0	20.31	2
Pazopanib	L	59	2.9	10.52	2
Diclofenac	M	62	1.8	3.58	2
Inotersen	N	7	2.0	24.49	2
Ciclosporin	L	150	3.2	11.36	1
Lithium	N	64	2.8	9.58	1
Lansoprazol	A	134	-	10.15	0
Riluzole	N	4	0.5	9.37	0
COVID-19 vaccine	J	916	-0.3	1.03	0
Mycophenolic acid	L	144	3.0	9.85	0
Omeprazol	A	130	2.0	4.76	0

ATC – Anatomical Therapeutics Classification; BS – Bibliographic Score; IC_{025} – Bottom end of the 95% confidence interval of the information component (IC); ROR – Reporting Odds Ratio

In our assessment, it was possible to determine that among the main drugs evaluated, 5 of them had no bibliographic references regarding their nephrotoxic role (according to our BS), whereas 6 of the drugs could be considered potentially nephrotoxic based on a BS of 1-2. According to this BS, only 5 of these evaluated drugs have a well-established nephrotoxic role, meeting the criteria of BS ≥ 3.

It is worth noting that 4958 (67.7%) of the reported notifications were considered severe, mainly due to the need for hospitalization (37.7%). In the end, 311 (4.2%) notifications were fatal, with immunosuppressive medications being involved in more than half of the notifications with fatal outcomes (50.2%). However, omeprazole with 19 (6.1%) notifications (ROR 4.76; IC_{025} 2.0) and lansoprazole also with 19 (6.1%) notifications (ROR 10.15; IC_{025} not determined) were the active ingredients most reported in these notifications with the worst prognosis (see Table 7).

Table 7. Active Ingredients Most Frequently Reported in Association with Fatal Drug-Associated Nephrotic Syndrome (top-10)

Reported active ingredients (WHODrug)	Number of Notifications	Percentage of Notifications
Omeprazole	19	6.1
Lansoprazole	19	6.1
Bevacizumab	19	6.1
Pantoprazole	17	5.5
COVID-19 vaccine	17	5.5
Esomeprazole	14	4.5
Ciclosporin	12	3.9
Sunitinib	11	3.9
Adalimumab	11	3.5
Axitinib	9	2.9

DISCUSSION

Our study identified and classified the medications most frequently associated with the development of nephrotic syndrome in the world's largest database for collecting reports of adverse drug reactions, over a period of 55 years. These data highlight how rare, underreported, or underdiagnosed this entity is, as the notifications obtained represent only 0.019% of all notifications reported during this period. It is worth noting the low mortality of these notifications, with only 4.2% of them having a fatal outcome. These data were comparable to those found in the general population described in VigiBase, with a mortality rate of 4.1%. Additionally, this study is among the first to evaluate VigiBase to determine the main medications reported in the assessment of nephrotic syndrome. For this evaluation, we used IC_{025} for disproportionality analysis, corroborated by calculating the ROR among the main identified medications to strengthen the association with the studied phenotype. This study, resulting from the analysis of the WHO pharmacovigilance database, suggests the association of several medications with the development of nephrotic syndrome, proposing potential new nephrotoxins.

Of the most relevant medications evaluated, approximately 31% could be considered potential "new nephrotoxins" based on their bibliographic score of 0. Among these are 2 proton pump inhibitors - lansoprazole and omeprazole, which respectively showed an ROR of 10.15 and 4.76, demonstrating some associative strength with nephrotic syndrome, more prominently with lansoprazole. In fact, in a deeper literature review, although there are references suggesting that proton pump inhibitors (PPIs) may be associated with the development of proteinuria,[24] possibly due to their tubulointerstitial involvement,[25] the authors could not find other previous support describing cases where PPIs may be associated with the development of nephrotic syndrome. Additionally, both omeprazole and lansoprazole were the top 2 medications reported in notifications associated with fatal outcomes.

Riluzole, another identified and classified medication with a BS of 0, despite presenting an IC_{025} of only 0.5 - suggesting a very tenuous connection with the phenotype in question, showed an ROR of 9.37, which suggests a more significant association. Indeed, the absence of new bibliographic references describing the association between riluzole and nephrotic syndrome suggests that it should also be considered a potential new nephrotoxin, confirmation of which requires targeted studies.

From the perspective of the COVID-19 vaccine, another medication considered by us as a potential new nephrotoxin based on a BS of 0, upon further evaluation beyond the BS, it was possible to find literature associating this vaccine with the development of nephrotic syndrome.[26] The pathogenesis seems to result from the activation of

angiotensin-converting enzyme 2 receptors after administration of the vaccine, resulting in podocyte effacement.[27] Finally, among the medications that in our bibliographic score did not reveal evidence of nephrotoxicity for nephrotic syndrome, mycophenolic acid stands out, which showed an association with this entity with an IC_{025} of 3.0 and an ROR of 9.85. This association, which the authors could not find in a more in-depth literature search, is all the more equivocal given the known role of this medication in the treatment of this entity, where it is known to have a protective role on podocytes.[28] Therefore, since it cannot be excluded that this association actually reflects an observer bias,[29] the development of targeted studies is required to confirm this medication-phenotype linkage hypothesis.

Other medications with low literary evidence of their association with nephrotic syndrome were those that returned a BS of 1. Among these, cyclosporine stands out, which already has a known nephrotoxic history but associated with tubulointerstitial lesions.[30] From the perspective of nephrotic syndrome development, cyclosporine demonstrated a significant association with it both, through an IC_{025} of 3.22, but mainly through an ROR of 11.36. The development of cyclosporine nephropathy, mainly after 36 months of continuous CSA usage, is a possibility, mainly through the development of arteriolopathy that can occur with or without striped tubulointerstitial lesions.[31] Lastly, lithium, a widely used drug in the treatment of bipolar disorders,[32] demonstrated an association with nephrotic syndrome by presenting an IC_{025} of 2.8 and an ROR of 9.58. Although moderate in disproportionality indices, this association is scientifically supported. It complements the already known phenotypes of nephrotoxicity such as nephrogenic diabetes insipidus, renal tubular acidosis, and chronic tubulointerstitial nephropathy.[33] Lithium-induced nephrotic syndrome is a rare condition that can occur even with normal therapeutic lithium serum levels.[34]

Among the most frequently reported drug classes in our study, the class of antineoplastics and immunomodulators - ATC L, was the most notified and involved in the notifications found, being the class that showed the strongest association with nephrotic syndrome. Among these medications, sunitinib stands out with an IC_{025} of 4.0 and an ROR of 20.31, an antineoplastic agent used for the treatment of unresectable and/or metastatic gastrointestinal stromal tumors (GIST). Interestingly, the summary of product characteristics (SPC) does not mention nephrotic syndrome as a potential adverse event or complication. However, this phenotype is described as a rare but serious complication of this medication.[35] Data from the French registry revealed that patients treated with sunitinib and with nephrotic proteinuria demonstrated segmental and focal glomerulosclerosis, thrombotic microangiopathy, and acute tubular necrosis as associated histological findings.[36]

Also, bevacizumab showed high associations with this phenotype, notably with its ROR of 19.10. This medication, also indicated for the metastatic treatment of colon cancer, already contains a reference to the development of proteinuria in its summary of product characteristics (SPC). Acting on the VEGF signaling pathway, this medication is associated with the development of nephrotic syndrome in 0.6%-19.7% of patients.[37,38] Renal biopsies of patients with proteinuria demonstrated the development of thrombotic microangiopathy and membranoproliferative glomerulonephritis in probable relation to the damage that occurs after VEGF inhibition.[39]

Finally, among the medications showing the highest disproportionality associated with nephrotic syndrome, we consider penicillamine, which exhibits a significantly elevated IC_{025} of 6.8 and an exceptionally high ROR of 231.28, demonstrating the very strong linkage of this medication with this phenotype. Indeed, the association of this medication-phenotype pair has been known for many years,[40] with 60%-70% of patients developing proteinuria with penicillamine reaching nephrotic syndrome levels,[41] in the context of membranous glomerulonephritis development.[42]

From a mortality perspective, although they appear at the lower end of the top-10 list of most frequently reported medications, proton pump inhibitors (PPIs) were the most reported in notifications that involved fatal outcomes. While the study was not designed to provide reasons for this finding, the authors may speculate that it could be due to the stronger association these medications have with the development of acute kidney injury (AKI), as PPIs are known to be associated with AKI, particularly tubulointerstitial nephritis.[43] However, specific studies need to be conducted to establish the actual reason for the more frequent association of PPIs with mortality described in nephrotic syndrome notifications.

Few studies have addressed this topic in a manner that allows for a comparative analysis between our results and those of other studies. One of the studies found reported 4 cases of drug-induced podocitopathies, involving tamoxifen, penicillamine, and pembrolizumab-axitinib.[44] Indeed, in the data collected by us, penicillamine was the most reported medication, involved in 169 notifications with the high degree of association as reported above. Tamoxifen was reported in only 10 cases, with an IC_{025} of -0.1. As for the other 2 medications described in this study, pembrolizumab (without association with axitinib) was reported in 29 cases, and axitinib (alone) in 30 cases, for which it was not possible to obtain the IC_{025} value.

The field of glomerular disorders and podocytopathies has been evolving in recent years, particularly in oncology and the renal manifestations associated with its use. As highlighted by Garnier *et al*, the introduction of new anti-cancer medications in recent years has on one hand, somewhat sidelined medications historically associated

with these types of disorders, and brought to the forefront medications such as tyrosine kinase inhibitors or immune checkpoint inhibitors.[45]

This study presents several strengths. By analyzing a database that collects worldwide data, it reinforces the validity of the obtained data, as they reflect realities distributed worldwide, attenuating biases associated with data reports confined to a single region. Moreover, by collecting data based on the MedDRA and WHO drug dictionaries, it ensures standardization of nomenclatures and data processing methods, minimizing biases introduced by researchers. The preferential application of IC_{025} ensured the homogeneity of results, as this disproportionality score is integrated into VigiBase, eliminating calculation errors by the authors. Lastly, by covering more than 50 years of data from over 150 countries, it allows for the identification of a wide range of medications, reflecting global prescription practices.

However, this study also comes with limitations. Firstly, it relies on spontaneous notifications which inherently carry biases. These notifications can originate from trained healthcare professionals, as well as from consumers or non-medical individuals like family or friends, thus reducing the accuracy of the correct medication-phenotype pair. Underreporting biases are also a concern, potentially leading to an underestimation of the frequency of adverse drug reactions and falsely portraying medications as safer than they are. Selective reporting bias is another issue, where newer (Weber effect) or severe adverse reactions, or those linked to well-known medications, are more likely to be reported, creating a skewed perception of risk. Moreover, due to the frequent involvement of multiple medications in the reports collected, determining the true "suspected drug" can be challenging and may lead to misattribution. Lastly, recall and information biases can distort clinical information provided in reports, potentially attributing causality incorrectly to a different medication.[46] Additionally, relying on spontaneous notifications does not guarantee that the observed manifestation is indeed an adverse reaction. The reporting of these manifestations may be subject to reporting biases, with a bias towards reporting reactions that are either more severe or unexpected. Furthermore, with the majority of notifications reporting more than one medication, it is impossible to affirm that the suspected medication is indeed responsible for the reaction.

Finally, the use of a bibliographic score whose composition was decided solely by the authors based on their relevance to the area in question, without validation, makes this score less credible, even though the authors confirmed the suggestion of the score using bibliographic sources such as PubMed,[47] Web of Science,[48] Google Scholar[49] and Embase.[50]

Despite these limitations, this study reviewed the main medications associated with the development of nephrotic syndrome, as well as those that have a stronger association with this phenotype, attempting to uncover some medications that may be considered as new nephrotoxins.

CONCLUSION

Drug-associated nephrotic syndrome is rare (0.019% of all ADRs in VigiBase from 1968 to 2023), suggesting potential under reporting or under recognition of this condition. The most frequently implicated drug classes are antineoplastic/immunomodulating agents (33.2%) and systemic anti-infectives (28.6%). This study identifies several medications with high IC_{025} and RORs, highlighting their significant association with nephrotic syndrome, and identifies others that may be potential new nephrotoxins.

This study emphasizes the necessity for ADR notifications from all clinicians, advocating for a more proactive role in reporting such incidents. Vigilance through pharmacovigilance, including tools like ROR and IC_{025}, helps in identifying nephrotoxins and understanding their patterns of nephrotoxicity. Such vigilance and reporting are crucial for enhancing medication safety and reducing renal iatrogenesis.

Learning points/Take home messages

- Drug-associated nephrotic syndrome is infrequently reported in VigiBase
- Medications from ATC class L (Antineoplastic and immunomodulating agents) and ATC class J (Antiinfectives for systemic use) are predominantly implicated in reported adverse reactions.
- Medications from ATC class M (Musculo-skeletal system) demonstrate the strongest association with nephrotic syndrome
- Proton pump inhibitors are the most frequently implicated class associated with fatal reports
- Clinicians need to take a more active role in reporting adverse drug reactions.

Data availability statement

The data will be available for consultation if deemed necessary.

Disclaimer

The data presented in this study were sourced from VigiBase. The interpretation and reporting of these findings are solely the responsibility of the author(s) and should not be construed as an official policy or interpretation of the Uppsala Monitoring Centre.

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