



Single-Center Analysis of the Potential Inappropriate Use of Intravenous Medications in Hospitalized Patients in China

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ABSTRACT

This study categorizes the types of inappropriate intravenous prescriptions in hospitalized patients in China. Prescription data from 2016 were retrospectively analyzed based on predefined categories of inappropriateness. Of the 123,521 patients included, 89.2% received intravenous medications, contributing to 80% of the patients' hospital medication costs. Of significant concern, antibiotics and traditional Chinese medicines were administered to 44.3% and 14.5% of hospitalized patients, respectively. Overall, 11.4% of all intravenous prescriptions were classified as inappropriate, with improper diluent and diluent volumes being the primary cause. A team-based collaborative approach is necessary to address this widespread issue in China. (*Clin Ther.* 2019;41:1631–1637) © 2019 Elsevier Inc. All rights reserved.

INTRODUCTION

A Chinese epidemiologic survey in hospitalized patients at 156 public hospitals in 30 provinces and municipalities found that 93.1% of patients in 2016

received intravenous medications.¹ Although often not evidence based, traditional Chinese medicines (TCMs) and antibiotics represent a concerning proportion of intravenous medications. The following factors contribute to this high rate of intravenous infusions: increased health care spending, rapid urban expansion, the aging population, expanded medical coverage, living standard improvements, and irrational prescribing.² The excessive administration of intravenous medications creates concerns about the patient safety profile. Data from the China National Reports on Adverse Drug Reaction (ADR) Monitoring presented the following: the incidence of ADRs from intravenous infusions increased annually from 55.8% in 2011 to 58.7% in 2013, and the number of ADRs related to TCM injections has also increased rapidly, from 66,000 cases in 2011 to 121,000 cases in 2013.³

However, data are lacking on types of inappropriate intravenous medications (prescribing, compounding, and administration) in Chinese hospitals. Understanding this information can identify areas of process improvement and can enhance the patient

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safety profile. This study aimed to categorize types of inappropriate use of intravenous medications through a retrospective analysis of an integrative medicine–pharmacy–nursing Intravenous Prescription Early Warning and Assessment System.

METHODS

We analyzed hospitalized patients who received intravenous medications with discharge dates from January 1, 2016, to December 31, 2016, at a major Chinese tertiary academic center. The medical ethics committee approved this study (number 201612647). We collected the following patient demographic and clinical characteristics from the Intravenous Prescription Early Warning and Assessment System we developed and medication records: age, sex, hepatic and renal functions, insurance type, source of hospital admission, and inpatient unit. Patients were categorized as either children (<18 years), adults (18 to 59 years), or the elderly (≥ 60 years). The following information on patient's intravenous medications was collected: medication name and dosage, diluent choice and volume, administration route(s), and cost. Medications were classified based on the Anatomical Therapeutic Chemical classification proposed by the World Health Organization (WHO).⁴

Inappropriate Prescription Categories

We categorized inappropriate prescriptions into the following 8 categories: (1) contraindicated in patients with hepatic insufficiency (aspartate transaminase or alanine transaminase of 80 to 1000 U/L or total bilirubin of 34.2 to 1000 $\mu\text{mol/L}$), (2) contraindicated in patients with renal insufficiency (creatinine clearance < 60 mL/min), (3) contraindicated in pediatric patients, (4) overdosing, (5) improper diluent volume, (6) improper diluent choice, (7) improper administration routes, and (8) improper coadministration of drugs resulting in incompatibilities.

Statistical Analysis

All analyses were conducted with SPSS version 18.0 (IBM, Armonk, N Y). A descriptive analysis was conducted on the patient's demographic, clinical, and medication characteristics. Certain medication categories were grouped and analyzed, including antibiotics, TCMs, and hormonal medications. They were selected based on the potential of overuse and safety concerns in China.^{2,5,6} Mean (SD) was

computed for continuous data. Frequencies and percentages were calculated for categorical variables.

RESULTS

As shown in [Figure 1](#) and [Table I](#), the total number of patients discharged was 123,521, and 89.2% (110,227) patients received intravenous medications. Among patients who received intravenous medications, 54.1% were men, 8.7% were pediatric patients, 29.4% were elderly patients, 44.3% received antibiotics, 14.5% received TCMs, and 29.2% received hormonal medications. The top 3 drugs for antibiotics were latamoxef, piperacillin and tazobactam, and ceftazidime; the top TCMs were *kangai*, *salvianolate*, and *xingnaojing*; and the top hormonal medications were dexamethasone, methylprednisolone, and prednisolone. The total cost of intravenous medications was US\$115 million, an average of US\$1044 per patient per visit. Overall, intravenous medications accounted for ~80% of the total medication costs during inpatient stays. A more detailed analysis is provided (see [Supplemental Table I](#) in the online version at doi:10.1016/j.clinthera.2019.05.009).

Inappropriate Types of Intravenous Medications

Of the 3,139,322 prescriptions analyzed, 357,399 were considered inappropriate, reaching a prevalence rate of 11.4%. These prescriptions were administered to 71,373 patients and accounted for 64.8% (71,373 of 110,227) of the patients who received intravenous medications. As shown in [Figure 1](#), the top 5 most common inappropriate categories were compounding with improper diluents (54.5%) or improper diluent volume (21.9%), contraindicated to patients with renal insufficiency (21.9%) or with hepatic insufficiency (6.2%), and coadministration of drugs leading to incompatibilities (5.3%). As shown in [Table I](#), inappropriate intravenous prescriptions were more likely seen in patients aged ≥ 45 years (68.8%), admitted to the surgery department (40.3%), and patients paying out of pocket for medical bills (44.3%). Overdosing was most likely in men (62.3%) and elderly patients (32.9%).

Inappropriate Categories of Intravenous Medications

As shown in [Figure 1](#), the top 5 drug classes administered inappropriately were blood and blood-forming organs (54.2%), gastrointestinal tract and

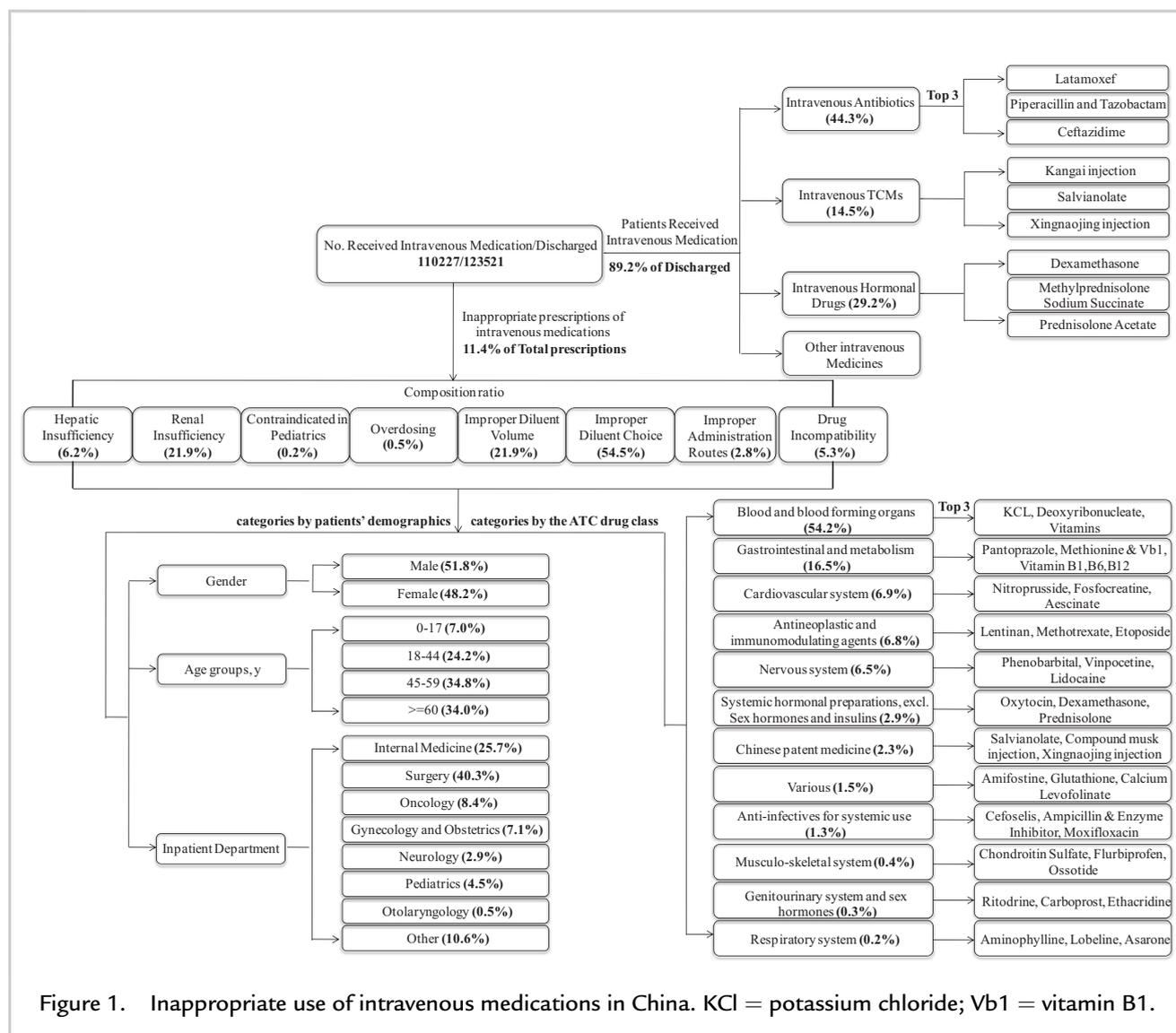


Figure 1. Inappropriate use of intravenous medications in China. KCl = potassium chloride; Vb1 = vitamin B1.

metabolism (16.5%), cardiovascular system (6.9%), antineoplastic and immune-modulating agents (6.8%), and nervous system (6.5%). Potassium chloride, pantoprazole, deoxyribonucleotide, lentinan, and oxytocin accounted for >60% of the inappropriate intravenous medications administered.

An analysis of inappropriate types of intravenous prescriptions for each drug category is provided (see [Supplemental Table II](#) in the online version at doi:10.1016/j.clinthera.2019.05.009). Within blood and blood-forming organs, the most common types were compounding with improper diluents (55.2%), followed by contraindicated use in renal insufficiency (27.7%). Within gastrointestinal tract and metabolism, the most inappropriate types were

compounding with improper diluents (46.3%), followed by improper diluent volumes (39.5%). Together, these 2 categories accounted for 70.7% of the total inappropriate orders.

DISCUSSIONS

This retrospective analysis reveals that almost 90% of the inpatients who received intravenous medications, a finding similar to the 93.1% rate reported in the hallmark 2016 study.¹ Although in some surgical units where intravenous administration may be needed, for example, oxytocin in gynecology and obstetrics, factors such as physician knowledge and patient demand of intravenous therapies and reimbursements might have contributed to this high

Table I. Potential inappropriate prescribing of intravenous medications by patients' demographic characteristics.

Variable (Composition ratio, %)	Total Intravenous Medication Prescriptions	Inappropriate Intravenous Medication Prescriptions	Hepatic Insufficiency*	Renal Insufficiency*	Contraindicated in Pediatric Patients	Overdosing	Improper Diluent Volume	Improper Diluent Choice	Improper Administration Routes	Drug Incompatibility
Sex										
Male	54.1	51.8	63.8	49.8	53.9	62.3	53.6	49.7	54.5	59.8
Female	45.9	48.2	36.2	50.2	46.1	37.8	46.4	50.3	45.5	40.2
Age groups, years										
0–17	8.7	7.0	13.5	0.7	100.0	8.9	7.5	6.9	12.2	21.8
18–44	26.2	24.2	28.8	6.1	0.0	26.9	23.3	28.1	25.3	18.4
45–59	35.7	34.8	34.2	31.6	0.0	31.3	33.7	36.5	31.3	32.0
≥60	29.4	34.0	23.6	61.7	0.0	32.9	35.5	28.5	31.2	27.8
Inpatient department										
Internal medicine	24.3	25.7	42.4	29.3	2.1	18.4	32.8	20.3	25.1	16.9
Surgery	38.1	40.3	27.0	52.2	41.0	31.8	27.8	45.5	40.9	27.8
Oncology	9.0	8.4	1.8	5.7	2.3	4.0	8.1	8.6	8.0	16.8
Gynecology and obstetrics	5.6	7.1	5.8	2.4	0.1	3.7	5.8	9.1	4.2	1.3
Neurology	2.7	2.9	0.7	1.6	0.3	8.5	6.6	2.2	1.8	8.4
Pediatrics	4.7	4.5	11.9	0.6	40.6	4.9	5.5	3.9	7.3	19.3
Otolaryngology	1.7	0.5	0.3	1.0	2.1	0.9	0.3	0.4	0.6	0.5
Other	13.9	10.6	10.1	7.1	11.5	27.9	13.2	10.1	12.1	9.1
Residential addresses										
Regions in Hunan										
Eastern	27.2	26.3	24.1	25.4	25.7	30.4	29.3	25.4	29.4	25.6
Northern	17.1	17.4	17.7	17.6	12.8	16.6	16.4	17.8	16.5	16.5
Southern	17.2	17.4	19.0	17.9	14.3	18.5	15.9	17.6	16.3	16.2
Central	23.2	24.2	20.8	26.5	15.6	21.9	23.5	24.4	22.7	22.7
Western	6.0	5.9	6.1	5.7	10.0	6.0	5.9	5.9	5.1	6.1
Other	9.2	8.9	12.4	6.9	21.7	6.6	9.1	9.0	10.0	13.0
Insurance types										
Urban resident basic medical insurance	6.7	6.7	7.8	6.2	16.2	6.8	7.4	6.5	7.4	8.7
Urban employee basic medical insurance	24.8	24.2	19.5	27.0	5.5	20.9	26.3	23.1	23.6	19.8
New rural co- operative medical system	23.2	24.6	26.9	28.8	19.8	16.7	22.9	24.6	21.2	21.6

Table 1. (Continued)

Variable (Composition ratio, %)	Total Intravenous Medication Prescriptions	Inappropriate Intravenous Medication Prescriptions	Hepatic Insufficiency*	Renal Insufficiency*	Contraindicated in Pediatric Patients	Overdosing	Improper Diluent Volume	Improper Diluent Choice	Improper Administration Routes	Drug Incompatibility
Out-of-pocket payment	45.3	44.5	45.8	37.9	58.6	55.6	43.4	45.9	47.8	50.0
Admission source										
Outpatient	82.7	86.0	79.6	93.6	73.4	65.5	82.0	87.2	70.9	78.5
Emergency room	16.2	13.1	19.1	5.6	26.5	31.8	16.8	12.0	27.2	20.1
Transferred	0.7	0.4	1.0	0.1	0.0	2.1	0.6	0.3	1.4	0.5
Other	0.5	0.5	0.3	0.5	0.1	0.6	0.5	0.5	0.4	0.9
Missing	0.0	0.1	0.0	0.2	0.0	0.0	0.1	0.1	0.1	0.0

*Hepatic or renal insufficiency was estimated by the last blood test before parenteral medication administration. Hepatic insufficiency was aspartate aminotransferase or alanine aminotransferase 80 to 1000 U/L or total bilirubin 34.2 to 1000 $\mu\text{mol/L}$, and renal insufficiency was creatinine clearance < 60 mL/min.

rate.^{2,7} The Chinese government has since adopted several measures and policies to curb the high rate of intravenous prescribing, such as prohibiting intravenous infusions at outpatient clinics in tertiary and secondary hospitals and the Zero Markup Policy to promote positive prescribing.⁸ These government initiatives are predicated on removing economic incentives, and this alone may not lead to improvement in intravenous prescribing.⁹ Additional efforts are needed, such as the implementation of the pharmacy-driven intravenous to oral drug switch. A pharmacist-managed proactive intravenous to oral switch program reduced use of intravenous drugs and costs without compromising clinical outcomes.¹⁰

Almost half of the patients received intravenous antibiotics, a concerning statistics considering the consequences of unsupported antibiotic prescribing. In a recent study that examined the use of antibiotics in China, 70% of inpatients received antibiotics; a proportion strikingly greater than the recommended 30% set by the World Health Organization. Furthermore, the percentage of antibiotic prophylaxis for type 1 incisions remained >90% in 2010, compared with <30% in European countries.¹¹ Inappropriate prescribing of antibiotics not only raises the concern of antibiotic resistance but also presents harm to patients. Antibiotics were the leading medication class that caused drug-induced anaphylaxis (39.3%) in a recent Chinese pharmacovigilance study.⁵ Multiple factors contribute to the misuse of antibiotics in China, such as inappropriate physician prescribing and patient demand for antibiotics and reimbursement.⁷ Policy changes, public education, and antimicrobial stewardship should be initiated to reduce the unjustified prescribing of antibiotics.¹² Approximately 15% of the patients in this analysis received TCMs, yet another area deserving further analysis. Two Chinese studies reported that TCMs are the second most common trigger of drug-induced anaphylaxis,^{5,6} with most cases (95.7%) involving injections. More scrutiny of prescribing of TCMs is warranted.

More than half (64.8%) of the patients in this study received intravenous medications inappropriately, and >70% of the inappropriateness was compounding with improper diluents or diluent volumes. This is consistent with the findings in a systematic review.¹³ For example, the major problem for blood and blood-forming organs drugs was the choice of diluents, attributing to >50%

of cases. More intravenous admixture services should be established in Chinese hospital pharmacies to provide intravenous compounding.

Approximately 30% of the intravenous medications were inappropriately administered to patients with renal or hepatic impairments, a number significantly higher than a report from Spain,¹⁴ which found 11.5%. Although the percentage was rather low (0.2%), certain medications were administered to pediatric patients that were considered contraindicated. The adjuvant immunopotentiating drugs of deoxyribonucleotide and lentinan were among the top medications prescribed to patients. Many of these prescriptions are considered off-label with questionable efficacy but high incidences of ADRs.¹⁵ Evaluations on off-label use should be conducted to promote evidence-guided prescribing.

Given the high rate of intravenous medications and widespread issue with inappropriate admixtures, we suggest the following solutions: (1) clinical pharmacists should actively participate in a multidisciplinary team and provide prescription review using pharmacists' expertise in medications; (2) pharmacy should work with the multidisciplinary team to develop local or national intravenous prescribing guidelines similar to the UK National Institute for Health and Care Excellence guidelines that pertain to intravenous prescribing¹⁴ to promote rational intravenous therapies; and (3) hospitals should fortify health information systems to provide clinical decision support to providers.

CONCLUSIONS

Our analysis suggests that intravenous medications were inappropriately prescribed and administered in hospitalized patients within China. This problem likely requires a multifaceted approach to resolve and requires collaboration from physicians, pharmacists, and nurses.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflict of interest regarding the content of this article.

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APPENDIX

Table S1. Patients' demographic and clinical characteristics

Variable (Composition ratio, %)	Discharged Patients	Patients Received Intravenous Medication	Patients Received Intravenous Antibiotics	Patients Received Intravenous TCM	Patients Received Intravenous Hormonal
Gender					
Male	50.41	51.06	53.27	50.97	46.59
Female	49.59	48.94	46.73	49.03	53.41
Age groups, y					
0–17	10.60	9.30	11.42	0.79	6.25
18–44	26.52	26.42	28.10	17.42	27.03
45–59	32.89	33.75	30.06	37.84	41.18
≥60	29.99	30.54	30.43	43.96	25.53
Inpatient Department					
Internal Medicine	22.43	24.21	21.12	29.78	21.25
Surgery	29.71	29.69	38.12	27.40	32.86
Oncology	8.34	8.33	1.91	12.13	20.79
Gynecology and Obstetrics	6.60	6.91	9.68	0.20	3.89
Neurology	4.03	4.41	1.88	9.68	1.33
Pediatrics	5.73	4.69	4.84	0.02	2.91
Otolaryngology	2.90	3.12	5.91	0.02	1.17
Other	20.26	18.63	16.55	20.77	15.80
Residential Addresses					
Eastern regions in Hunan	28.31	28.26	27.07	32.21	26.45
Northern regions in Hunan	16.99	17.13	17.09	16.83	17.90
Southern regions in Hunan	16.37	16.57	16.22	15.97	18.33
Central regions in Hunan	22.50	22.73	23.36	22.93	22.67
Western regions in Hunan	5.94	5.87	6.19	5.09	5.89
Other	9.89	9.44	10.06	6.98	8.75
Insurance Types					
Urban Residents' Basic Medical Insurance	7.11	7.12	7.34	6.98	6.50
Urban Employees' Basic Medical Insurance	25.61	25.84	23.13	31.42	24.79
New Cooperative Medical Scheme	22.06	22.87	23.07	23.12	25.37
Out-of-pocket payment	45.16	44.10	46.31	38.49	43.33
Other	0.06	0.07	0.14	0.00	0.01
Admission Source					
Outpatient	89.91	89.26	84.62	87.74	92.28
Emergency Room	9.43	10.05	14.65	11.36	6.96
Transferred	0.24	0.27	0.41	0.45	0.21
Other	0.42	0.42	0.32	0.45	0.55

TCM: Traditional Chinese Medicine

Table S2. Potential inappropriate prescribing of intravenous medications by patients' demographics

Variable (Composition ratio, %)	Total Intravenous Medication Prescriptions	Inappropriate Intravenous Medication Prescriptions	Hepatic Insufficiency [†]	Renal Insufficiency [†]	Contraindicated in Pediatrics	Overdosing	Improper Diluent Volume	Improper Diluent Choice	Improper Administration Routes	Drug Incompatibility
Gender										
Male	54.1	51.8	63.8	49.8	53.9	62.3	53.6	49.7	54.5	59.8
Female	45.9	48.2	36.2	50.2	46.1	37.8	46.4	50.3	45.5	40.2
Age groups, years										
0–17	8.7	7.0	13.5	0.7	100.0	8.9	7.5	6.9	12.2	21.8
18–44	26.2	24.2	28.8	6.1	0.0	26.9	23.3	28.1	25.3	18.4
45–59	35.7	34.8	34.2	31.6	0.0	31.3	33.7	36.5	31.3	32.0
>=60	29.4	34.0	23.6	61.7	0.0	32.9	35.5	28.5	31.2	27.8
Inpatient Department										
Internal Medicine	24.3	25.7	42.4	29.3	2.1	18.4	32.8	20.3	25.1	16.9
Surgery	38.1	40.3	27.0	52.2	41.0	31.8	27.8	45.5	40.9	27.8
Oncology	9.0	8.4	1.8	5.7	2.3	4.0	8.1	8.6	8.0	16.8
Gynecology and Obstetrics	5.6	7.1	5.8	2.4	0.1	3.7	5.8	9.1	4.2	1.3
Neurology	2.7	2.9	0.7	1.6	0.3	8.5	6.6	2.2	1.8	8.4
Pediatrics	4.7	4.5	11.9	0.6	40.6	4.9	5.5	3.9	7.3	19.3
Otolaryngology	1.7	0.5	0.3	1.0	2.1	0.9	0.3	0.4	0.6	0.5
Other	13.9	10.6	10.1	7.1	11.5	27.9	13.2	10.1	12.1	9.1
Residential Addresses										
Eastern regions in Hunan	27.2	26.3	24.1	25.4	25.7	30.4	29.3	25.4	29.4	25.6
Northern regions in Hunan	17.1	17.4	17.7	17.6	12.8	16.6	16.4	17.8	16.5	16.5
Southern regions in Hunan	17.2	17.4	19.0	17.9	14.3	18.5	15.9	17.6	16.3	16.2
Central regions in Hunan	23.2	24.2	20.8	26.5	15.6	21.9	23.5	24.4	22.7	22.7
Western regions in Hunan	6.0	5.9	6.1	5.7	10.0	6.0	5.9	5.9	5.1	6.1
Other	9.2	8.9	12.4	6.9	21.7	6.6	9.1	9.0	10.0	13.0
Insurance Types										
Urban Residents Basic Medical Insurance	6.7	6.7	7.8	6.2	16.2	6.8	7.4	6.5	7.4	8.7
Urban employee basic medical insurance	24.8	24.2	19.5	27.0	5.5	20.9	26.3	23.1	23.6	19.8
New Rural Co-operative Medical System	23.2	24.6	26.9	28.8	19.8	16.7	22.9	24.6	21.2	21.6
Out-of-pocket Payment	45.3	44.5	45.8	37.9	58.6	55.6	43.4	45.9	47.8	50.0
Admission Source										
Outpatient	82.7	86.0	79.6	93.6	73.4	65.5	82.0	87.2	70.9	78.5

(continued on next page)

Table S2. (Continued)

Variable (Composition ratio, %)	Total Intravenous Medication Prescriptions	Inappropriate Intravenous Medication Prescriptions	Hepatic Insufficiency [†]	Renal Insufficiency [†]	Contraindicated in Pediatrics	Overdosing	Improper Diluent Volume	Improper Diluent Choice	Improper Administration Routes	Drug Incompatibility
Emergency Room	16.2	13.1	19.1	5.6	26.5	31.8	16.8	12.0	27.2	20.1
Transferred	0.7	0.4	1.0	0.1	0.0	2.1	0.6	0.3	1.4	0.5
Other	0.5	0.5	0.3	0.5	0.1	0.6	0.5	0.5	0.4	0.9
Missing	0.0	0.1	0.0	0.2	0.0	0.0	0.1	0.1	0.1	0.0

[†] Hepatic or renal insufficiency was estimated by the last blood test before parenteral medication administration. Hepatic insufficiency was aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 80–1000 units/L or total bilirubin (TBIL) 34.2–1000 μ mol/L, and renal insufficiency was creatinine clearance < 60 mL/min.

Table S3. Potential inappropriate prescriptions by drug class and potential inappropriate prescription categories

Drug Class [†]	Total Inappropriate Intravenous Prescriptions (%)	Hepatic Insufficiency (%)	Renal Insufficiency (%)	Contraindicated in Pediatrics (%)	Overdosing (%)	Improper Diluent Volume (%)	Improper Diluent Choice (%)	Improper Administration Routes (%)	Drug Incompatibility (%)
Blood and blood forming organs	54.2	5.7	27.7	0.1	0.0	6.8	55.2	1.6	2.8
Gastrointestinal and metabolism	16.5	4.6	0.5	0.0	0.0	39.5	46.3	0.9	8.1
Cardiovascular system	6.9	0.2	4.4	0.0	2.2	41.7	44.0	4.9	2.5
Antineoplastic and immunomodulating agents	6.8	5.6	14.4	0.0	0.3	25.3	37.9	4.6	11.9
Nervous system	6.5	9.6	23.5	0.5	0.8	38.6	19.3	2.0	5.6
Systemic hormonal preparations, excl. Sex hormones and insulins	2.9	0.0	0.0	0.1	0.0	6.6	76.9	4.9	11.4
Chinese patent medicine	2.3	0.0	0.0	0.0	0.0	40.5	31.6	0.2	27.6
Various	1.5	2.0	5.5	0.0	0.2	0.0	78.1	14.0	0.1
Anti-infectives for systemic use	1.3	12.0	18.6	3.2	9.1	6.3	19.2	13.2	18.5
Musculo-skeletal system	0.4	17.6	15.2	0.0	3.5	23.7	38.6	1.5	0.0
Genitourinary system and sex hormones	0.3	8.3	1.2	0.0	0.0	4.8	85.2	0.5	0.0
Respiratory system	0.2	0.0	0.0	14.9	28.0	0.0	52.0	4.4	0.6

[†] Drugs were categorized into Anatomical Therapeutic Chemical classification which were formulated by the WHO Collaborating Centre for Drug Statistics Methodology.