A concise drug alerting rule set for Chinese hospitals and its application in computerized physician order entry (CPOE)

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Abstract

Background: A minimized and concise drug alerting rule set can be effective in reducing alert fatigue.

Objectives: This study aims to develop and evaluate a concise drug alerting rule set for Chinese hospitals. The rule set covers not only western medicine, but also Chinese patent medicine that is widely used in Chinese hospitals.

Setting: A 2600-bed general hospital in China.

Methods: In order to implement the drug rule set in clinical information settings, an information model for drug rules was designed and a rule authoring tool was developed accordingly. With this authoring tool, clinical pharmacists built a computerized rule set that contains 150 most widely used and error-prone drugs. Based on this rule set, a medication-related clinical decision support application was built in CPOE. Drug alert data between 2013/12/25 and 2015/07/01 were used to evaluate the effect of the rule set.

Main outcome measure: Number of alerts, number of corrected/overridden alerts, accept/override rate.

Results: Totally 18,666 alerts were fired and 2803 alerts were overridden. Overall override rate is 15.0% (2803/18666) and accept rate is 85.0%.

Conclusions: The rule set has been well received by physicians and can be used as a preliminary medical order screening tool to reduce pharmacists’ workload. For Chinese hospitals, this rule set can serve as a starter kit for building their own pharmaceutical systems or as a reference to tier commercial rule set.

Keywords: Medication-related clinical decision support, Chinese patent medicine, Drug alerting rule, Alert fatigue

Background

Computerized physician order entry (CPOE) with medication-related clinical decision support (CDS) is an effective solution to reduce drug-related problems and pharmacist workload (Hammar et al. 2015; Claus et al. 2015). Most medication-related decision support functions, such as dosage checking and drug–drug interaction (DDI) checking, are typically implemented by a set of computerized drug alerting rules. One major problem faced by drug alerting rules is the alert fatigue (Nanji et al. 2014), which is usually caused by highly exhaustive and sensitive rules. Recent related work shows override rates can be as high as 53.6% (Nanji et al. 2014), 87.6% (Topaz et al. 2015), and 93% (Bryant et al. 2013) respectively. To address this issue, lots of work has been focused on constructing minimized and concise drug rule sets. For example, Shah et al. (2006) built a tiered medication knowledge subset from a commercial knowledge base. The subset contains clinical significant drug contraindications, and only interrupts physicians for severe alerts. Phansalkar et al. (2012) developed a minimum set of 15 high-severity, clinically significant DDIs from several commercial knowledge bases. Classen et al. (2011)
identified 7 most common DDIs by reviewing multiple sources. The public DDI knowledge base SFINX (Swedish, Finnish, INteraction X-referencing) tiers DDIs according to clinical significance (A-D), which enables threshold settings for automated warnings (Andersson et al. 2015).

**Aim of the study**

The aim of this study to build and evaluate a concise rule set suitable for Chinese hospitals. Compared to existing related work, this rule set not only covers the western medicine, but also includes various Chinese patent medicine (CPM) that is extensively used by Chinese hospitals. For example, a typical Chinese hospital (DaYi Hospital, ShanXi Province, China) uses 1981 drugs, and 462 (23.3%) are Chinese patent medicine.

**Ethical approval**

This study was approved by the medical ethics committee of DaYi Hospital. All collected data have been de-identified by the information department of the hospital.

**Methods**

**Settings and materials**

DaYi Hospital was established in 2011 and is the largest general hospital (2600-bed) in ShanXi Province, China. Until 2013, all the drug checking work in DaYi was performed manually by clinical pharmacists. At the drug dispensing time, the pharmacists would inspect medication orders submitted by the physicians. Unqualified orders would be returned to physicians and recorded by the pharmacists. The recorded medication errors between 2011 and 2013 were used to analyze the most frequent and error-prone drug rules. These records are the initial resource for building the concise rule set.

In 2013, we initiated the KTP (Knowledge Translation Platform) project (Zhang et al. 2015). One of KTP’s goals is to build a medication-related CDS for CPOE, in order to help pharmacists reduce work load and assist the drug checking process. At the beginning of KTP, a preliminary question is: whether to develop own medication-related CDS or use a commercial one. Although there are already mature commercial products on the Chinese market, e.g. Wolters Kluwer/Medicom PASS (Prescription Automatic Screening System), we have our own considerations for not choosing such off-the-shelf systems. (1) Although the rule base of commercial products may be much more comprehensive and detailed, it is still necessary to tier and routinely tailor the complete rule set to suit local hospital situations. For pharmacists, there is not much workload advantage over maintaining a local-developed rule set. (2) From the perspective of the KTP project, the pharmaceutical knowledge is an inseparable part of the entire knowledge base. Inside the KTP knowledge base, there are semantic relations between drug and other medical entities. For example, many clinical rules (e.g. if [Use of Aspirin] == true || [Use of Clopidogrel] == true, recommend [INR monitor]) and clinical treatment protocols (predefined order sets or clinical pathways) involves drug entities. If using third-party products, even if the vendors open their knowledge base or provide external access interfaces, the integration and interaction between different systems (e.g. mapping of drug entities across systems) can be complex and effort-taking. Therefore, we decided to develop an own system.

**Information model**

To implement a computerized rule set, an information model of drug alerting rules is designed (Fig. 1). It defines 11 rule types (Table 1), including dosage (single intake), daily dosage (accumulated intake), administration route, frequency, skin test, solvent, solvent dosage, DDI, contra-indication, and prescription restriction. These rule types are designed according to pharmacists’ drug checking requirements. However, there are also other rule types, such as personalized dosing algorithms (e.g. children or elder patients with different body weights and body surface areas, or patients with renal insufficiency based on creatinine clearance). In the current development phase, we haven’t supported such rules because they require lots of patient context data, such as body weight, body surface area, Crcl rate, etc. These data mostly reside in heterogeneous formats in external systems, such as HIS (Hospital Information System), LIS.
| Rule type            | Description                                                                 | Example                                                                                                                                                      |
|---------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dosage              | Defines maximum dosage for one medical order                               | Maximum dosage of Ambroxol injection is 2 doses                                                                                                             |
|                     |                                                                             | [Dosage] \leq 2 doses                                                                                                                                          |
| Daily dosage        | Defines maximum daily accumulated dosage                                   | Maximum daily dosage of ShuXueNing injection (Ginkgo biloba extract) is 4 doses                                                                            |
|                     |                                                                             | [DailyDosage] \leq 4 doses                                                                                                                                       |
| Administration route| Defines allowed administration route                                        | Cobamamide injection should be administrated by intramuscular injection                                                                                    |
|                     |                                                                             | [AdministrationRoute] = \{intramuscular\}                                                                                                                     |
| Frequency           | Defines allowed frequency                                                  | Ceftriaxone injection frequency should be qd (1/day)                                                                                                      |
|                     |                                                                             | [Frequency] = \{qd\}                                                                                                                                           |
| skin test           | Defines whether skin test flag should be specified in the medication order  | Lidocaine hydrochloride injection needs skin test                                                                                                           |
|                     |                                                                             | [SkinTest] = true                                                                                                                                              |
| Dissolvent          | Defines allowed dissolvent                                                 | Dissolvent for pHGF injection can only be 10% glucose injection                                                                                              |
|                     |                                                                             | [Dissolvent] = \{10\% glucose\}                                                                                                                                |
| Dissolvent dosage   | Defines maximum dissolvent dosage                                         | Dissolvent dosage for iron sucrose injection is 100 ml                                                                                                     |
|                     |                                                                             | 100 ml \leq [DissolventDosage] \leq 100 ml                                                                                                                   |
| Pregnancy risk      | Assigns each drug to FDA pregnancy category, which contains five categories: | FDA pregnancy category of Ribavirin is X                                                                                                                     |
|                     | ABCDX. Category X should never be applied to pregnant patients               | [PregnancyRiskLevel] = X                                                                                                                                       |
| Drug-drug interaction (DDI)| Defines synergistic, antagonistic, etc. interactions between drugs | Warfarin and Vitamin K have antagonistic interaction                                                                                                         |
|                     |                                                                             | Interaction (Warfarin, Vitamin K)                                                                                                                              |
| Contra-indication   | Defines drug-disease and drug-symptom conflicts                            | Clopidogrel cannot be used against patients with active peptic ulcer                                                                                         |
|                     |                                                                             | [Contra-indication] = \{active peptic ulcer\} \& \& \{gastrointestinal hemorrhage\} \& \& false \check passed if result is true |
| prescription restriction | Restricts the prescription of certain drugs for some departments or physicians | For third-line antibiotics such as Vancomycin, only chief physicians have prescription rights. Pediatrics departments cannot prescribe Vancomycin |
|                     |                                                                             | [RestrictedDepartment] = \{pediatrics\}, [RestrictedPhysician] = \{ID1, ID2, \ldots\}                                                                          |
Laboratory Information System), EMR (Electronic Medical Record), etc. How to extract high-quality and well-structured data in expected formats from various sources is a non-trivial task. In the next development phase, we will try to solve this data acquisition problem and support more rule types.

**Authoring tool**

Based on the above information model, the database schema for drug alerting rules can be decided, and a corresponding rule authoring tool has been developed (Fig. 2). The tool was developed as a web-based application.

**Results**

**Drug alerting rule set**

Based on the recorded medication errors between 2011 and 2013, the pharmacists used the rule authoring tool to define a rule set that was able to cover the most widely used and error-prone drugs. The first version of the rule set was created in June 2013, and contained 150 drugs. The detailed rule set is provided in “Appendix”.

**Medication-related CDS based on the rule set**

With the rule set, a medication-related clinical decision support was developed and integrated into CPOE (Fig. 3). Reasoning of the rules is executed by a home-grown rule engine (refer to [http://ktp.brahma.top/Display/TestRuleEngine](http://ktp.brahma.top/Display/TestRuleEngine), [http://ktp.brahma.top/Pages/Evaluation/RuleEngine/Index.html](http://ktp.brahma.top/Pages/Evaluation/RuleEngine/Index.html)). The CPOE was also developed by our research team, under the product name “MIAS (Medical Information Automation System)”. The interaction between CPOE and CDS was implemented by web services. Whenever the physician submits orders, CPOE will call the drug checking web service of CDS to trigger the rule engine. CDS-detected alerts are then returned.
to CPOE, and CPOE displays them to the physician as warnings (Fig. 3b). The physician can either cancel order submission or override the alert. All detected alerts are also sent to the notification area (Fig. 3a) for review. In exceptional cases due to patient status, physicians may state their reasons for overriding the alert. While reviewing the drug alerts, physicians can use infobutton (Fig. 3c) to retrieve related drug labels (Fig. 3d). For pharmacists, we provide a backend web portal for viewing the status (accepted or overridden) and override reason for each alert. The information flow of drug alert status is automatically directed and tracked by the system, which has greatly reduced the necessity of face-to-face communication and telephone calls between physicians and pharmacists.

In this system, only physicians have the right to change the status of an alert (accept or override). Pharmacists only have read-only rights for alert statuses, but they can edit (increase threshold or change rule content) or deactivate corresponding rules if they found many occurrences of an unreasonable alert.

**Evaluation of the rule set in CPOE**

The computerized rule set was first implemented in the inpatient CPOE on 2013/12/25 (The outpatient CPOE was provided by another vendor, and had not been integrated with our system). Until now, the system has been used in 49 inpatient departments for more than 2 years. In order to evaluate the actual effect of the rule set, system log data between 2013/12/25 and 2015/07/01 were collected. During this period, totally 68,182 inpatient visits were enrolled into the system and 2,747,140 medication orders were submitted.

For the submitted medication errors, totally 18,666 alerts were detected by the CDS, and 2803 alerts were overridden by physicians. Therefore, the overall override rate is 15.0% (2803/18,666), and accept rate is 85%. Among the 18,666 alerts, Chinese patent medicine (CPM) takes up 38.4% (7168 in 18,666).

According to Tables 2 and 3, several results caught our attention and we further analyzed these results.

1. Among the detected alerts, “daily dosage” rule type has the highest alert occurrence rate (12,212 alerts in total 18,666). We dived into the “daily dosage” alerts, and found four of the top five drugs are CPM, i.e. “Salvia TMP injection (4039 alerts),” “Thin Chi glycopeptide injection (1050 alerts),” “Shuxuening injection (876 alerts)” and “Fufangkushen Injection (761 alerts),” which are responsible for the majority of “daily dosage” alerts. CPM is mostly extracted or manufactured from Chinese traditional herbs. Compared to western synthesized chemical medicine, though herbs take much longer time to take effect, they also have fewer side effects and adverse reactions. In fact, CPM usually plays an auxiliary or supportive role in treatment regimens. For this reason, some physicians relaxed their vigilance and didn’t pay enough attention when using CPM. This also explains why CPM has a noticeable percentage in all the detected alerts (38.4%).

2. The “dissolvent dosage” rule type has the highest override rate (67.9%). The 67.9% override rate is remarkably high compared to other rule types, which means about 2/3 “dissolvent dosage” alerts have been overridden. We consulted with the clinical pharmacists, and found many alerts were related to patients with certain conditions, e.g. renal deficiency or heart failure. For such patients, it is reasonable to use smaller dosage than required by the drug fact sheet. Such false-positive cases have added up to the overridden alerts. To address this issue, we are currently considering using more patient context data to exclude such false-positive alerts.
| Drug name                      | Drug name (Chinese) | Alert type       | Alerts | Overridden alerts | Override rate (%) |
|-------------------------------|--------------------|------------------|--------|-------------------|-------------------|
| Ambroxol injection            | 氨溴索注射液        | Daily dosage     | 4938   | 22                | 0.4               |
| Salvia TMP injection          | 丹参川芎嗪注射液   | Daily dosage     | 4039   | 0                 | 0.0               |
| Injection esomeprazole        | 注射用埃索美拉唑   | Daily dosage     | 1261   | 1239              | 98.3              |
| Thin Chi glycopeptide injection| 薄芝糖肽注射液     | Daily dosage     | 1050   | 2                 | 0.2               |
| Shuxuening injection          | 舒血宁注射液        | Daily dosage     | 876    | 0                 | 0.0               |
| Fufangkushen injection        | 复方苦参注射液     | Daily dosage     | 761    | 4                 | 0.5               |
| Lidocaine hydrochloride injection| 盐酸利多卡因注射液| Skin test        | 691    | 287               | 41.5              |
| Injection cefathiamidine      | 注射用头孢硫脒     | Daily dosage     | 488    | 0                 | 0.0               |
| Injection thymopentin         | 注射用胸腺五肽     | Administration route | 413  | 277               | 67.1              |
| Calcium gluconate injection  | 葡萄糖酸钙注射液   | Dissolvent dosage| 307    | 0                 | 0.0               |
| Iron sucrose injection        | 葡萄糖酸铁注射液   | Dissolvent dosage| 298    | 0                 | 0.0               |
| Injection ambroxol            | 注射用氨溴索       | Administration route | 248  | 0                 | 0.0               |
| Injection aminophylline       | 氨茶碱注射液       | Dissolvent dosage| 229    | 161               | 70.3              |
| Injection pantoprazole        | 注射用泮托拉唑     | Dissolvent dosage| 219    | 111               | 50.7              |
| Yinxingdangmo injection       | 银杏达莫注射液     | Dissolvent dosage| 203    | 102               | 50.2              |
| Injection omeprazole          | 注射用奥美拉唑     | Administration route | 198  | 191               | 96.5              |
| Injection pantoprazole        | 注射用泮托拉唑     | Administration route | 133  | 46                | 34.6              |
| Injection of fat-soluble vitamins II | 注射用脂溶性维生素II | Dissolvent dosage | 151   | 10                | 7.6               |
| Ceftriaxone for injection     | 注射用头孢曲松     | Frequency        | 116    | 56                | 48.3              |
| Injection cefamandole ester   | 注射用头孢孟多酯   | Prescription restriction | 113  | 0                 | 0.0               |
| Injection pancreatic kalikrein | 注射用胰肽原酶     | Administration route | 113   | 0                 | 0.0               |
| Leucovorin injection          | 注射用阿糖胞苷    | Administration route | 112   | 0                 | 0.0               |
| Injection cefoxitin           | 注射用头孢他啶西丁 | Prescription restriction | 110  | 0                 | 0.0               |
| Injection omeprazole          | 注射用奥美拉唑     | Dissolvent dosage| 103    | 61                | 59.2              |
| Oxytocin injection            | 红霉素注射液       | Dissolvent dosage| 96     | 0                 | 0.0               |
| Heparin sodium injection      | 肝素钠注射液       | Administration route | 91    | 0                 | 0.0               |
| Sodium for injection cefodizime| 注射用头孢地嗪钠 | Prescription restriction | 87    | 0                 | 0.0               |
| Alprostadil injection         | 前列地尔注射液     | Administration route | 80    | 28                | 35.0              |
| Furosemide injection          | 吡塞米注射液       | Dissolvent dosage| 70     | 51                | 72.9              |
| Injection esomeprazole        | 注射用埃索美拉唑   | Frequency        | 60     | 0                 | 0.0               |
| Salvia TMP injection          | 丹参川芎嗪注射液   | Dissolvent dosage| 57     | 0                 | 0.0               |
| Injectable piperacillin sodium and tazobactam sodium | 注射用哌拉西林钠他唑巴坦 | Prescription restriction | 53  | 0                 | 0.0               |
| Cefoperazone sulbactam        | 注射用头孢吡肟舒巴坦 | Prescription restriction | 51    | 0                 | 0.0               |
| Kangai injection              | 康艾注射液         | Dissolvent dosage| 47     | 0                 | 0.0               |
| Leucovorin injection          | 注射用叶酸钙     | Frequency        | 43     | 0                 | 0.0               |
| Levofoxacin injection         | 注射用左氧氟沙星 | Dissolvent dosage| 38     | 21                | 55.3              |
| Injection torasemide          | 注射用托拉塞米     | Frequency        | 38     | 0                 | 0.0               |
| Large plants Rhodiola injection| 大株红景天注射液 | Dissolvent dosage| 37     | 0                 | 0.0               |
| Cefpodoxime                  | 注射用头孢呋吡酮 | Prescription restriction | 36  | 0                 | 0.0               |
| Xuebijing injection           | 血必净注射液       | Dissolvent dosage| 36     | 26                | 72.2              |
| Injection of fat-soluble vitamins II | 注射用脂溶性维生素II | Daily dosage | 33     | 3                 | 9.1               |
| Cefazidime for injection      | 注射用头孢他啶    | Prescription restriction | 30   | 0                 | 0.0               |
| Injection imipenem cilastatin sodium | 注射用亚胺培南西司他丁钠 | Prescription restriction | 28  | 0                 | 0.0               |
| Sodium for injection aescinate | 注射用七叶皂苷钠 | Daily dosage | 24     | 3                 | 12.5              |
| Torasemide injection          | 注射用托拉塞米     | Frequency        | 23     | 0                 | 0.0               |
| Shuxuening injection          | 舒血宁注射液       | Dissolvent dosage| 21     | 17                | 81.0              |
3. The "skin test" rule type has the second highest override rate (41.5%). Investigation reveals that this high override rate is caused by the discrepancy in physicians' understanding of the "skin test" rule. In this system, the skin test rule is not designed as a mandatory requirement for the current specific patient, but a general risk reminder for nurses. That means, if there is potential allergic risk (either from medical literature or drug fact sheet) for a certain drug, physicians should set the skin test flag for corresponding medication orders. If not, the skin test rule will give an alert. When it comes to the drug administrating phase, the nurses will investigate this flag as well as patient's specific conditions (e.g. known allergy history towards certain drugs) to judge whether skin test is needed. However, many physicians treated the "skin test" rule as patient-specific flags, i.e. if a certain drug has potential allergic risk, but the physician already knows the current patient is not allergic to this drug, he/she will not set the flag and override the skin test alert.

Besides the above analysis for certain rule types, there are also high alert occurrence and override rates for several individual drugs, which are caused by different reasons and need case-by-case investigation. Based on these periodical retrospective analyses, pharmacists can continually improve the rule set (e.g. change threshold, revise rule content, deactivate rules) to better suit clinical use.

**Discussion**

The primary contribution of this study is a concise drug alerting rule set oriented to Chinese hospitals. As the rule set was built based on the historical data from a large-scale (2600-bed) general hospital with high patient throughput (e.g. 68,182 inpatient visits from 2013/12/25 to 2015/07/01), the rule set should be able to reflect the medication use profile of large populations and may serve as a reference for other Chinese hospitals.

In this study, the computerized rule set can be used as a "preliminary screening tool" against physicians' medication orders. In DaYi Hospital, pharmacists need to
check 4968 medication orders per day on average, and unqualified orders have to be returned to physicians. This is a time-consuming and laborious work. With the drug alerting CDS, many potential mistakes can be ruled out before they reach the final checkpoint of pharmacists. According to the evaluation result, physicians have revised 85% of detected medication orders. In the long run, the system will not only alleviate the workload of pharmacists (many drug use errors can be revised by the physicians without pharmacists’ intervention) but also enhance the workflow efficiency (avoid the “reject-revise-resubmit” process).

This study has several limitations or arguments:

1. The proposed rule set is not suitable for procedural drug rules. For example, the preparation of azithromycin solution is a multi-step procedure. First, azithromycin is dissolved with sterilized water to formulate into 0.1 g/ml. Then, add it to 250–500 ml 0.9% NaCl or 5% glucose solution to get a 1.0–2.0 mg/ml concentration. This procedural logic cannot be easily represented as a single succinct dissolvent rule.

2. The current rule set doesn’t support complex personalized dosing algorithms. In certain contexts, such as children or elder patients with different body weights and body surface areas, or patients with renal insufficiency based on creatinine clearance, more complicated personalized dosing algorithms are needed. To support them, the information model needs further extension to represent such individualized knowledge.

3. DDI rule subtyping. In current system implementation, all DDI rules are treated as one rule type. However, it’s better to design more DDI sub-types in order to achieve more fine-grained alerts. For example, the SFINX project (Andersson et al. 2015) tiers DDIs according to clinical significance (A–D), which enables fine-grained threshold settings for automated warnings.

4. Lack of complete evaluation. In this study, the accept and override rates can be easily calculated from the log data. However, it is not so easy to calculate accuracy and specificity, which requires reviewing every overridden alert in order to identify true positives and false positives. In the future, we will build a “closed-looped” alert tracking workflow, in which the state changes (either by physicians or pharmacists) and change reasons (e.g. why physician override an alert, and why pharmacists reject overriding an alert) of each alert are tracked and logged by the system.

5. Use of clinically identified ADEs. ADEs (adverse drug events) are valuable data for analyzing drug use and medication-related CDS. In China, we have a multi-level ADE reporting mechanism. Level 1: Physicians submit detected ADE and related clinical data (patient demographics, symptoms, drug use info, etc.) to the hospital’s pharmacy department. Level 2: Pharmacists submit confirmed ADEs to drug regulatory authorities, i.e. China SFDA (a counterpart of US FDA). Level 3: China SFDA evaluates drug risks based on nation-wide collected ADEs. Although this ADE-reporting mechanism is well designed, it’s a sad reality that it hasn’t lived up to its maximum benefit, largely due to the wide-spread under-reporting problems. Most ADE events were concealed or neglected in daily practices, and the few reported ADEs cannot be used as a solid and complete data source for analyzing physicians’ drug use and evaluating our rule set. To address this issue, we are currently cooperating with clinical pharmacists to detect unreported ADEs from clinical documents (e.g. patient daily progress notes) by natural language processing (NLP) technologies.

6. Coverage of the rule set. One basic assumption of this study is that drug alerts conform to Pareto-alike distribution, where small portion of drug rules accounts

| Alert type         | Alerts | Overridden alerts | Override rate (%) |
|--------------------|--------|-------------------|-------------------|
| Daily dosage       | 12,212 | 34                | 0.3               |
| Dissolvent dosage  | 2299   | 1560              | 67.9              |
| Administration route| 1391   | 542               | 39.0              |
| Dissolvent         | 964    | 312               | 32.4              |
| Skin test          | 691    | 287               | 41.5              |
| Prescription restriction | 595 | 36       | 0.0               |
| Frequency          | 300    | 56                | 18.7              |
| Dosage             | 151    | 5                 | 3.3               |
| DDI                | 63     | 7                 | 11.1              |
| Total              | 18,666 | 2803              | 15.0              |
for the majority of alerts. As a supporting case, one US study in 2005 (Reichley et al. 2005) used a commercial drug alerting rule set. It contains 48,262 rules for 1537 drugs, but 90% of alerts are focused on 58 drugs. From their daily work experience, the pharmacists in DaYi hospital also hold the same opinion that small set of drugs generate majority of errors. However, to further verify this assumption, a further evaluation is needed to get the coverage rate of the rule set. This requires a full set for all drugs on the Chinese market, and a parallel comparison of the full set and concise set on a large-scale and long-term patient drug use data set. A coverage rate greater than 80% should be ideal. Otherwise, more rules may have to be added to the rule set.

7. Another problem of the rule set is how to keep up with the latest clinical evidence. Occasionally published guidelines or case reports will necessitate adding or revising rules. For example, the China SFDA (State Food and Drug Administration) periodically publish ADE (adverse drug events) reports collected all round the country. A well-maintained rule set should keep up with these public sources. Currently, our research team is developing a semi-automatic program based on NLP, which will help pharmacists extract structured contents from the public ADE reports.

Generally speaking, the overall 85.0% accept rate indicates the rule set has been well received by physicians [compared to the override rates reported in other recent studies, e.g. 53.6% (Nanji et al. 2014), 87.6% (Topaz et al. 2015)] and is effective in reducing pharmacists’ workload. Moreover, the pharmacists are continually analyzing (i.e. analyze those drug alerts with high override rates), improving (e.g. raise alert threshold to reduce false positive alerts) and expanding (i.e. add more drugs and rules) the drug rule set, which will further improve its accuracy and coverage. However, due to the various complex and individualized patient statuses, such a computerized rule set is never meant to substitute the routine work of pharmacists, but can be used an effective supportive tool.

Conclusions
In this study, a concise drug alerting rule set for Chinese hospitals was constructed by pharmacists. The case study in a Chinese hospital indicates the medication-related CDS based on the rule set has been well received by physicians. For other hospitals, they may use this rule set as a starter kit for building their own medication-related CDS systems or use it to tier commercial rule bases.

Authors’ contributions
YZ and XL made the data analysis and wrote the manuscript. WC provided clinical advisory opinions to the study result. HL and HD supervised the entire study. QS further processed the results, and made the graphs and charts. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
Please contact corresponding author for data request.

Funding
This study is supported by Chinese National High-tech R&D Program (2012AA02A601), Humanities and Social Sciences Foundation of Ministry of Education of China (15YJC630106), and Natural Science Foundation of Zhejiang Province of China (LQ16G020006). This study is also supported by the Research Center of Information Technology & Economic and Social Development, Zhejiang Province, China.

Appendix
See Tables 4 and 5.
| Drug | Drug (Chinese name) | Rule content | Rule type |
|------|--------------------|--------------|-----------|
| Compound matrine injection<sup>a</sup> | 复方苦参注射液<sup>a</sup> | 2–3 dose | Dosage |
| Injection aescinate<sup>a</sup> | 注射用七叶皂苷钠<sup>a</sup> | 10–20 mg | Dosage |
| Injection of Ginkgo biloba extract<sup>a</sup> | 银杏叶提取物注射液<sup>a</sup> | ≤4 dose | Dosage |
| Salvia ligustrazine injection<sup>a</sup> | 丹参川芎嗪注射液<sup>a</sup> | ≤2 dose | Dosage |
| Ambroxol injection | 盐酸氨溴索注射液 | ≤2 dose | Dosage |
| Phosphate sodium for injection | 磷酸钠注射液 | ≤2 dose | Dosage |
| Thin chi glycopeptide injection<sup>a</sup> | 薄芝糖肽注射液<sup>a</sup> | ≤2 dose | Dosage |
| Citicoline injection | 胞二磷胆碱注射液 | ≤2 dose | Dosage |
| Tiopronin injection | 硫普罗宁注射液 | ≤2 dose | Dosage |
| Injection cefathiamidine | 注射用头孢硫脒 | ≤1 dose | Dosage |
| ShuXueNing injection<sup>a</sup> | 舒血宁注射液 | ≤2 dose | Dosage |
| Injection esomeprazole | 注射用埃索美拉唑 | 20–40 mg | Dosage |
| Flurbiprofen injection | D-脑洛芬酯注射液 | 50 mg | Dosage |
| Injection lentinan | 注射用香菇多糖 | 1 mg | Dosage |
| Hydrocortisone injection | 氢化可的松注射液 | 50–100 mg | Dosage |
| Xiaoaiping injection<sup>a</sup> | 消癌平注射液<sup>a</sup> | 2–4 ml | Dosage |
| Calcium gluconate injection | 葡萄糖酸钙注射液 | 1–2 g | Dosage |
| Sodium phosphate injection | 注射用磷酸肌酸钠 | ≤1 dose | Dosage |
| Javanica oil emulsion injection<sup>a</sup> | 鸦胆子油乳注射液<sup>a</sup> | 10–30 ml | Dosage |
| Injection ulinastatin | 注射用乌司他丁 | 100,000U | Dosage |
| Injection of Ginkgo biloba extract<sup>a</sup> | 银杏叶提取物注射液<sup>a</sup> | 5 dose | Daily dosage |
| Compound matrine injection<sup>a</sup> | 复方苦参注射液<sup>a</sup> | 3 dose | Daily dosage |
| Salvia ligustrazine injection<sup>a</sup> | 丹参川芎嗪注射液<sup>a</sup> | 2 dose | Daily dosage |
| Ambroxol injection | 盐酸氨溴索注射液 | 2 dose | Daily dosage |
| Phosphate sodium for injection | 磷酸钠注射液 | 2 dose | Daily dosage |
| Thin chi glycopeptide injection<sup>a</sup> | 薄芝糖肽注射液<sup>a</sup> | 2 dose | Daily dosage |
| Citicoline injection | 胞(二)磷胆碱注射液 | 2 dose | Daily dosage |
| Tiopronin injection | 硫普罗宁注射液 | 2 dose | Daily dosage |
| Injection aescinate<sup>a</sup> | 注射用七叶皂苷钠<sup>a</sup> | 20 mg | Daily dosage |
| Injection cefathiamidine | 注射用头孢硫脒 | 1 dose | Daily dosage |
| Injection of fat-soluble vitamins I | 注射脂溶性维生素I | 1 dose | Daily dosage |
| Injection of fat-soluble vitamins II | 注射脂溶性维生素II | 1 dose | Daily dosage |
| Injection of water-soluble vitamins | 注射用水溶性维生素 | 1 dose | Daily dosage |
| L-carnitine injection | 左旋肉碱注射液 | Iv push | Administration route |
| Omeprazole injection (Losec) | 奥美拉唑注射液（罗赛克） | Iv push | Administration route |
| Omeprazole injection (AoXiKang, Luoren) | 奥美拉唑注射液（奥西康, 罗润） | Iv drip | Administration route |
| Injection thymopentin | 注射用胸腺五肽 | Intramuscular injection, subcutaneous injection | Administration route |
| Injection cobamamide | 注射用腺苷钴胺 | Intramuscular injection | Administration route |
| Ambroxol injection | 注射用腺苷钴胺 | Iv drip | Administration route |
| Furosemide injection | 呋塞米注射液 | Iv | Administration route |
| Pantoprazole injection | 注射用泮托拉唑 | Iv push | Administration route |
| Pancreatic kininogenase for injection | 注射用胰腺激肽原酶 | Intramuscular injection | Administration route |
| Leucovorin injection | 叶酸注射液 | Iv drip | Administration route |
| L-carnitine injection | 左旋肉碱注射液 | Iv | Administration route |
| Heparin sodium injection | 肝素钠注射液 | Subcutaneous injection, Iv | Administration route |
| Alprostadil injection | 前列地尔注射液 | Iv | Administration route |
| Ceftriaxone for injection | 头孢曲松钠注射液 | 1/day | Frequency |
| Injection esomeprazole | 注射用埃索美拉唑 | 1/day, 1/12 h | Frequency |
| Leucovorin injection | 叶酸注射液 | 1/day, 1/6 h | Frequency |
| Drug                                      | Drug (Chinese name)            | Rule content | Rule type |
|-------------------------------------------|--------------------------------|--------------|-----------|
| Injection torasemide                      | 注射用托拉塞米                  | 1/day        | Frequency |
| Torasemide injection                      | 托拉塞米注射液                  | 1/day        | Frequency |
| Injection ulinastatin                     | 注射用乌司他丁                  | 1–3/day      | Frequency |
| Lidocaine hydrochloride injection         | 盐酸利多卡因注射液             | Skin test required | Skin Test |
| Furosemide injection                      | 呋塞米注射液                    | NaCl, sterile water | Dissolution |
| Sodium heparin injection                  | 肝素钠注射液                    | NaCl, sterile water | Dissolution |
| Brain carnosine injection                 | 脑肌肽注射液                    | NaCl, 5% glucose | Dissolution |
| Tanreqing injection                       | 痰热清注射液                   | NaCl, 5% glucose | Dissolution |
| Pantoprazole injection                    | 注射用泮托拉唑                 | NaCl         | Dissolution |
| Injection carbazochrome sodium sulfonate  | 注射用卡络磺酸                 | NaCl         | Dissolution |
| Edaravone injection                       | 依达拉奉注射液                 | NaCl         | Dissolution |
| Lipoic acid injection                     | 硫辛酸注射液                    | NaCl         | Dissolution |
| Xuebijing injection                       | 血必净注射液                   | NaCl         | Dissolution |
| Iron sucrose injection                    | 熊糖铁注射液                   | NaCl         | Dissolution |
| Injection of fat-soluble vitamins I       | 注射脂溶性维生素I               | Glucose, sterile water | Dissolution |
| Injection of fat-soluble vitamins II      | 注射脂溶性维生素II              | Glucose, sterile water | Dissolution |
| Paclitaxel liposome for injection         | 紫杉醇脂质体注射液             | Glucose, sterile water | Dissolution |
| Injection of liposomal amphotericin B     | 注射用两性霉素B脂质体           | Glucose, sterile water | Dissolution |
| Polyene phosphatidylcholine injections    | 多烯磷脂酰胆碱注射液            | Glucose, sterile water | Dissolution |
| Injection brevica nine                   | 注射用灯盏花素                 | NaCl, 0.9% NaCl | Dissolution |
| Aminophylline injection                   | 氨茶碱注射液                   | Glucose      | Dissolution |
| Injection of Ginkgo biloba extract        | 银杏叶提取物注射液             | Glucose      | Dissolution |
| Amiodarone injection                      | 胺碘酮注射液                    | 5% glucose   | Dissolution |
| Injection pHGF                            | 注射用促肝细胞生长素           | 10% glucose  | Dissolution |
| Ginkgo leaf extract and dipyridamole injection | 银杏达莫注射液               | 0.9% NaCl, 5% glucose, 10% glucose | Dissolution |
| Omeprazole injection                      | 奥美拉唑注射液                  | 0.9% NaCl    | Dissolution |
| Calcium gluconate injection              | 葡萄糖酸钙注射液                | 10% glucose  | Dissolution |
| Oxytocin injection                        | 缩宫素注射液                    | NaCl         | Dissolution |
| TanReQing injection                       | 喹那替注射液                    | 5% glucose   | Dissolution |
| ShuXueNing injection                      | 舒血宁注射液                   | 5% glucose   | Dissolution |
| Ginkgo leaf extract and dipyridamole Injection | 银杏达莫注射液               | 500 ml       | Dissolution dosage |
| Levofloxacin                              | 左氧氟沙星                      | 250 ml       | Dissolution dosage |
| Pantoprazole injection                    | 注射用泮托拉唑                 | 100 ml       | Dissolution dosage |
| Xuebijing injection                       | 血必净注射液                   | 100 ml       | Dissolution dosage |
| Iron sucrose injection                    | 熊糖铁注射液                   | ≤100 ml      | Dissolution dosage |
| Injection esomeprazole                   | 注射用埃索美拉唑               | 100 ml       | Dissolution dosage |
| Omeprazole injection                      | 奥美拉唑注射液                  | 100 ml       | Dissolution dosage |
| Salvia ligustrazine injection             | 丹参川芎嗪注射液               | 250–500 ml   | Dissolution dosage |
| Large plants Rhodiola injection           | 大株红景天注射液               | 250 ml       | Dissolution dosage |
| Triazolam tablets                         | 三唑仑片                        | FDA pregnancy category X—use on pregnant women is forbidden | Pregnancy risk |
| Ribavirin                                 | 利巴韦林                         |             | Pregnancy risk |
| Estradiolvalerate                        | 戊酸雌二醇片                    |             | Pregnancy risk |
| Fluorouracil Injection                    | 氟尿嘧啶注射液                  |             | Pregnancy risk |
| Misoprostol tablets                       | 米索前列醇片                    |             | Pregnancy risk |
| Simvastatin                               | 辛伐他汀                         |             | Pregnancy risk |
| Avi A capsules                            | 阿维A胶囊                         |             | Pregnancy risk |
| Drug                                      | Drug (Chinese name)                                      | Rule content                                      | Rule type            |
|-------------------------------------------|---------------------------------------------------------|---------------------------------------------------|----------------------|
| Estazolam tablets                         | 艾司唑仑片                                              | Pregnancy risk                                   |                      |
| Bicalutamide tablets                      | 比卡鲁胺片                                              | Pregnancy risk                                   |                      |
| Gosereulin acetate sustained-release implants | 醋酸戈舍瑞林缓释植入剂                                   | Pregnancy risk                                   |                      |
| Finasteride tablets                       | 非那雄胺片                                              | Pregnancy risk                                   |                      |
| Fluvasatin                                | 氟伐他汀                                               | Pregnancy risk                                   |                      |
| Fluorumacil implants                      | 氟尿嘧啶植入剂                                         | Pregnancy risk                                   |                      |
| Mifepristone misoprostol tablets          | 米非司酮米索前列醇片                                   | Pregnancy risk                                   |                      |
| Levonorgestrel                            | 左炔诺孕酮                                              | Pregnancy risk                                   |                      |
| Estradiol                                 | 雌二醇                                                  | Pregnancy risk                                   |                      |
| Injection cefamandole ester               | 注射用头孢孟多酯                                       | Restricted antibiotics. Only chief physicians and above have the prescription right. Resident physicians cannot directly prescribe these drugs | Prescription restriction |
| Injection cefoxitin                       | 注射用头孢西丁                                          | Prescription restriction                          |                      |
| Sodium for injection cefodizime           | 注射用头孢地嗪钠                                       | Prescription restriction                          |                      |
| Injectable piperacillin sodium and tazobactam sodium | 注射用哌拉西林钠他唑巴坦钠                           | Prescription restriction                          |                      |
| Cefoperazone sulphactam                   | 注射用头孢哌酮舒巴坦                                   | Prescription restriction                          |                      |
| Cefoperazone                              | 注射用头孢哌酮                                         | Prescription restriction                          |                      |
| Ceftazidime for injection                 | 注射用头孢他啶                                         | Prescription restriction                          |                      |
| Injection imipenem cilastatin sodium      | 注射用亚胺培南西司他丁钠                                 | Prescription restriction                          |                      |
| Meropenem for injection                   | 注射用美罗培南                                         | Prescription restriction                          |                      |
| Fluconazole injection                     | 氟康唑注射液                                            | Prescription restriction                          |                      |
| Vancomycin injection                      | 注射用万古霉素                                         | Prescription restriction                          |                      |
| Itraconazole oral solution                | 伊曲康唑口服液                                         | Prescription restriction                          |                      |
| Minocycline hydrochloride capsules        | 盐酸米诺环素胶囊                                       | Prescription restriction                          |                      |
| Moxifloxacin injection                    | 莫西沙星注射液                                         | Prescription restriction                          |                      |
| Injectable piperacillin sulphactam        | 注射用哌拉西林舒巴坦                                   | Prescription restriction                          |                      |
| Injection voriconazole                    | 注射用伏立康唑                                         | Prescription restriction                          |                      |
| Azithromycin for injection                | 注射用阿奇霉素                                         | Prescription restriction                          |                      |
| Injection caspofungin                     | 注射用卡泊芬净                                         | Prescription restriction                          |                      |
| Injection teicoplanin                     | 注射用泰考拉宁                                         | Prescription restriction                          |                      |
| Linezolid injection                       | 利奈唑胺注射液                                         | Prescription Restriction                          |                      |
| Moxifloxacin tablets                      | 莫西沙星片                                              | Prescription restriction                          |                      |
| Injection of amphotericin B liposome      | 注射用两性霉素B脂质体                                   | Prescription restriction                          |                      |

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| Drug 1                        | Drug 2                        | Description                                                                 |
|------------------------------|------------------------------|----------------------------------------------------------------------------|
| Vitamin C injection          | Vitamin K1 injection         | Mixture prone to turbidity<sup>a</sup>                                     |
| Four-vitamin injection       | Injection of fat-soluble vitamins I | Same ingredient. Duplicate therapy<sup>b</sup>                             |
| Methylprednisolone sodium succinate for injection | Insulin injection | Methylprednisolone sodium succinate for injection increases requirements for insulin or oral hypoglycemic agents in diabetics<sup>c</sup> |
| Methylprednisolone sodium succinate for injection | Recombinant human insulin injection | Methylprednisolone sodium succinate for injection increases requirements for insulin or oral hypoglycemic agents in diabetics<sup>c</sup> |
| Methylprednisolone sodium succinate for injection | Protamine recombinant human insulin injection | Methylprednisolone sodium succinate for injection increases requirements for insulin or oral hypoglycemic agents in diabetics<sup>c</sup> |
| Salvia ligustrazine injection<sup>b</sup> | Vitamin K1 Injection | Antagnistic effect<sup>a</sup>                                             |
| Ginkgo biloba extract injection | Injection calf blood protein extract | Antagnistic effect<sup>a</sup>                                             |
| Selegiline                   | Pseudoephedrine              | MAO inhibitors—Amphetamine and derivatives                                  |
|                              | Diethylpropion               | MAO inhibitors—selective serotonin reuptake inhibitors (SSRIs)               |
|                              | Fluoxetine                   | MAO inhibitors—narcotic analgesics                                          |
|                              | Paroxetine                   | MAO inhibitors—narcotic analgesics                                          |
|                              | Citalopram                   | MAO inhibitors—narcotic analgesics                                          |
|                              | Escitalopram                 | MAO inhibitors—narcotic analgesics                                          |
|                              | Sertraline                   | MAO inhibitors—narcotic analgesics                                          |
|                              | Fluvoxamine                  | MAO inhibitors—narcotic analgesics                                          |
|                              | Duloxetine                   | MAO inhibitors—narcotic analgesics                                          |
|                              | Venlafaxine                  | MAO inhibitors—narcotic analgesics                                          |
|                              | Mepenidine                   | MAO inhibitors—narcotic analgesics                                          |
|                              | Fentanyl                     | MAO inhibitors—narcotic analgesics                                          |
|                              | Tramadol                     | MAO inhibitors—narcotic analgesics                                          |
|                              | Amitriptyline                | MAO inhibitors—narcotic analgesics                                          |
|                              | Amoxapine                    | MAO inhibitors—narcotic analgesics                                          |
|                              | Selegiline—tricyclic antidepresants (TCAs) | MAO inhibitors—narcotic analgesics                                          |
|                              | Clarithromycin               | Irinotecan—strong CYP3A4 inhibitors                                         |
|                              | Erythromycin                 | Irinotecan—strong CYP3A4 inhibitors                                         |
|                              | Amiodarone                   | Irinotecan—strong CYP3A4 inhibitors                                         |
|                              | Verapamil                    | Irinotecan—strong CYP3A4 inhibitors                                         |
|                              | Diltiazem                    | Irinotecan—strong CYP3A4 inhibitors                                         |
|                              | Ketoconazole                 | Irinotecan—strong CYP3A4 inhibitors                                         |
|                              | Itraconazole                 | Irinotecan—strong CYP3A4 inhibitors                                         |
|                              | Fluconazole                  | Irinotecan—strong CYP3A4 inhibitors                                         |
|                              | Voriconazole                 | Irinotecan—strong CYP3A4 inhibitors                                         |
|                              | Cicetidine                   | Irinotecan—strong CYP3A4 inhibitors                                         |
|                              | Clarithromycin               | HMG Co-A reductase inhibitors—CYP3A4 inhibitors                             |
|                              | Erythromycin                 | HMG Co-A reductase inhibitors—CYP3A4 inhibitors                             |
|                              | Amiodarone                   | HMG Co-A reductase inhibitors—CYP3A4 inhibitors                             |
|                              | Verapamil                    | HMG Co-A reductase inhibitors—CYP3A4 inhibitors                             |
|                              | Diltiazem                    | HMG Co-A reductase inhibitors—CYP3A4 inhibitors                             |
|                              | Ketoconazole                 | HMG Co-A reductase inhibitors—CYP3A4 inhibitors                             |
|                              | Itraconazole                 | HMG Co-A reductase inhibitors—CYP3A4 inhibitors                             |
|                              | Fluconazole                  | HMG Co-A reductase inhibitors—CYP3A4 inhibitors                             |
|                              | Voriconazole                 | HMG Co-A reductase inhibitors—CYP3A4 inhibitors                             |
|                              | Roxithromycin                | HMG Co-A reductase inhibitors—CYP3A4 inhibitors                             |

<sup>a</sup>Severe DDI reported from literature, including rhabdomyolysis and liver damage.

<sup>b</sup>Severe DDI reported from literature, including rhabdomyolysis and liver damage.

<sup>c</sup>Severe DDI reported from literature, including rhabdomyolysis and liver damage.
## Table 5 continued

| Drug 1      | Drug 2           | Description                                                                 |
|-------------|------------------|------------------------------------------------------------------------------|
| Ergotamine  | Clarithromycin   | Ergot alkaloids and derivatives—CYP3A4 inhibitors                           |
| 1           | Erythromycin     |                                                                              |
| 1           | Ketoconazole     |                                                                              |
| 1           | Itraconazole     |                                                                              |
| 1           | Voriconazole     |                                                                              |
| Tizanidine  | Ciprofloxacin    | Tizanidine—CYP1A2 inhibitors                                                |
| 1           | Fluvoxamine      |                                                                              |
| 1           | Mexiletine       |                                                                              |
| 1           | Propafenone      |                                                                              |
| 1           | Amiodarone       |                                                                              |
| 1           | Erythromycin     |                                                                              |
| 1           | Ketaconazole     |                                                                              |
| 1           | Itraconazole     |                                                                              |
| 1           | Voriconazole     |                                                                              |
| Zolmitriptan| Moclubamine      | Triptans—MAO inhibitors                                                    |
| 1           | Methylene blue   |                                                                              |
| Chloroquine |                 | QT prolonging agents. Any of two drugs have synergistic effect              |
| Moxifloxacin|                 |                                                                              |
| Sotalol     |                 |                                                                              |
| Clarithromycin|                |                                                                              |
| Citalopram  |                 |                                                                              |
| Amiodarone  |                 |                                                                              |
| Erythromycin|                 |                                                                              |
| Haloperidol |                 |                                                                              |
| Droperidone |                 |                                                                              |
| Domperidone |                 |                                                                              |
| Propranolol |                 |                                                                              |
| Sevoflurane |                 |                                                                              |
| Chlorpromazine|               |                                                                              |
| Arsenic trioxide|            |                                                                              |
| Azithromycin|                 |                                                                              |

* Means these rules are added by the local pharmacists; others are from the work published by other researchers (Phansalkar et al. 2012)

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Received: 19 May 2016   Accepted: 18 November 2016
Published online: 01 December 2016

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