Routine Use of the "ADE Scorecards", an Application for Automated ADE Detection in a General Hospital

Emmanuel Chazard[a], Michel Luyckx[b], Jean-Baptiste Beuscart[c], Laurie Ferret[a], Régis Beuscart[a]

[a] *Public Health Department, Lille University Hospital; UDSL EA 2694; Univ Lille Nord de France; F-59000 Lille, France.*
[b] *Hospital Pharmacy, Lille University Hospital; UDSL EA 4481; Univ Lille Nord de France; F-59000 Lille, France.*
[c] *Geriatrics Department, Lille University Hospital; UDSL EA 2694; Univ Lille Nord de France; F-59000 Lille, France.*

Abstract

Retrospective detection of Adverse Drug Events (ADEs) is challenging, notably because ADEs result from complex interactions between many factors. Data mining techniques have recently emerged in the field of automated retrospective ADE detection. The "ADE Scorecards" are a research application based on data-mining that has been built in the framework of the PSIP European Project, and potentially enables automated ADE retrospective detection. The objective of this paper is to evaluate the use of the ADE Scorecards in a real-life healthcare situation. For that purpose, the ADE Scorecards have been implemented in a French general hospital and have been used by the physicians and pharmacists for three years (corresponding to 73,000 inpatient stays). According to the results, 2% of the analyzed inpatient stays have a potential ADE with hyperkalemia, and 1% of them have a potential ADE with vitamin K antagonist overdose. In practice, the application, which was first designed to be a standalone web-based application for the physicians, has been used as a part of a more global quality improvement approach led by the pharmacists.

Keywords:

Adverse Drug Events, Adverse Drug Reactions, Data Mining, Data Reuse, Electronic Health Records.

Introduction

Adverse Drug Events (ADEs) can be defined as "injur(ies) due to medication management rather than the underlying condition of the patient" [1]. This definition emphasizes that ADEs are due to a combination of causes, including drugs (drug administration, dose variations, and drug discontinuations) and characteristics of the patient (such as age, diseases, renal and hepatic functions) [2]. This complexity explains why skill is required to properly detect ADE cases.

Retrospective ADE detection consists of analyzing past hospital stays to discover cases where ADEs occurred. Several such approaches have been developed [3-4], and can be grouped into 2 categories: expert-operated methods and automated methods. The first ones mainly consist of retrospective medical chart reviews and reporting systems. The development of automated methods is more recent and tries to address under-declaration and under-detection biases. Automated methods include natural language processing of discharge summaries [5-8], and data mining of electronic health records (EHRs) [9].

Based on data mining, an application has been developed within the PSIP European Project (Patient Safety through Intelligent Procedures in medication). This application, named "ADE Scorecards" [10], is a surveillance tool that enables researchers to automatically detect potential past ADE cases by highlighting the potential causes (drugs, biological context, demographics, etc) and the outcome. Those potential ADE cases can then be confirmed by experts and used for physicians' training. This application has been installed in five hospitals (2 Danish, 2 French and 1 Bulgarian) as a proof of concept. It has been routinely used by the physicians and pharmacists of a French general hospital over three years.

The objective of this paper is to present the application and show the results of its use in a real-life situation.

Materials and Methods

EHRs from the Denain General Hospital

A structured description of past hospital stays is automatically extracted from the EHRs of the Denain General Hospital, in the North of France. Those records fit a data model that has been designed previously [11], and only uses routinely-collected data: no additional data has to be specifically recorded. The data model includes medical and administrative information (e.g. age, gender, admission date), diagnoses (ICD10 codes), medical procedures, drugs administered daily to the patient (ATC codes), laboratory results (IUPAC codes), and free-text records anonymized using the FASDIM procedure [12].

Adverse Drug Events detection rules

Knowledge about ADEs is generally described using ADE detection rules. An ADE detection rule is made of one or more Boolean conditions that may lead to an outcome, with a given probability, such as $C_1 \& \dots \& C_k \rightarrow O$. This is a simplified notation, as in addition the rule implicitly requires that time constraints are respected: the condition must precede the outcome, and still be active when the outcome occurs. That representation is widely used either for prospective ADE prevention or retrospective ADE detection [13]. In this work we use a set of 236 rules that have been discovered in a previous work by data mining of EHRs [9]. In that work, routinely-collected inpatient data have been used to identify potential outcomes. Then, by mean of data-mining techniques (such as decision trees and association rules), conditions statistically associated with those outcomes have been identified. Finally, the rules

have been filtered, reorganized and validated by pharmacology experts. Those rules involve 1 to 4 conditions (demographic characteristics, drug administrations or discontinuations, laboratory results, or diagnoses) and an outcome that can be detected in the data (e.g. "Hyperkalemia", "International Normalized Ratio elevation", etc.). The rules include 56 kinds of outcomes. They are described as a set of structured XML files, including:

- mappings that enable transformation of the raw data into Boolean variables with temporal attributes,

- the set of rules,

- a lexicon for automated translation into English, French, Danish or Bulgarian, and

- a set of free-text explanations that explain each rule and provide bibliographic references in each language.

The ADE Scorecards, a retrospective ADE detection tool

The ADE Scorecards are a web-based application that enables users to detect and display potential past ADE cases in a user-friendly interface. The process relies on two steps (Figure 1).
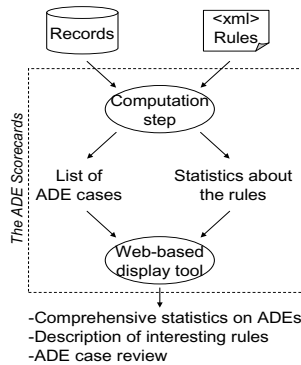

Figure 1 – The 2 parts of the ADE Scorecards

Figure 2 – Contextualized statistics (underlined)

The *computation step* consists in running the ADE detection rules on the inpatient stays that are extracted from the EHRs. Several contextualized statistics are computed for each rule in each medical department (Figure 2). They allow contextualized behavior of the application. Indeed, previous works have demonstrated the need for such contextualization in the field

of ADE detection [14]. As a result of that first step, several inpatient stays are flagged as "potential ADEs" (these cases are not always real ADEs; they have to be confirmed).

The second step, *web-based display tool*, consists of displaying the potential ADE cases, the related ADE detection rules, and statistics. For that purpose, a web-based application has been developed using a Human-centered design process [15]. It preserves the anonymity of the patients. Finally, the users are provided with contextualized information: the potential ADE cases are detected in their medical unit, the statistics are contextualized, and only the ADE detection rules that are useful in their medical unit are displayed. A free demonstration of the application is available on the Web [16]. Finally, a case facility allows users to visualize each potential ADE case, enabling the physicians to form their own opinions on the detected cases.
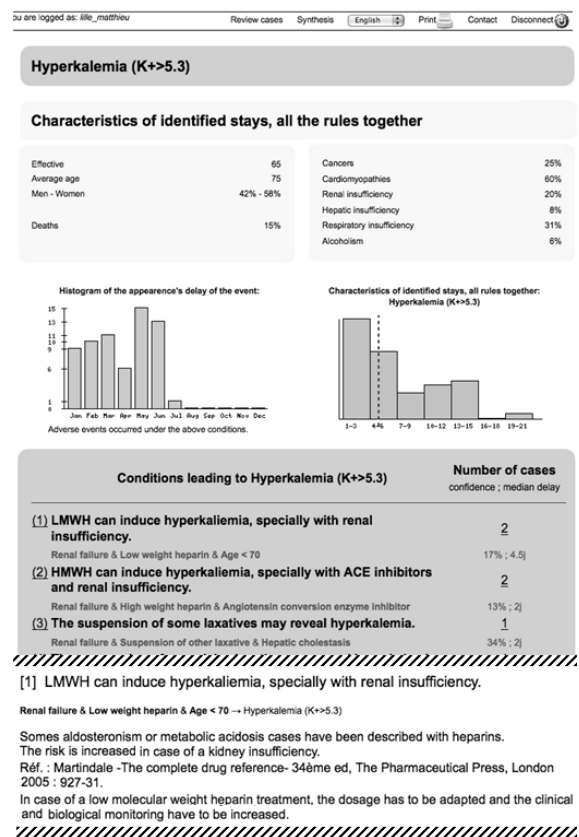
Figure 3 – Scorecard of potential ADEs with hyperkalemia (hatched lines denote a truncation of the screenshot)

Quantitative observation of the application

The data are analyzed from January 2007 to August 2012. Some statistics are computed to describe the patients and their medical backgrounds, especially the characteristics that are known to have a strong interference with medications. Comparisons are performed using Chi-2 tests and Student's t-tests with a 5% alpha risk. Confidence intervals are computed with a 5% alpha risk.

The number of potential ADE cases detected by the application is broken down by medical department and year. A focus is placed on the most frequent outcomes:

- Hyperkalemia: defined as $K^+ > 5.5$ mmol/l in this case. This ionic problem may induce lethal cardiac rhythm troubles.

- INR increase: defined as INR>5 in this case (INR=international normalized ratio of the prothombin time). Such a disorder could induce a severe hemorrhage. A frequent cause is a vitamin K antagonist (VKA) overdose or a VKA biological availability increase.

Qualitative preliminary evaluation of the use of the application in real-life

The daily use of the Scorecards is observed from January 2010 to December 2012 by a human-factors specialist and a pharmacist. They observe how the application is used in practice by analyzing log files, interviewing users and analyzing staff meetings that use the outputs of the tool. This observation is the preliminary study of a more complete and structured evaluation.

Results

Description of the inpatient stay database

The number of inpatient stays analyzed is shown in Table 2. Only the inpatient stays that present the following characteristics are analyzed: there is at least one drug administration, the patient is hospitalized for at least 2 days, and the patient is hospitalized in a medical department where the ADE Scorecards are implemented. The general characteristics of the inpatient stays are displayed in Table 1. Those characteristics are compared between the medical departments in Table 3.

Table 1 – Description of the inpatients stays analyzed

Parameter	Estimated value
General characteristics	
Age (years)	60.2
Length of stay (days)	8.01
Proportion of men	40.8%
Abnormal laboratory results	
INR increase	2.46%
Hyperkalemia	5.43%
Chronic diseases (ICD10 codes)	
Renal insufficiency	2.02%
Hepatic insufficiency	4.90%
Administered drugs	
VKA	8.34%
Diuretics	23.3%
Main medical department	
Cardiology	24.4%
Geriatrics	3.75%
Gynecology Obstetrics	10.0%
Internal medicine	18.4%
Pneumology	15.8%
Surgery	27.7%

Table 2 – Number of inpatient stays and stays analyzed

Year	Total number of stays	Number of stays analyzed
2007	10,244	6,084
2008	11,338	6,271
2009	12,469	6,215
2010	14,747	6,490
2011	15,042	6,274
2012 (Jan-Aug)	9,996	4,301
TOTAL	73,836	35,635

Table 3 – Comparison of the inpatients stays between medical departments (p<0.001 in each line of the table)

Department	Cardi-ology	Geri-atrics	Gyn. Obs.	Int. med.	Pneu-mo.	Sur-gery
Age (years)	67.6	82.4	28.0	69.7	67.8	57.6
Length of stay (days)	8.19	11.6	6.56	10.5	11.8	8.42
Men	42.8%	28.8%	0.00%	39.4%	63.2%	37.8%
Renal insufficiency	3.04%	4.83%	0.04%	4.20%	2.04%	0.60%
Hepatic insufficiency	13.7%	2.42%	0.04%	6.26%	2.34%	1.47%
VKA	15.5%	12.9%	0.00%	13.7%	14.8%	1.67%
Diuretics	41.1%	30.1%	0.00%	31.6%	35.4%	12.9%

ADEs or not, many abnormal laboratory results are observed during the hospitalizations as defined in the "Material and Methods" section. Their incidence rate is displayed in Table 4.

Table 4 – Proportion of stays with an abnormal laboratory result detected during the hospitalization (being ADEs or not)

Parameter	Estimated value
INR increase	2.46% [2.30% ; 2.62%]
Hyperkalemia	5.43% [5.19% ; 5.67%]

Estimated number of ADEs

This section presents the number of potential ADE cases detected by the ADE Scorecards (without expert validation).

Table 5 displays the number and proportion of potential ADE cases with INR increase year after year (see also Figure 4). Those proportions are detailed by medical department in Table 6.

Table 5 – Potential ADE cases with INR increase (* 2012: from January to August)

Year	Number	Proportion
2007	67	1.10% [0.84%;1.36%]
2008	60	0.96% [0.72%;1.20%]
2009	71	1.14% [0.88%;1.41%]
2010	49	0.76% [0.54%;0.97%]
2011	61	0.97% [0.73%;1.22%]
2012*	45	1.05% [0.74%;1.35%]
TOTAL	*353*	*0.99% [0.89%;1.09%]*

*Table 6 – Potential ADE cases with INR increase
by medical department (comparison: p<0.001)*

Department	Proportion
Cardiology	1.36% [1.07%;1.65%]
Geriatrics	0.00% [0.00%;0.00%]
Gynecology Obstetrics	0.00% [0.00%;0.00%]
Internal medicine	1.63% [1.27%;1.99%]
Pneumology	2.12% [1.67%;2.56%]
Surgery	0.14% [0.05%;0.23%]

Table 7 displays the number and proportion of potential ADE cases with hyperkalemia year after year (see also Figure 4). Those proportions are detailed by medical department in Table 8.

*Table 7 – Potential ADE cases with Hyperkalemia
(* 2012: from January to August)*

Year	Number	Proportion
2007	145	2.38% [2.00%;2.77%]
2008	146	2.33% [1.95%;2.70%]
2009	125	2.01% [1.66%;2.36%]
2010	108	1.66% [1.35%;1.98%]
2011	120	1.91% [1.57%;2.25%]
2012*	81	1.88% [1.48%;2.29%]
TOTAL	*725*	*2.03% [1.89%;2.18%]*

*Table 8 – Potential ADE cases with Hyperkalemia
by medical department (comparison: p<0.001)*

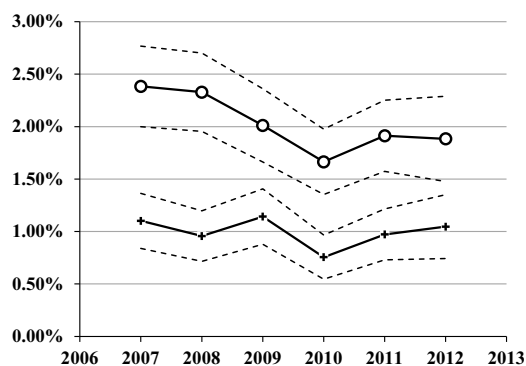| Department	Proportion
Cardiology	2.65% [2.25%;3.05%]
Geriatrics	3.36% [2.22%;4.51%]
Gynecology Obstetrics	0.00% [0.00%;0.00%]
Internal medicine	2.68% [2.22%;3.14%]
Pneumology	2.77% [2.26%;3.27%]
Surgery	0.88% [0.66%;1.10%]

*Figure 4 – incidence rates of potential ADEs
("+":INR increase; "o": Hyperkalemia;
"---": 95% confidence intervals)*

Qualitative preliminary evaluation

The ADE Scorecards are routinely used in two ways. Some of the physicians or head nurses use the application monthly to view the statistics and review some cases. The most important use, however, is made by the pharmacists of the hospital. Every month in every department, the pharmacists use the application to plan a meeting with all the physicians. Since the ADE Scorecards were installed, some interesting cases detected by the application have been used to support the discussion. The pharmacists report that, formerly, their recommendations could sometimes be perceived as "too theoretical". By means of the ADE Scorecards, they can now support their recommendations with visual display of real ADE cases from the department they meet. Moreover, the ADE Scorecards are able to detect complex pharmacokinetic drug interactions that are rarely known and that previously would not be discussed with the physicians. According to the users of the Scorecards, about half the detected cases are real ADE cases involving a cause-to-effect relationship between the potential causes highlighted by the application and the outcome. According to them, this ratio is sufficient to use the application as a support tool for morbidity and mortality reviews, after expert filtering.

Discussion

Initially designed in a research project, the ADE Scorecards have demonstrated after three years of daily use that they can also support real-life healthcare. The application enables users to detect past ADE cases and highlights the causal conditions that are linked with some outcomes. It also allows computation of longitudinal statistics about ADEs.

In this study we estimate a 2% incidence rate of ADEs with hyperkalemia and a 1% incidence rate of ADEs with INR increase. Those figures, provided for two specific outcomes, are consistent with the literature. According to the literature, ADEs occur in 2.4 to 5.2 per 100 hospitalized adult patients [17-21]. In [22], 2.8 ADEs occur for 100 patients*days, this could correspond to 5-10% of the stays.

However, the incidence rates that are displayed in this study are related to *potential* ADEs and not *confirmed* ADEs. The ADE cases should be validated by means of an expert review. The qualitative evaluation suggests that the accuracy of the detection should be around 50%. A quantitative expert-operated review performed on a limited sample previously showed a precision (positive predictive value) of 52% in the field of hyperkalemia [9]. A more complete quantitative evaluation is still in progress: it consists of a case review (detected and undetected cases) performed by pharmacology experts.

The curves on Figure 4 suggest a small decrease of the ADE incidence rates of Hyperkalemia over the observation period. As the patients may differ from one year to the next, a simple statistical comparison of proportions would not be sufficient. A more complete study is also in progress, in order to adjust incidence rates with the patients' medical background, by means of propensity scores.

The application was initially designed for a wide use by the physicians as a standalone tool. The qualitative evaluation suggests that the ADE Scorecards are more likely to be used as a support to a more global quality improvement approach, led by pharmacists. For instance, the ADE Scorecards enable pharmacists to quickly find ADE cases, and those cases -as well as their user-friendly scrollable representations- are easy to validate or not, and to use in morbidity and mortality re-

views. The qualitative evaluation that is still in progress principally aims at highlighting usability problems and suggesting improvements of the tool.

Conclusion

The ADE Scorecards have demonstrated utility in real-life healthcare, especially as a support to more traditional quality improvement approaches. Complementary studies must be performed to compute the precision of the ADE detection, and to assess whether the use of the application is associated with a change in the ADE incidence rates.

References

[1] Institute Of Medicine. Preventing Medication Errors. Washington, DC: The National Academic Press; 2007.

[2] Nebeker JR. Clarifying Adverse Drug Events: A Clinician's Guide to Terminology, Documentation, and Reporting. Ann Intern Med. 2004;140:795-801.

[3] Bates DW, Evans RS, Murff H, Stetson PD, Pizziferri L, Hripcsak G. Detecting adverse events using information technology. J Am Med Inform Assoc. 2003 Mar-Apr;10(2):115-28.

[4] Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. Qual Saf Health Care. 2004 Aug;13(4):306-14.

[5] Cantor MN, Feldman HJ, Triola MM. Using trigger phrases to detect adverse drug reactions in ambulatory care notes. Qual Saf Health Care. 2007 Apr;16(2):132-4.

[6] Gysbers M, Reichley R, Kilbridge PM, Noirot L, Nagarajan R, Dunagan WC, et al. Natural language processing to identify adverse drug events. AMIA Annu Symp Proc. 2008:961.

[7] Melton GB, Hripcsak G. Automated detection of adverse events using natural language processing of discharge summaries. J Am Med Inform Assoc. 2005 Jul-Aug;12(4):448-57.

[8] Aramaki E, Miura Y, Tonoike M, Ohkuma T, Masuichi H, Waki K, Ohe K. Extraction of adverse drug effects from clinical records. Stud Health Technol Inform. 2010;160(Pt 1):739-43.

[9] Chazard E, Ficheur G, Bernonville S, Luyckx M, Beuscart R. Data Mining to generate Adverse Drug Events detection rules. IEEE Trans Inf Technol Biomed. 2011 Nov;15(6):823-30. Epub 2011 Aug 22.

[10]Chazard E, Baceanu A, Ferret L, Ficheur G. The ADE Scorecards: a tool for Adverse Drug Event detection in Electronic Health Records. Stud Health Technol Inform. 2011.

[11]Chazard E, Merlin B, Ficheur G, Sarfati JC, PSIP Consortium, Beuscart R. Detection of adverse drug events: pro-

posal of a data model. Stud Health Technol Inform. 2009;148:63-74.

[12]Chazard E, Mouret-Kubiak C, Ficheur G, Beuscart R. Déidentification automatisée de courriers médicaux : la méthode FASDIM. Revue d'Épidémiologie et de Santé Publique, Volume 60, Supplement 1, March 2012, Page S18.

[13]Handler SM, Altman RL, Perera S, Hanlon JT, Studenski SA, Bost JE, et al. A systematic review of the performance characteristics of clinical event monitor signals used to detect adverse drug events in the hospital setting. J Am Med Inform Assoc. 2007 Jul-Aug;14(4):451-8.

[14]Chazard E, Bernonville S, Ficheur G, Beuscart R. A Statistics-based Approach of Contextualization for Adverse Drug Events Detection and Prevention. Stud Health Technol Inform. 2012;180:766-70.

[15]ISO 13407:1999, Human-centered design processes for interactive systems.

[16]Free demonstration of the ADE Scorecards. [cited 2012 December 10]. Available from: http://psip.univ-lille2.fr/prototypes/public/

[17]Bates DW, O'Neil AC, Boyle D, Teich J, Chertow GM, Komaroff AL, Brennan TA. Potential identifiability and preventability of adverse events using information systems. J Am Med Inform Assoc, 1994. 1(5): p. 404-11.

[18]Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, Laffel G, Sweitzer BJ, Shea BF, Hallisey R, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA. 1995;274:29-34.

[19]Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA 1997.

[20]Nebeker JR, Hoffman JM, Weir CR, Bennett CL, Hurdle JF. High rates of adverse drug events in a highly computerized hospital. Arch Int Med 2005.

[21]Senst BL, Achusim LE, Genest RP, Cosentino LA, Ford CC, Little JA, Raybon SJ, Bates DW. Practical approach to determining costs and frequency of adverse drug events in a health care network. Am J Health-Sys Pharm 2001.

[22]Jha AK, Kuperman GJ, Teich JM, Leape L, Shea B, Rittenberg E, Burdick E, Seger DL, Vander Vliet M, Bates DW. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. J Am Med Inform Assoc, 1998. 5(3): p. 305-14.

Address for correspondence

Emmanuel Chazard
Clinique de Santé Publique, CHRU de Lille
150 rue Yersin
59037 Lille Cedex
France
emmanuel.chazard@univ-lille2.fr