Analysis of Adverse Drug Reactions reported in SQUH for Preventability

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Background & Aim

Adverse drug reactions (ADRs) are an important cause of morbidity and mortality in health care. Preventable adverse drug reactions commonly occur as a result of an inappropriate pattern of care, drug interactions, inadequate monitoring or administration of a drug to which a patient has had a previous allergic reaction or medication error that could have been detected, controlled, and avoided. A number of studies have explored the ability of a hospital's ADR database to identify common and repeated patterns of preventable adverse drug events (ADEs).

This study was carried out to analyses ADRs reported in SQUH over 2 years and to classify these ADRs according to the causative drug, drug class and the causality relationship.

Method

•A retrospective analysis of ADRs reported to Medicine Information Service (MIS) , pharmacy department, SQUH over 2 years from April 2011 to March 2013.

• Spontaneous reports are submitted on the designated ADR report form to MIS. These reports were entered in a database for documentation and further analysis.

• All ADRs were categorized according to:

1. Causative drug, 2. Drug class based on the **WHO ATC classification**.

3. Causality analysis (was according to the **WHO-UMC causality assessment system** categorized to : Certain, Probable/Likely, Possible, Unlikely,Conditional/Unclassified).

• A random sample of ADRs during admission was selected for analysis of preventability and severity.

• Preventable ADRs (pADR) were identified using preventability criteria adapted from **Schumock and Thornton** with modification (*See table 1*).

• The severity of pADRs was determined according to **Hartwig Severity scale**. Which categorised the severity into mild (level 1, 2), moderate (level 3,4, 5) and severe (level 6, 7) (*See table 2*).

• Data collection was done by 3 researchers who searched MIS ADR reports database and the patient electronic records (i.e. patient clinical notes, drug chart and laboratory results).

Table 1: Preventability criteria for ADR's

#	Category
1	Drugs involved were not appropriate for the patient's clinical condition.
2	Dose, route, or frequency of administration was not appropriate for the patient's age, weight, or disease.
3	Required therapeutic drug monitoring or other necessary laboratory tests were not performed or not performed frequently enough.
4	Patient has a history of allergy or previous reaction to the drug.
5	A known drug interaction was the suspected cause of the reaction.
6	A serum drug concentration above the therapeutic range was documented.
7	A medication error was associated with the reaction.

Table 2: Hartwig Severity Scale

Level		Severity
Level 1	An ADR occurred but required no change in treatment with the suspected drug.	Mild
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required No increase in length of stay (LOS)	Mild
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An antidote or other treatment was required. No increase in length of stay (LOS).	Moderate
Level 4	(A) Any level 3 ADR which increases length of stay by at least 1 day. OR (B) The ADR was the reason for the admission.	Moderate
Level 5	Any level 4 ADR which requires intensive medical care.	Moderate
Level 6	The adverse reaction caused permanent harm to the patient.	Severe
Level 7	The adverse reaction either directly or indirectly led to the death of the patient.	Severe

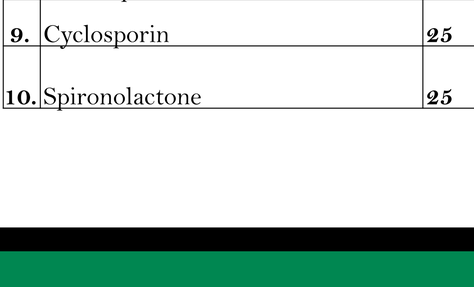
Results

Part 1: Analysis of All ADRs reported

A total of 1299 ADRs were reported and documented in MIS database between April 2011 and March 2013.

- 91.7 % of reported ADRs were done by pharmacists.
- The highest number of ADRs were reported in adults (n= 848, 65%), followed by elderly >65 years old (n=241, 19%). In children, 13% of all ADRS (n=165) occurred in children between 2-18 years old while only 3% (n=38) occurred in children < 2 years of age.
- Causality analysis of ADR's was completed for 1061 ADR reports. Majority of ADRs (74%) were assessed as probable in its causality. (s*ee **figure 1).***
- Analysis for pADR criteria and severity is summarized in table 5 & figure 3.

Figure 1 : Causality of ADR's



Analysis by drug and drug class:

- The 10 drugs most frequently associated with ADR's are listed in table 3.
- The most frequently associated drug class with ADR's were summarized in figure2.
- Table 4 lists the top five drug classes mostly associated with ADR's, the drugs involved in each class and examples of ADR's frequently reported with these drugs.

Table 3: Drugs most frequently associated with ADR's

#	Drugs	No.
1.	Enoxaparin	42
2.	Vancomycin	41
3.	Lisinopril	34
4.	Metformin	32
5.	Aspirin	27
6.	Liposomal amphotericin (Ambisome)	27
7.	Ceftriaxone	26
8.	Amlodipine	25
9.	Cyclosporin	25
10.	Spironolactone	25

Figure 2: Drug classes most frequently associated with ADR's

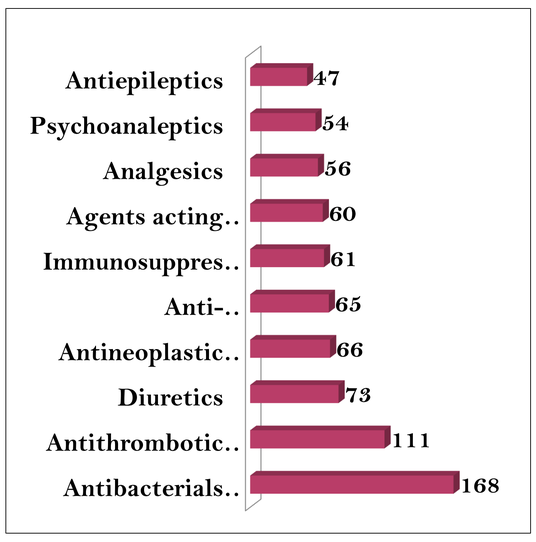


Table 4 : Drug Classes Mostly Associated With ADRs

Drug Class	No. of ADRs	Drug involved	No.	Most Common ADRs caused by the drug
ANTIBACTERIALS FOR SYSTEMIC USE (J01)	168	Vancomycin	41	Skin Reaction (19),Renal toxicity (12), Red Man Syndrome (4)
		Ceftriaxone	25	Skin reactions (12), Hepatic toxicity (4), Diarrhea (4)
		Amoxicillin & clavulanic acid	12	Skin reactions (7), Gastrointestinal discomfort (2)
		Meropenem	9	Hypokalemia (3), Drug induced fever (2), Skin reactions (2)
ANTITHROMBOTIC AGENTS (B01)	111	Enoxaparin	39	Hematuria (13), GI bleeding (5), Bleeding from other sites (9), Anemia (5), Thrombocytopenia (4)
		Aspirin	27	GI bleeding (9), Bleeding from other sites (7)
		Warfarin	11	GI bleeding (2), Bleeding from other sites (2), Drowsiness (2)
		Aspirin /Clopidogril combination	10	GI bleeding (8)
		Clopidogril	7	GI bleeding (4)
DIURETICS (C03)	73	Spironolactone	22	Hyperkalemia (18)
		Furosemide	19	Hypokalemia (6)
		Hydrochlorothiazide	19	Hyponatremia (7), Hypokalmeia (5)
ANTINEOPLASTIC AGENTS (L01)	66	Vincristine	7	Peripheral neuropathy (4)
		Hydroxyurea	4	Irritability (2)
		Oxaliplatin	4	Hypersensitivity reactions (3)
		Nilotinib	4	Vomiting/Abdominal pain (1), Constipation (1), Hyperbillirubinemia (1), Skin reactions & headache (1)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS (M01)	65	Diclofenac	23	GI bleeding (9), Renal toxicity (4)
		Celecoxib	11	Skin reactions (5)
		Ibuprofen	8	Skin reactions (4)

Part 2: Preventability analysis

860 ADRs out of all ADRs were reported in the inpatient setting. A random sample of 162 ADR reports was selected for the preventability analysis.

•27 reports were **excluded** for the following reasons:

1. Missing or wrong medical record number (n=5)
2. ADRs were later diagnosed as disease related rather than drug/related (n=2)
3. ADR's were reported prior to admission or led to admission (n=20).

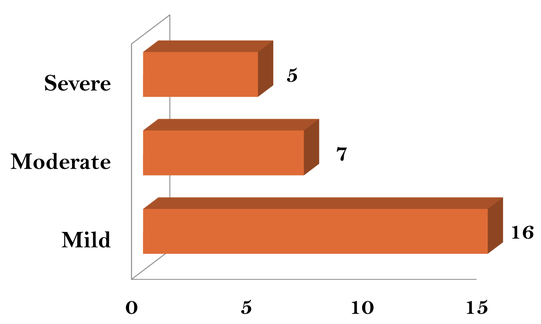
•Out of 135 ADR's that were analyzed for preventability assessment, **only 28 (20.7%) were considered pADR**. ***Table 5*** summarizes the preventability codes assigned for the ADR cases.

•All pADRS were categorized according to severity as summarized in figure 3.

Table 5: Distribution of Preventability Criteria

Preventability Code	Criterion	No. of times code used
1	Drug involved not appropriate for the patient's clinical condition	3
2	Dose, route, or frequency of administration was not appropriate for the patient's age, weight, or disease.	9
3	Required therapeutic drug monitoring or other necessary laboratory tests were not performed or not performed frequently enough	4
4	Patient has a history of allergy or previous reaction to the drug	6
5	A known drug interaction was the suspected cause of the reaction	6
6	A serum drug concentration above the therapeutic range was documented.	1
7	A medication error was associated with the reaction	2

Figure 3: Severity of Preventable ADRs



Reason for Occurrence of the pADRs

(1) Drug interaction or the administration of a combination of drugs that can cause the same ADR.

(2) Drug prescribed despite documented history of drug allergy, and

(3) Inappropriate administration of an IV medication such as wrong infusion rate and drug concentration (e.g. vancomycin)

Description of all reasons for the occurrence of pADRs is summarized in ***table 6***.

Table 6: Reason for Occurrence of the pADRs

Drug involved/ number of cases	no.	Description of the preventable ADR	Severity
Lisinopril and Spironolactone (2) **Irbesartan (1)** **Aspirin/clopidogril (1)** **Contrast media (1)** **Liposomal amphotericin (1)**	6	Drug interaction/ OR a combination of drugs that can cause the same ADR	Moderate (3) Mild (3)
Vancomycin (2) **Phenytoin (1)** **Piperacillin/Tazobactam (1)**	4	Inappropriate administration of an IV medication (i.e. wrong infusion rate or drug concentration)	Moderate (4)
Maprotiline (1) **Natalizumab (1)** **Cisplatin (1)**	3	The patient has been on this medicine before and experienced the same ADR	Mild (3)
Celecoxib (1) **Aspirin(1)**	2	Drug prescribed despite documented history of drug allergy	Severe (1) Mild (1)
Aspirin (1) **Aspirin /NSAID combination (1)**	2	Patient has a history of Gastrointestinal bleeding, or gastric/Peptic ulcer and should not be on this medication	Mild (2)
Enoxaparin (2)	2	Anti-Xa level was not done	Mild (1) Severe(1)
Mycophenolate (1)	1	Therapeutic drug levels not checked/documented.	Mild (1)
Diclofenac (1)	1	Allergy not documented	Severe (1)
Nilotinib (1)	1	Off license use	Mild (1)
Amiodarone (1)	1	Patient had high thyroid levels before starting however started on the drug without close monitoring	Moderate (1)
Spironolactone (1)	1	Patient receiving the medication from health institution and proper history of the dose was not documented.	Mild (1)
Vancomycin (1)	1	Vancomycin level was 36.6 then increased to 40	Moderate (1)
Warfarin (1)	1	Drug is category X in pregnancy	Severe (1)
Mirtazapine (1)	1	Inappropriate use in elderly patient	Mild (1)

Conclusion

Our study has identified certain drug classes with high risk of developing ADRs. The risk of the identified classes of drugs has been well documented by previous analysis done in SQUH and corroborate with other studies. Analysis of a hospital database identified adverse drug effects of medications due to inappropriate use of medication. Identifying reasons for these pADRs need to be explored used a larger number of sample with aim to improve the current drug-use system.

References

1. Schumock et. al.. *Hosp Pharm.* 1992; 27:538.
2. Winterstein et. Al. Am J Hosp. Pharm. 59.18 (2002): 1742-1749.
3. Hartwig et. al. *Am J Hosp Pharm* 1992; 49: 2229 – 2232.

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