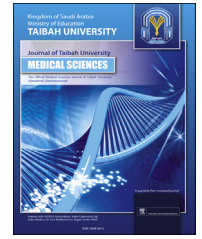Taibah University

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Original Article

Contraindicated medications administered to inpatients with renal insufficiency in a Saudi Arabian hospital that has a computerized clinical decision support system

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الملخص

هدف البحث: تهدف هذه الدراسة إلى تحديد أنواع مختلفة من الأدوية المحظور استخدامها وأعطيت للمرضى الذين يعانون من القصور الكلوي، من قبل الأطباء الذين تجاوزوا التحذيرات التي تقدمها أنظمة دعم القرارات السريرية الحاسوبية.

طرق البحث: تمت هذه الدراسة بأثر رجعي على جميع المرضى المنومين، خلال الفترة من ١ يناير إلى ٣١ ديسمبر ٢٠١٠م، بمستوى كرياتينين > ١٠٧ مجم/ دسل في مستشفى رئيس في المنطقة الشرقية، بالمملكة العربية السعودية. تم استخدام مربع كاي واختبار الانحدار اللوجستي متعدد المتغيرات لتقييم العوامل المرتبطة لاحتمال زيادة المرضى الذين يتلقون الأدوية المحظورة، نظرا لتجاوز الأطباء التحذيرات من أنظمة دعم القرارات السريرية الحاسوبية.

النتائج: تلقى ما مجموعه ٣١٤ مريضا دواء واحدا على الأقل من الأدوية التي يتم التخلص منها عن طريق الكليتين و/أو محتملة الضرر للكليتين. كان ١٤٪ من هذه الأدوية محظورا وأسفر عن تحذير في النظام ومع ذلك أعطيت للمرضى. الأدوية المحظورة حددت بأربعة أدوية: الأسبرين، وجليكلازايد، ونيتروفيورانتوين، وسبيرونولاكتون، ويمثل الأسبرين ٦٠٪ من جميع الأدوية المعطاة للمرضى. أظهر الانحدار اللوجستي متعدد المتغيرات أن احتمالات أخذ هذه الأدوية الأربعة المحظورة تزيد لدى المرضى الذين يعانون من قصور كلوي حاد بعد ضبط العوامل الخارجية.

الاستنتاجات: لازال الأطباء يتجاوزون التحذيرات التي تقدمها أنظمة دعم القرارات السريرية الحاسوبية ويقومون بإعطاء أدوية محظورة لمرضى القصور الكلوي. هذه الأدوية تنحصر في عدد محدود من الأدوية. وأكدت هذه الدراسة أيضا أن قاعدة بيانات الأدوية في النظام قد تحتاج إلى تحديث بمدخلات من الأطباء المستخدمين للنظام.

الكلمات المفتاحية: القصور الكلوي؛ نظام دعم القرارات السريرية؛ تجاوز؛ تحذير؛ الأدوية المحظورة

Abstract

Objective: The aim of this study was to determine various types of contraindicated medications that are administered to patients with renal insufficiency by physicians who override alerts provided by the Computerized Decision Support Systems (CDSS).

Methods: This retrospective study incorporated all admitted patients during the period from January 1st through December 31st, 2010, with serum creatinine levels >1.7 mg/dL in a major tertiary hospital in the Eastern Province of the Kingdom of Saudi Arabia (KSA). Chi-square and multivariate logistic regression tests were used to evaluate the factors associated with the increased likelihood of patients receiving contraindicated medication due to physicians overriding the CDSS alert.

Results: A total of 314 patients received at least one medication that was renally cleared and/or potentially nephrotoxic. Fourteen percent of these medications were contraindicated and resulted in a system alert and yet were administered to the patients. The administered

contraindicated medications were limited to 4 drugs: aspirin, gliclazide, nitrofurantoin, and spironolactone, with aspirin accounting for approximately 60% of all of the medications received by patients. Multivariate logistic regression showed that the odds of receiving these four contraindicated drugs increased in those with severe renal insufficiency (OR = 23.4, 95% CI 9.9–54.9, $p < 0.001$) after adjusting for confounding factors.

Conclusion: Physicians override the CDSS alerts and prescribe medications that are contraindicated for patients with renal impairment. These medications are limited in number. This study also emphasizes that the medication database system might need to be updated with input from the physicians using the system.

Keywords: Alert; Clinical decision support system; Contraindicated medications; Override; Renal insufficiency

Introduction

The high prevalence of renal insufficiency in hospital populations and the fact that most drugs and their active metabolites are eliminated through the kidney makes this group of patients highly vulnerable for adverse drug events.[1] Physicians need to consider adjusting the dosage to the level of renal function when prescribing medications to avoid an over dosage, toxicity or further worsening of renal function. With the large number of drugs introduced each year that have varying relationships with the function of the kidney, it is hard for any physician to accurately recall these relations from memory. It is no surprise that several studies have demonstrated high rates of inappropriate dosing for patients with renal insufficiency.[2–4] In a large case-control study, Chertow et al. revealed that the inappropriate prescription of nephrotoxic or renally cleared medications occurred at a rate of 70% in patients hospitalized with renal impairment.[5] In another study, the authors indicated that among 1648 patients, 67% of the drugs prescribed were not adjusted to individual renal function levels.[6] To address this problem, the Institute of Medicine and other influential organizations have endorsed clinical decision support systems (CDSS) as an important strategy for reducing medication errors.[7]

In Saudi Arabia, just as in other parts of the world, medication error is a major concern. Khoja et al. found that 18.7% of all of the prescriptions in an inpatient setting are medication errors.[8] In a paediatric setting, Al- Jeraisy et al. found that overall medication errors were present in 56 per 100 medication orders.[9] Even though reducing medication error is important for all of the patients receiving medical care, patients with renal insufficiency are of particular importance. Not only are they at an increased risk of medication errors and adverse drug events but also the prevalence of chronic kidney disease (CKD) in the Kingdom has been increasing at a fast rate over the last three decades as a result of social and demographic changes.[10,11]

With the mandatory introduction of hospital information systems by the Saudi Ministry of Health, integrating CDSS with the Computerized Physician Order Entry (CPOE) can advise physicians on appropriate dosing for patients at varying levels of renal function at the point of care.[12] However, a number of studies have shown that CDSS had limited success in reducing medication errors.[13–15] The most cited explanation was clinician noncompliance with the alert or advice provided by these systems.[16,17]

Frequent clinically unjustified alerts presented to physicians as they enter their drug orders may result in what has been termed "alert fatigue", which may cause physicians to override clinically important alerts or to even totally abandon the decision support system.[18,19] However, at the same time, medications that result in such alerts are considered by the CDSS knowledge base to be of high risk and are harmful to patients with a compromised kidney reserve. Insight into the medications to which physicians tend to override contraindications may reveal potential problems in the CDSS knowledge database that need to be updated or a lack of knowledge of the medication risks risk by treating physicians that may require more physician training. To better understand these issues, this study aimed to determine the types of contraindicated medications administered to patients with renal insufficiency by physicians who override CDSS alerts in a major Ministry of Health hospital in Saudi Arabia. The study will also examine the factors associated with such overrides.

Materials and Methods

Study setting

This study was conducted in a major Ministry of Health referral hospital providing tertiary care in the Eastern Province, Saudi Arabia. This 600-bed hospital utilizes a commercial electronic medical record (EMR) supported by CDSS that was mandated by the Ministry of Health. This system supports all orders, laboratory results, and patient medication information in the hospital. Computerized order checking for patient-specific parameters with decision support algorithms, including drug–drug interaction, allergies, and drug lab and drug disease interactions, are fully functional. In addition, the system provides advice alerts on drug dosing and avoidance. This study was approved by the Hospital Institutional Review Board.

CDSS and internal logic relevant to renal insufficiency

Each time a newly measured serum creatinine is added by the Lab in the EMR, an estimated creatinine clearance (eCrCl) is calculated according to Cockcroft–Gault (CG) equation.[20] Utilizing a list of drugs that are either renally cleared and/or are potentially nephrotoxic, the internal logic of the commercial CDSS was designed to trigger an *avoid alert* if the physician attempts to order one of the contraindicated drugs according to the most recently calculated eCrCl and predetermined safe cut-off point for

the drug. The system provides a screen alert message and the established recommendations for completing the order.

Data source

During the one-year period (from January 1st through December 31st, 2009), patients with serum creatinine levels >1.7 mg/dL were candidates to be included in the study. Detailed prescriptions, age, sex, serum creatinine, body weight, and type of treating physician (specialist: yes/no) were abstracted from the electronic medical record. A detailed examination of the data was performed for medications that are renally cleared and/or potentially nephrotoxic. The most recent documented values for weight, serum creatinine and eGFR prior to each prescription of a medication that was renally cleared and/or potentially nephrotoxic were used to estimate kidney function just prior to the prescription of such medication. These medications were then categorized according to the CDSS internal database into two types: 1) *contraindicated medications*, if the administered medication was considered to be contraindicated given the kidney function just prior to its administration (irrespective to the drug type or group); 2) *not a contraindicated medication*, if the medication was renally cleared and/or nephrotoxic but not contraindicated given the level of renal function just prior to its administration. Patients <18 years and those who had a renal transplant, were on dialysis, or were diagnosed with acute kidney injury (AKI) were excluded from the study.

Estimation of kidney function

Renal function in adults is usually reported on the basis of eGFR normalized to a body surface area of 1.73 m^2 and derived from the Modification of Diet in Renal Disease (MDRD) formula. However, published information on the effects of renal insufficiency on drug elimination is usually stated in terms of eCrCl as a surrogate for the glomerular filtration rate. For potentially toxic drugs, the eCrCl calculated from the CG formula is used to adjust the dosages.[20] The National Kidney Disease Education Program (NDKEP) in the US recommends that the GFR estimated from the MDRD study or eCrCl estimates from the CG equations for adults can be used for drug dosing.[21]

For this study, the two methods used to calculate estimated kidney function were the Cockcroft−Gault equation[20] and the abbreviated MDRD study equation.[22]

Cockcroft − Gault creatinine clearance (mL/min)

$$= \left(\frac{(140 - \text{age}) * [\text{lean body weight(kg)}] * C}{[\text{serum creatinie (μmol/L)}]} \right)$$

(C = 1.23 for males, 1.04 for females)

Abbreviated MDRD eGFR (mL/min/1.73 m^2) =

$$175 * [\text{serum creatinine (μmol/L)}/88.4]^{-1.154}$$
$$* (\text{age})^{-0.203} * (0.742 \text{ if female}) * (1.212 \text{ if black})$$

Statistical analysis

We first described the study population with the means and standard deviations for continuous variables and proportions for categorical variables. Fisher's exact test was used for univariate analysis followed by multivariate logistic regression (enter method) to determine the physician and patient characteristics associated with ordering contraindicated medications. The dependent variable was the admission of a contraindicated medication (yes/no). The independent variables included patient age, sex, severity of renal insufficiency (sever vs. mild/moderate), shift during which the prescription was given (8 am−4 pm/4p m−8 am) and day that the prescription was given (weekend/weekday). The physician specialist status (specialist/not specialist) was also included. All analyses were performed using STATA v.11 (Stata Corp, College Station, Texas).

Results

Out of the 314 prescriptions that were renally cleared and/ or potentially nephrotoxic, 44 (14%) were for contraindicated medications. The mean (SD) age of this study group was 54.5 (18.6) years, 55.4% were male, 18.5% had severe renal insufficiency, and approximately 83% of the orders were given by a non-specialist, Table 1.

Table 2 demonstrates that the contraindicated medications ordered were limited to only 4 types, 59.1% (n = 26) were for aspirin, 29.6% (n = 13) were for gliclazide, and 9.1% (n = 4) were for nitrofurantoin; and only one patient received spironolactone.

Table 3 presents the patient characteristics according to whether they received one of the four contraindicated medications. Of the patients who received a contraindicated medication, 56.8% (n = 25) were given to patients aged >65 years compared to 28.2% (n = 76) among patients who did not receive a contraindicated medication, P = 0.001. A high percentage of patients who received contraindicated medications were patients with severe renal insufficiency, 70.5% (n = 31) compared to only 10% (n = 27) among those who were not given a contraindicated medication, P < 0.001.

Table 4 presents the results of the multivariate logistic regression confirming that after adjusting for all of the confounding factors, patients with severe renal insufficiency were more likely to receive one of the four contraindicated medications despite the alert compared to patients with a milder renal insufficiency (OR 23.4, 95% CI 9.9−54.9; P < 0.001).

Discussion

In this study, 314 patients with serum creatinine >1.7 mg/ dL received at least one medication that was renally cleared and/or potentially nephrotoxic. Fourteen percent of those were for contraindicated medications that resulted in a system alert and were still administered to the patients by the ordering physician despite the alert. Administered contraindicated medications included 4 drugs: aspirin, gliclazide,

Table 1: Patient characteristics.

Characteristic	Number n = 314	%
Age in years[a], mean (SD)	54.5 (18.6)	
Total medication, median(interquartile range)	14(7−24)	
Gender		
Male	174	55.4
Female	140	44.6
Estimated creatinine clearance[b]		
Sever renal insufficiency	58	18.5
Mild/Moderate renal insufficiency	256	81.5
Day time[c]		
8 am−4 pm	203	64.6
5 pm−7 am	111	35.4
Day of the week		
Week days	254	80.9
Weekends	60	19.1
Specialist		
Yes	55	17.5
No	259	82.5
Type of medication[d]		
Contraindicated	44	14.0
Not contraindicated	270	86.0

[a] The number is the mean and standard deviation.
[b] Severe renal insufficiency is ≤ 10 mL/min; mild/moderate renal insufficiency is 11−50 mL/min.
[c] Day time: the time of day the order was entered.
[d] Contraindicated: physician ordered a contraindicated medication; not contraindicated: physician ordered a medication that was not contraindicated and did not produce an avoid alert.

Table 3: Characteristics of the patients who received one of the four contraindicated medications.

Variables	Patient with contraindicated medication n = 44	Patient without contraindicated medication n = 270	P-value
Age in years			
<55	15(34.1)	145(53.7)	
55−65	4(9.1)	49(18.1)	<0.001
>65	25(56.8)	76(28.2)	
Gender			
Male	21(47.7)	153(56.7)	
Female	23(52.3)	117(43.3)	0.27
Day of the week			
Weekday	39(88.6)	215(79.6)	
Weekend	5(11.4)	55(20.4)	0.16
Shift of the day			
8 am−4 pm	25(56.8)	177(65.6)	
4 pm −8 am	19(43.2)	93(34.4)	0.41
Level of renal insufficiency[a]			
Severe renal insufficiency	31(70.5)	27(10.0)	
Mild/ moderate renal insufficiency	13(29.5)	243(90.0)	<0.001
Specialist			
No	32(72.7)	228(84.4)	
Yes	12(27.3)	42(15.6)	0.07

[a] Severe renal insufficiency is ≤10 mL/min; mild/moderate renal insufficiency is 11−50 mL/min.

nitrofurantoin, and spironolactone with aspirin, which accounted for approximately 60% of these medications.

Several studies on the effectiveness of CDSS alerts to reduce the prescription of the contraindicated medications to patients with a renal insufficiency found a wide range of effectiveness of alerts by these systems, with most of these studies finding reduced levels of effectiveness, mostly due to noncompliance by physicians.[5,23−25] In our study, and similar to other studies, the administration of contraindicated medications to patients with renal insufficiency is still high in hospitals that implemented CDSS, although it is lower compared to previous studies: 14% in our study vs. a range of 19.9%−47% among other studies.[17,26,27] There are three main explanations for the discrepancy between our study and the previous studies. First, a variation in the definition of error could explain this difference. In our study, error was defined as

Table 4: Multivariate logistic regression for the factors associated with the increased likelihood of receiving one of the four contraindicated medications.

Characteristics	OR[a]	95% CI	P-value
Age			
18− <55	1		
55− < 65	1.9	0.5−7.1	0.34
≥65	6.1	2.4−15.4	<0.001
Level of renal insufficiency[b]			
Mild/moderate renal insufficiency	1		
Sever renal insufficiency	23.4	9.9−54.9	<0.001
Gender			
Male	1		
Female	1.3	0.6−2.9	0.51
Day time			
8 am−4 pm	1		
5 pm−7 am	1.4	0.6−3.2	0.41
Day of the week			
Week days	1		
Weekends	0.5	0.2−1.7	0.28
Consultant			
No	1		
Yes	2.26	0.9−5.9	0.10

[a] OR = Odds ratio.
[b] Severe renal insufficiency is ≤10 mL/min; mild/moderate renal insufficiency is 11−50 mL/min.

Table 2: Administered contraindicated medications according to the patient characteristics.

Drugs	Total	Creatinine clearance		Gender		Age
		≤10	11−50	Male	Female	Mean (SD)
Aspirin	26 (59.1)	26	0	12	14	60.1 (22.4)
Gliclazide	13 (29.6)	4	9	6	7	62.4 (16.7)
Nitrofurantoin	4 (9.1)	0	4	3	1	78.7 (4.2)
Spironolactone	1 (2.2)	1	0	0	1	48 (0)

administering drugs that are contraindicated given the level of renal impairment, while other studies defined error as a combination of the administration of contraindicated drugs and/or the administration of an inappropriate dose. Second, there are major variations in the drug information sources used by the systems in these different studies.[28] Some drugs that are marked as contraindicated in one source are not considered to be such in another source. Third, there are variations in the definition and classification of renal impairment among these sources; some sources categorized renal function into five different stages,[29] while others divided renal function into three categories, which leads to some drugs being considered to be contraindicated in some studies but not in others.[30]

In a study by Salomon et al.,[31] in a setting with no CDSS system, the authors found that among 886 prescriptions that were four drugs that were either renally cleared and/or potentially nephrotoxic, 14% received contraindicated medications, which is similar to the percentage in our study hospital with a fully functioning CDSS system. This might indicate that physicians in our study hospital were noncompliant to the system alerts. Our study did not interview physicians to determine their reasons for noncompliance with the decision support recommendations. However, some of the causes for noncompliance have been examined in previous studies.[32–34] One proposed cause is that CDSS systems provide alerts for reordering or renewing medication orders that were previously tolerated by the patient.[33] Noncompliance can also result when the physician feels that he/she knows more about the specific clinical condition of the patient than the CDSS. Physicians often see their patients on a daily basis and are likely to be familiar with changes in their medical condition. This level of information may not be available to the CDSS or may be in a format that cannot be utilized by the logic of the system.[34] Another factor that was suggested is the clinical usefulness of the alert itself. Spina et al.[32] found that 86% of the alerts were actually not useful. On the other hand, it is also possible that noncompliance could be caused by a lack of knowledge among physicians about the necessity of withholding such medications in patients with a renal insufficiency.[23]

In our study, most of the overridden orders were for aspirin. Other overridden orders were for nitrofurantoin, gliclazide, and spironolactone. Interestingly, the chronic effects of these medications on the progression of renal insufficiency, as presented in the literature, are contradicting and inconclusive at best. For example, the BNF indicates that aspirin should be used with caution and should to be avoided in cases of severe renal impairment.[35] Others have also indicated that aspirin has exacerbating effects in patients with CKD in a dose-dependent manner.[36] That is in contrast to other studies that indicated that aspirin might be safe for use in patients with diagnosed advanced renal insufficiency stages 4–5 without an adverse effect on the progression of the disease.[37] BNF indicated that nitrofurantoin should be avoided altogether if the eGFR is less than 60 mL/min.[35] Furthermore, nitrofuration product information also indicated that it is contraindicated in patients with eCrCl values below 60 ml/min.[38] In contrast, the literature review by Oplinger et al. indicated that the data supporting the contraindication of nitrofurantoin for patients with eCrCl values less than 60 mL/min are

nonexistent.[39] Gliclazide, like other sulfonylureas, has increased potency as the renal function decreases and is considered in some literature to be contraindicated in severe renal failure.[40] Other recent studies, however, indicated that it is a preferred sulfonylurea with no need for dose adjustment.[41] Finally, spironolactone is considered by some published studies to be well tolerated in select patients with early stage renal insufficiency, although strict monitoring over the first few months is suggested.[42]

Given this inconsistency, it is possible that the physicians in this study hospital are not only accustomed to and frequently use these medications in everyday practice but are also familiar with the indecisiveness about the effect of these medications in the medical community. It is no surprise that many physician override the *avoid alert* when they try to administer these drugs to their patients.

Our study investigated the factors that are associated with noncompliance and the eventual receipt of one of these four contraindicated medications. Older people were at a higher risk for receiving these contraindicated medications. We also found a surprising negative association between noncompliance with these medications and the level of renal dysfunction. Salomon et al.[31] suggested that this unexpected pattern does not reflect the quality of the physician order but the fact that the same medication order that is considered to be contraindicated in patients with severe renal insufficiency is considered to be appropriate in patients with mild/moderate renal insufficiency. We believe that more studies are needed to verify Salomon's argument.

There are several limitations of the current study. First, the study was conducted in only one Ministry of Health affiliated hospital using a commercial CDSS system. Accordingly, the results may not be generalizable to other hospitals or other systems. Second, this study did not examine the adverse effects on the involved patients; therefore, we do not know what harmful effect, if any, the overridden alerts had on these patients. Third, the unavailability of the data on the demographic characteristics of both the patients and treating physicians, other comorbidities, and main underlining disease of the patient is another limitation of the study. Including these factors in our analysis would have better explained the different reasons that physicians override alerts.

Conclusion

Our study has two main conclusions. First, physicians override the CDSS alerts and prescribe medications that are considered to be contraindicated by the CDSS knowledge database for patients with reduced renal function. Second, these medications are limited in number, and thus, physicians could be encouraged to replace these medications with other safer medications or at least be educated about the contraindications. More studies are needed to determine physicians' perceptions about the system and the factors related to their noncompliance to its alerts. More studies are also needed to evaluate the system information, system integration, and its alliance with the organizational and clinical workflow.

The paucity of these types of studies in Saudi Arabia makes this study of great importance and an incentive for

future studies, particularly as the Saudi government is moving forward with implementing these systems in hospitals nationwide. Decision makers need to realize that such research must guide the development of new hospital information technology, particularly in relation to the selection of future systems and their flexibility to be adjusted to accommodate physicians' experience and evidence based medicine.

Authors contribution

All authors have significantly contributed to the manuscript. That included: conceptualizing the idea and study design, data acquisition, data analysis and data interpretations. All authors were also involved in drafting the article or critically revised it.

Conflict of interest

The authors have no conflict of interest to declare.

References

1. Nygaard HA, Naik M, Ruths S, Kruger K. Clinically important renal impairment in various groups of old persons. **Scand J Prim Health Care 2004 Sep**; 22(3): 152−156.
2. Long CL, Raebel MA, Price DW, Magid DJ. Compliance with dosing guidelines in patients with chronic kidney disease. **Ann Pharmacother 2004 May**; 38(5): 853−858.
3. Nash IS, Rojas M, Hebert P, et al. Reducing excessive medication administration in hospitalized adults with renal dysfunction. **Am J Med Qual 2005 Mar**; 20(2): 64−69.
4. Sheen SS, Choi JE, Park RW, Kim EY, Lee YH, Kang UG. Overdose rate of drugs requiring renal dose adjustment: data analysis of 4 years prescriptions at a tertiary teaching hospital. **J Gen Intern Med 2008 Apr**; 23(4): 423−428.
5. Chertow GM, Lee J, Kuperman GJ, et al. Guided medication dosing for inpatients with renal insufficiency. **JAMA 2001 Dec 12**; 286(22): 2839−2844.
6. Falconnier AD, Haefeli WE, Schoenenberger RA, Surber C, Martin-Facklam M. Drug dosage in patients with renal failure optimized by immediate concurrent feedback. **J Gen Intern Med 2001 Jun**; 16(6): 369−375.
7. Institute of Medicine Committe on Data Standards for Patient Safety (CoDSfPS). *Patient safety: achieving a new standard for care*. Washington DC: National Academies Press; 2004.
8. Khoja T, Neyaz Y, Qureshi NA, Magzoub MA, Haycox A, Walley T. Medication errors in primary care in Riyadh City, Saudi Arabia. **East Mediterr Health J 2011 Feb**; 17(2): 156−159.
9. Al-Jeraisy MI, Alanazi MQ, Abolfotouh MA. Medication prescribing errors in a pediatric inpatient tertiary care setting in Saudi Arabia. **BMC Res Notes 2011**; 4: 294.
10. Annual Report. *Saudi center for organ transplantation* (Accessed 2015). Available from URL: http://www.scot.org.sa; 2009.
11. Al-Sayyari AA, Shaheen FA. End stage chronic kidney disease in Saudi Arabia. A rapidly changing scene. **Saudi Med J 2011 Apr**; 32(4): 339−346.
12. Field TS, Rochon P, Lee M, Gavendo L, Baril JL, Gurwitz JH. Computerized clinical decision support during medication ordering for long-term care residents with renal insufficiency. **J Am Med Inf Assoc 2009 Jul**; 16(4): 480−485.
13. Nebeker JR, Hoffman JM, Weir CR, Bennett CL, Hurdle JF. High rates of adverse drug events in a highly computerized hospital. **Arch Intern Med 2005 May 23**; 165(10): 1111−1116.
14. Linder JA, Ma J, Bates DW, Middleton B, Stafford RS. Electronic health record use and the quality of ambulatory care in the United States. **Arch Intern Med 2007 Jul 9**; 167(13): 1400−1405.
15. Welch WP, Bazarko D, Ritten K, Burgess Y, Harmon R, Sandy LG. Electronic health records in four community physician practices: impact on quality and cost of care. **J Am Med Inf Assoc 2007 May**; 14(3): 320−328.
16. Moxey A, Robertson J, Newby D, Hains I, Williamson M, Pearson SA. Computerized clinical decision support for prescribing: provision does not guarantee uptake. **J Am Med Inf Assoc 2010 Jan**; 17(1): 25−33.
17. Sellier E, Colombet I, Sabatier B, et al. Effect of alerts for drug dosage adjustment in inpatients with renal insufficiency. **J Am Med Inf Assoc 2009 Mar**; 16(2): 203−210.
18. Nanji KC, Slight SP, Seger DL, et al. Overrides of medication-related clinical decision support alerts in outpatients. **J Am Med Inf Assoc 2014 May**; 21(3): 487−491.
19. McCoy AB, Waitman LR, Lewis JB, et al. A framework for evaluating the appropriateness of clinical decision support alerts and responses. **J Am Med Inf Assoc 2012 May**; 19(3): 346−352.
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. **Nephron 1976**; 16(1): 31−41.
21. National Institute of Diabetes and Digestive and Kidney Diseases. *Health professionals CKD and drug dosing information for providers. Estimation of kidney function for prescription medication dosage in adults* http://nkdepnih.gov/resources/CKD-drug-dosing.shtml; 2014 [cited 2014 Aug 29].
22. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. **Ann Intern Med 2006 Aug 15**; 145(4): 247−254.
23. Terrell KM, Perkins AJ, Hui SL, Callahan CM, Dexter PR, Miller DK. Computerized decision support for medication dosing in renal insufficiency: a randomized, controlled trial. **Ann Emerg Med 2010 Dec**; 56(6): 623−629.
24. Patwardhan MB, Kawamoto K, Lobach D, Patel UD, Matchar DB. Recommendations for a clinical decision support for the management of individuals with chronic kidney disease. **Clin J Am Soc Nephrol 2009 Feb**; 4(2): 273−283.
25. Oppenheim MI, Vidal C, Velasco FT, et al. Impact of a computerized alert during physician order entry on medication dosing in patients with renal impairment. **Proc AMIA Symp 2002**: 577−581.
26. Galanter WL, Moja J, Lambert BL. Using computerized provider order entry and clinical decision support to improve prescribing in patients with decreased GFR. **Am J Kidney Dis 2010 Nov**; 56(5): 809−812.
27. Schedlbauer A, Prasad V, Mulvaney C, et al. What evidence supports the use of computerized alerts and prompts to improve clinicians' prescribing behavior? **J Am Med Inf Assoc 2009 Jul**; 16(4): 531−538.
28. Khanal A, Castelino RL, Peterson GM, Jose MD. Dose adjustment guidelines for medications in patients with renal impairment: how consistent are drug information sources? **Intern Med J 2014 Jan**; 44(1): 77−85.
29. Joint Formulary Committee. *British national formulary*. 67th ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2014.
30. Arnoff GR, Berns JS, Brier ME. *Drug prescribing in renal failure*. 5 ed. Philadelphia, PA: American College of Physicians; 2007.
31. Salomon L, Deray G, Jaudon MC, et al. Medication misuse in hospitalized patients with renal impairment. **Int J Qual Health Care 2003 Aug**; 15(4): 331−335.

32. Spina JR, Glassman PA, Belperio P, Cader R, Asch S. Clinical relevance of automated drug alerts from the perspective of medical providers. **Am J Med Qual 2005 Jan**; 20(1): 7−14.

33. Hsieh TC, Kuperman GJ, Jaggi T, et al. Characteristics and consequences of drug allergy alert overrides in a computerized physician order entry system. **J Am Med Inf Assoc 2004 Nov**; 11(6): 482−491.

34. Galanter WL, Polikaitis A, DiDomenico RJ. A trial of automated safety alerts for inpatient digoxin use with computerized physician order entry. **J Am Med Inf Assoc 2004 Jul**; 11(4): 270−277.

35. Joint Formulary Committee, British Medical Association, Pharmaceutical Society of Great Britain. BMJ Group & Pharmaceutical Society. London, UK: British National Formulary; 2011.

36. Kuo HW, Tsai SS, Tiao MM, Liu YC, Lee IM, Yang CY. Analgesic use and the risk for progression of chronic kidney disease. **Pharmacoepidemiol Drug Saf 2010 Jul**; 19(7): 745−751.

37. Evans M, Fored CM, Bellocco R, et al. Acetaminophen, aspirin and progression of advanced chronic kidney disease. **Nephrol Dial Transpl 2009 Jun**; 24(6): 1908−1918.

38. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. **Arch Intern Med 2003 Dec 8**; 163(22): 2716−2724.

39. Oplinger M, Andrews CO. Nitrofurantoin contraindication in patients with a creatinine clearance below 60 mL/min: looking for the evidence. **Ann Pharmacother 2013 Jan**; 47(1): 106−111.

40. Krepinsky J, Ingram AJ, Clase CM. Prolonged sulfonylurea-induced hypoglycemia in diabetic patients with end-stage renal disease. **Am J Kidney Dis 2000 Mar**; 35(3): 500−505.

41. Abe M, Okada K, Soma M. Antidiabetic agents in patients with chronic kidney disease and end-stage renal disease on dialysis: metabolism and clinical practice. **Curr Drug Metab 2011 Jan**; 12(1): 57−69.

42. Edwards NC, Steeds RP, Chue CD, Stewart PM, Ferro CJ, Townend JN. The safety and tolerability of spironolactone in patients with mild to moderate chronic kidney disease. **Br J Clin Pharmacol 2012 Mar**; 73(3): 447−454.