# A Computer Prescribing Order Entry–Clinical Decision Support system designed for neonatal care: results of the 'preselected prescription' concept at the bedside

Béatrice Gouyon, Silvia Iacobelli, E. Saliba, Catherine Quantin, A. Pignolet, Evelyne Jacqz-Aigrain, Jean-Bernard Gouyon

# A Computer Prescribing Order Entry–Clinical Decision Support system designed for neonatal care: results of the 'preselected prescription' concept at the bedside

B. Gouyon* MD, S. Iacobelli* MD PhD, E. Saliba† MD PhD, C. Quantin‡ MD PhD, A. Pignolet* PhD, E. Jacqz-Aigrain§ MD PhD and J. B. Gouyon* MD PhD

*Centre d'Etudes Périnatales de l'Océan Indien (EA 7388), CHU de La Réunion, Saint Pierre, La Réunion, †Service de médecine néonatale, CHU de Tours, Tours, ‡CIC 1432, CHRU de Dijon, Dijon, and §CIC 1426, Pharmacologie Pédiatrique et Pharmacogénétique, Hôpital Robert Debré, Paris, France*

## SUMMARY

*What is known:* **The neonatal intensive care units (NICUs) are at the highest risk of drug dose error of all hospital wards. NICUs also have the most complicated prescription modalities. The computerization of the prescription process is currently recommended to decrease the risk of preventable adverse drug effects (pADEs) in NICUs. However, Computer Prescribing Order Entry–Clinical Decision Support (C.P.O.E./C.D.S.) systems have been poorly studied in NICUs, and their technical compatibility with neonatal specificities has been limited.**

*Objectives:* **We set up a performance study of the preselected prescription of drugs for neonates, which limited the role of the prescriber to choosing the drugs and their indications.**

*Methods:* **A single 29 bed neonatal ward used this neonatal C.P.O.E./C.D.S. system for all prescriptions of all hospitalized newborns over an 18-month period. The preselected prescription of drugs was based on the indication, gestational age, body weight and post-natal age. The therapeutic protocols were provided by a formulary reference (330 drugs) that had been specifically designed for newborns. The preselected prescription also gave complete information about preparation and administration of drugs by nurses. The prescriber was allowed to modify the preselected prescription but alarms provided warning when the prescription was outside the recommended range. The main clinical characteristics and all items of each line of prescription were stored in a data warehouse, thus enabling this study to take place.**

*Results:* **Seven hundred and sixty successive newborns (from 24 to 42 weeks' gestation) were prescribed 52 392 lines of prescription corresponding to 65 drugs; About 30·4% of neonates had at least one out of licensed prescription; A prescription out of the recommended range for daily dose was recorded for 1·0% of all drug prescriptions.**

*What is new?:* **The C.P.O.E./C.D.S. systems can currently provide a complete preselected prescription in NICUs according to dose rules, which are specific to newborns and also comply with local specificities (therapeutic protocols and formulation of drugs). The role of the prescriber is limited to the choice of drugs and their indications. The prescriber still retains the possibility of modifying each item of the prescription, with all other prescription items being calculated by the C.P.O.E. system. In these conditions, the prescribers rarely modified the preselected prescription and the rate of out of range prescription was low. A multicentric study is required to confirm and extend these observations.**

*Conclusions:* **This study showed the feasibility of preselected prescription in NICUs and a low rate of out of range prescriptions. The preselected prescription could play a key role in lowering the dose error rate in NICUs.**

Correspondence: J. B. Gouyon, Centre d'Etudes Périnatales de l'Océan Indien (EA 7388), CHU de La Réunion, Boulevard François Mitterrand, 97448 Saint Pierre, Réunion, France. Tel.: +262 692620981; fax: +262 35 92 93; e-mail: jean-bernard.gouyon@chu-reunion.fr

## BACKGROUND

It is widely recognized that neonatal intensive care units (NICUs) have the highest rate of drug error (DE) associated with handwritten prescriptions of all hospital care units.[1,2] The rate of dose error in NICUs can reach 16·4%.[3] The lower the gestational age (GA) and birth weight are, the higher the risk of dose error is.[1,4–6] Therefore, a precise tailoring of neonatal prescription is required, especially in preterm infants. Depending on the drug, individual dose adaptation relies on patients' characteristics such as GA, body weight (BW), post-natal age, clinical conditions and associated drugs at the time of prescription.[7,8] However, this does not suppress the risks associated with the unlicensed and off-label (UOL) drugs, which are involved in 45% to 65% of prescriptions in NICUs.[4,6,8–10]

Computerization of the prescription process is the best way to decrease the risk of preventable adverse drug effects (pADEs) in NICUs.[11] A recent meta-analysis of 16 eligible studies in adult patients found that Computer Prescribing Order Entry (C.P.O.E.) was associated with half as many drug errors [pooled risk ratio (RR) = 0·46; 95% CI: 0·35–0·60] and pADEs (RR = 0·47; 95% CI: 0·31–0·71) when C.P.O.E. systems were compared to manual paper prescribing.[12] In comparison, C.P.O.E. systems have been poorly studied in NICUs and the results are controversial. Three studies reported a reduction in drug error rate (by 100% and 42% respectively)[13,14] or in harmful ADEs (by 46%),[15] and a fourth found a 23% increase in drug error rate.[16]

It is important to stress that the efficiency of the C.P.O.E. systems has been closely related to the associated clinical decision support (C.D.S.) system[17]: it was recently reported that the implementation of C.P.O.E. systems in paediatric ICUs minimized patient identification errors but did not adequately prevent dose errors if the system did not include advanced C.D.S.[18]

In this context, the French Society of Neonatology wished the development of a C.P.O.E./C.D.S. system specifically dedicated to NICUs. This C.P.O.E./C.D.S. system was innovative in the

production of a preselected prescription. Thus, our pilot study aimed to assess the performance of this concept through the rate of out of range dose, the lower being the better.

## METHODS

### Main characteristics of the neonatal C.P.O.E./C.D.S

This neonatal C.P.O.E./ C.D.S. system provides a complete preselected drug prescription (Table 1). The preparation modalities are indicated for nurses or pharmacists with the reconstitution solute, the detailing of the dilution process (when multiple dilutions are required), the volume of rinsing and the volume of perfusion tubing to be added to the total drug volume.

Each item of the prescription can be modified by the prescriber, and the C.P.O.E. system immediately recalculates all other related items. As an example a screenshot of a dopamine prescription is shown in Fig. 1.

Alerts warn the prescriber when an item value is out of the recommended range (Table 1).

Warnings can be overlooked by the prescriber except when he/ she is asked for a dilution solute, which is incompatible with the drug. Main clinical characteristics and all items of prescription lines are stored in a data warehouse, thus making the material for this study available.

### Main characteristics of the drug formulary reference

The building up of a specific neonatal drug formulary reference was based on: 1 – the French specifications when available (agence-prd.ansm.sante.fr/ php/ ecodex/ index.php); 2 – the Pediatric and Neonatal Dosage Handbook of the American Pharmacists Association. Lexi-comp.[7]; 3 – the existing medical literature on the subject. However, it was considered essential to leave the final decision for drug protocols to each NICU. The local referring neonatologist and pharmacist were given the possibility of adding drugs to the formulary reference and of adapting recommendations (indications, dose) to the local protocols.

### The pilot study

A single 29 bed neonatal ward (NICU: 8; intermediate care: 11; neonatal medicine: 10) used this neonatal C.P.O.E./ C.D.S. system for all prescriptions of all hospitalized newborns over an 18-month period (March 2014 to September 2015).

Authorization to store data in a data warehouse was given by the 'Commission Nationale de l'Informatique et des Libertés' (National Data Protection and Privacy Commission. N°1854394).

According to a European Delphi survey,[19] unlicensed and off-label drugs were, respectively, defined by the use of a drug not covered by a marketing authorization – and the use of a drug already covered by a marketing authorization but used in an unapproved way, related to age, indication, drug dosage (daily dose, unitary dose, loading and maintenance dose, intervals between successive administrations).

An out of range daily dose was identified when the prescriber did not validate the preselected C.P.O.E. dose and chose a new dose out of the range proposed by the formulary reference; the dose was maintained and signed by the prescriber in spite of an explicit alarm.

### Statistical analysis

Results were presented in mean (SD) for continuous variables and percentage (%) for discontinuous variables.

## RESULTS

Seven hundred and sixty newborns were included. Birth weight and GA were 1336 ± 731 g and 35 ± 4 weeks gestational

Table 1. Main functional characteristics of a C.P.O.E./ C.D.S. system intended for a complete preselected drug prescription in NICUs

| Functional characteristics provided by the C.P.O.E/ C.D.S. system | Duties of the prescriber |
|---|---|
| Drug dose (international unit): unit dose/ Kg or dose/ Kg/ min or dose/ Kg/ day; loading and maintenance dose when required<br>Modality of administration (oral, IV, inhaled, rectal, etc.)<br>Frequency of dose administration, infusion rate (IV), concentration of the final solution, end of treatment, duration of treatment.<br>Preparation modalities for nurses and pharmacists: reconstitution solute; details of the dilution process (including multiple dilutions); volume of rinsing and volume of perfusion tubing to be added to the total drug volume.<br>All calculations<br>All prescription items are modifable by the prescriber, and any change is associated with immediate recalculation of all items as required<br>Collection of all hidden intakes of water, sodium, potassium, phosphorus and glucose associated with drug preparation (the prescriber will have to consider when he prescribes the nutrition)<br>Warnings: Low and high boundaries are available for: daily body weight (a change by ± 10% as compared to the previous value); unit dose; dose per day; frequency; infusion rate; concentration of the final solution; forbidden solute; unlicensed or out of license drug; redundant prescriptions (drugs of similar INN); interactions and incompatible drugs; renewal of the loading dose. | Enter gestational age and date of birth<br>Gives the body weight, once a day<br>Chooses the drug and its indication<br>Modifes or confrms a prescription after a warning. |

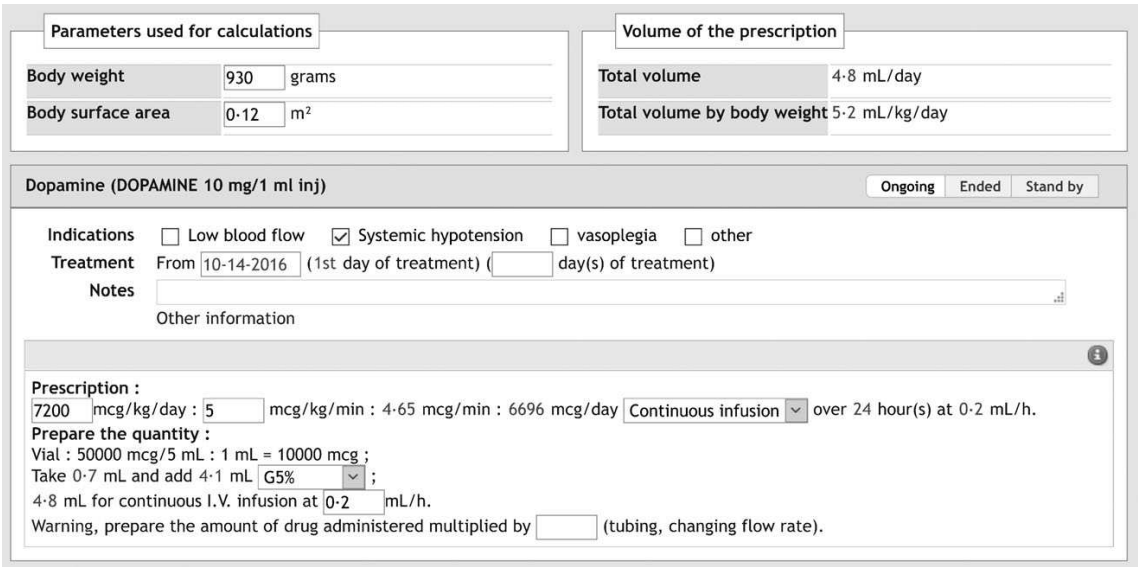


Fig. 1. A screenshot of a dopamine preselected prescription in a 930-g baby (the original was in French).

(WG; median: 36 weeks; 24–42). The sex ratio of males to females was 55 : 45.

52 392 lines of prescriptions were analysed and distributed among 12 812 edited and signed order sheets.

Sixty-five different drugs were prescribed during this study.

Out of label prescriptions:

- About 16.2% of the 52 392 drug prescriptions were off label (OL). The OL prescription rate in the NICU, intermediate care and medical neonatal unit was 26.4%, 12.3% and 5.4%, respectively.
- About 50.2% of the 12 812 order sheets included at least one OL drug prescription.
- About 30.4% of neonates had at least one OL drug prescription. Exposure to OL prescription was closely related to GA: 95.8% of the 143 preterm infants born at 24–31 WG; 19.2% of the 258 preterm infants at 32–36 WG; and 12.8% of the 359 term infants at 37–42 WG.
- About 73.1% of the prescribed drugs were concerned by at least one OL prescription. The 'Top Ten' OL drugs were as follows: Lactobacillus rhamnosus Lcr35 (Lcr Restituo), an oral probiotic agent (19.2% of OL prescriptions), intravenous (IV) sufentanil (11.5%), IV acetaminophen (7.6%), per oral (PO) acetaminophen (3.4%), IV ranitidine (3.2%), IV esomeprazole (2.6%), PO morphine (2.6%), nalbuphine (2.6%), betamethasone (2.6%) and ciprofoxacin (1.8%).
- One per cent (1.03%) of the daily doses were outside the value range proposed by the drug reference formulary. The corresponding rates of higher and lower daily dose were 0.36% and 0.69%, respectively. Drugs more frequently prescribed with overdose or underdose are reported in Table 2. Overdose and underdose affected 4.8% and 20% of the study population, respectively.

## DISCUSSION

In the present study, the drug prescription in one NICU was analysed over 18 months after implementation of a C.P.O.E./ C.D.S. system that allowed the preselection of the complete prescription. The study was made possible because of the computer storage of all items of all lines of prescription. The main result was a low rate of out of range daily dose, particularly in the field of overdose (0.36%).

Overall, C.P.O.E./ C.D.S. systems have been deemed to improve the safety of drug prescription.[12] Their use is now recommended by the American Academy of Pediatrics, both in NICUs and paediatric wards.[11] However, assessment of C.P.O.E./ C.D.S. systems in NICUs has been limited to some frequently prescribed drugs.[13,17] By contrast, we made the choice of a complete prescription process in which the prescribers' intervention was limited to the selection of the drug and its indication. We felt that this mode of prescription was a good solution to avoid some risks associated with a C.P.O.E. prescription such as: the wrong manipulation of a rolling menu, final solution concentration default and fatigue related to an high rate of alarms.

We considered it important not to limit the drug list to the most frequently prescribed drugs in NICUs because it has been shown that prescribing errors persist when handwritten prescription is occasionally performed in a mixed prescription system[4]; the rate of error in manual prescription of a rarely used drug is particularly elevated.

In this study, 16.2% of drug prescriptions were OL. It is worth noting that the prescriber was aware of the OL status of drug prescription as he/ she had to bypass a specific alarm and sign an order sheet highlighting the OL prescription lines. This rate of OL was inversely related to GA as previously observed in other studies[4,9] and was higher in the NICU than in other neonatal wards.

Table 2. Thirty-six drugs with the highest rates of out of range daily dose in a population of 760 newborns prescribed 65 drugs overall

| INN | Prescriptions number | % Overdose | % Underdose | % Out of range dose |
|---|---|---|---|---|
| Magnesium sulphate | 3 | 100 | | 100 |
| Cefaclor | 3 | | 100 | 100 |
| Erythromycin | 22 | 18.2 | 50 | 68.2 |
| Mycamine | 8 | 50 | | 50 |
| Atracurium Besylate | 10 | 40 | | 40 |
| Doxapram | 33 | | 39.4 | 39.4 |
| Heparin | 15 | | 26.7 | 26.7 |
| Betamethasone | 119 | | 21.0 | 21.0 |
| Midazolam | 285 | 12.6 | 7.4 | 20 |
| Furosemide | 734 | | 15.4 | 15.4 |
| Ranitidine | 185 | | 8.6 | 8.6 |
| Amikacin | 24 | 8.3 | | 8.3 |
| Phosphorus | 91 | | 7.7 | 7.7 |
| Imipenem/ cilastatin | 55 | | 7.3 | 7.3 |
| Fluconazole | 270 | 6.3 | 0.7 | 7.0 |
| Norepinephrine | 36 | | 5.6 | 5.6 |
| Acyclovir | 22 | | 4.5 | 4.5 |
| Phenobarbital | 134 | 3.0 | 1.5 | 4.5 |
| Alginate Na/ Bicarb. Na | 801 | 4.2 | | 4.2 |
| Sufentanyl | 910 | 0.1 | 3.7 | 3.8 |
| Ciprofoxacin | 133 | 3.8 | | 3.8 |
| Ibuprofen | 84 | | 3.6 | 3.6 |
| Hydrocortisone | 98 | 3.1 | | 3.1 |
| Insulin | 66 | 3.0 | | 3.0 |
| Cefotaxime | 684 | 2.9 | | 2.9 |
| Vancomycin | 504 | 0.2 | 2.7 | 2.9 |
| Poractant alpha | 47 | | 2.1 | 2.1 |
| Spironolactone | 896 | 1.6 | 0.4 | 2.0 |
| Phytomenadione | 1794 | 0.1 | 1.4 | 1.5 |
| Salbutamol IV | 286 | 1.4 | | 1.4 |
| Nalbuphine | 72 | 1.4 | | 1.4 |
| Acetaminophen | 1766 | 0.4 | 0.7 | 1.1 |
| Albumin | 94 | 1.1 | | 1.1 |
| Caffeine citrate | 4441 | 0.1 | 0.8 | 0.9 |
| Amoxicillin | 985 | 0.8 | | 0.8 |
| Gentamicin | 874 | 0.1 | 0.6 | 0.7 |

INN, international non-proprietary name of drugs.

Previous studies have shown similar observations in NICUs, the current rate of UOL ranging from 47 to 65%.[4,9] It was 40% below 32 WG in this study, which was similar to a 47% rate previously observed with handwritten prescription in the same neonatal ward.[4] Therefore, there is a mandatory need to reinforce the dose rules of UOL in neonatal formularies especially as the 'top ten' list of OL drugs in this study included high-risk drugs such as analgesics, antisecretory gastric drugs, steroids and a quinolone (Table 2).

Approximately 99% of the prescribed drugs fitted well with the formulary reference for daily dose. The 1% out of range daily dose was much lower than the values of 4% to 10% of dose errors reported with manual prescription.[1–4,6,13,17] The 1% out of range dose is also lower or similar to rates recorded in NICUs with other C.P.O.E. systems, which were all limited to some specific drug categories.[6,11,13,14,16,17]

Finally, a recent thesis from Utrecht University (the Netherlands) described an experimental C.P.O.E. system providing a 'by default' prescription at the bench.[20] The authors built a system that was similar to our preselected prescription and was able to provide safe and efficient support for a number of test scenarios from NICUs and paediatric intensive care units.

The main limit of this pilot study is the lack of a control period as C.P.O.E./ C.D.S. system assessment has been sometimes based on a before/ after design. We feel that such a design would be possible when a limited number of drugs are studied.[13,17] When the study design includes all prescribed drugs in a neonatal ward, the C.P.O.E./ C.D.S. implementation profoundly modifies medical and nursing practices, organization and thinking. It can simply be noted that the rate of out of range daily dose in this NICU was 3.1% of handwritten prescriptions before implementation of the C.P.O.E./ C.D.S. system[4] and 1% afterwards.

## CONCLUSION ON PERSPECTIVES

This study shows that preselected prescription is feasible for all drugs in NICUs. This should avoid or limit the heterogeneity of protocols in NICUs as it was recently observed for antibiotics in France.[21] The surrounding architecture of the C.P.O.E./ C.D.S. system can also allow the building up of drug use database, which is potentially useful for both benchmarking and pharmacoepidemiological studies.

## AUTHOR CONTRIBUTIONS

BG designed the technical and functional specifications, made critical design decisions, participated in and oversaw the front-line deployment, and drafted the manuscript. SI gave many relevant opinions and reviewed the final manuscript. ES as the president of the French Society of Neonatology gave many relevant opinions and reviewed the final manuscript. CQ gave relevant opinions and reviewed the manuscript. AP created the program allowing extraction and treatment from the database. EJA provided many relevant opinions and reviewed the final manuscript. JBG conceived the research project and participated in drafting the manuscript. All authors have read and approved the manuscript.

## ACKNOWLEDGEMENTS

The authors are pleased to acknowledge the hard work and dedication of the Perinatal Research Center of Reunion Island (EA 7833). Special thanks to Mss N Fouret (statistics), J Horri (participation in the elaboration of the safety process), I Germain (formatting the manuscript), C McNight (proofreading). The authors also thank the following for invaluable participation and/ or advice: Dr R Giniger, Mr C Cann, Dr F Bonsante and all participants in the B-PEN research program.

## CONFLICT OF INTEREST

No author has a conflict of interest to declare.

## FUNDING

The B-PEN research program was supported by a European Fund (FEDER grant no. 34018); the University Hospital of La Reunion Island and La Reunion Region.

REFERENCES


1. Kaushal R, Barker KN, Bates DW. How can information technology improve patient safety and reduce medication errors in children's health care? Arch Pediatr Adolesc Med, 2001;155:1002–1007.
2. Snijders C, van Lingen RA, Klip H, Fetter WP, van der Schaaf TW, Molendijk HA, NEOSAFE study group. Specialty-based, voluntary incident reporting in neonatal intensive care: description of 4846 incident reports. Arch Dis Child Fetal Neonatal Ed, 2009;94:F210–F215.
3. Campino Villegas A, López Herrera MC, García Franco M, Lopez de Heredia Goya I, Valls I Soler A. Medication prescription and transcription errors in a neonatal unit. An Pediatr (Barc), 2006;64:330–335 (in Spanish).
4. Horri J, Cransac A, Quantin C et al. Frequency of dosage prescribing medication errors associated with manual prescriptions for very preterm infants. J Clin Pharm Ther, 2014;39:637–641.
5. Hicks RW, Becker SC, Chuo J. A summary of NICU fat emulsion medication errors and nursing services: data from MEDMARX. Adv Neonatal Care, 2007;7:299–308.
6. Sorrentino E, Alegiani C. Medication errors in the neonate. J Matern Fetal Neonatal Med, 2012;25:91–93.
7. Taketomo CK, Hodding JH, Kraus DM. Pediatric and neonatal dosage handbook, 22nd edn. Hudson, OH: Lexi-comp, 2015–2016.
8. Gouyon JB, Cransac A, Sgro C. Medications errors in neonatal medicine: from prescription to administration. Arch Pediatr, 2012;19: 976–983 (in French).
9. Riou S, Plaisant F, Maucort Boulch D, Kassai B, Claris O, Nguyen KA. Unlicensed and off-label drug use: a prospective study in French NICU. Acta Paediatr, 2015;104: e228–e231.
10. Conroy S, McIntyre J. The use of unlicensed and off-label medicines in the neonate. Semin Fetal Neonatal Med, 2005;10:115–122.
11. Johnson KB, Lehmann CU, the Council on Clinical Information Technology of the American Academy of Pediatrics. Electronic prescribing in pediatrics: toward safer and more effective medication management. Pediatrics, 2013;131:1350–1356.
12. Nuckols TK, Smith-Spangler C, Morton SC et al. The effectiveness of computerized order entry at reducing preventable adverse drug events and medication errors in hospital settings: a systematic review and meta-analysis. Syst Rev, 2014;3:56.
13. Cordero L, Kuehn L, Kumar RR, Mekhjian HS. Impact of computerized physician order entry on clinical practice in a newborn intensive care unit. J Perinatol, 2004;24:88–93.
14. Taylor JA, Loan LA, Kamara J, Blackburn S, Whitney D. Medication administration variances before and after implementation of computerized physician order entry in a neonatal intensive care unit. Pediatrics, 2008;121:123–128.
15. Ferranti JM, Horvath MM, Jansen J, Schellenberger P, Brown T, DeRienzo CM, Ahmad A. Using a computerized provider order entry system to meet the unique prescribing needs of children: description of an advanced dosing model. BMC Med Inform Decis Mak, 2011;11:14.
16. Walsh KE, Landrigan CP, Adams WG, et al. Effect of computer order entry on prevention of serious medication errors in hospitalized children. Pediatrics, 2008;121: e421–e427.
17. Kazemi A, Ellenius J, Pourasghar F, Tofighi S, Salehi A, Amanati A, Fors UG. The effect of computerized physician order entry and decision support system on medication errors in the neonatal ward; experiences from an Iranian teaching hospital. J Med Syst, 2011;35:25–37.
18. Maat B, Bollen CW, van Vught AJ, Egberts TC, Rademaker CM. Impact of computerized physician order entry (CPOE) on PICU prescribing errors. Intensive Care Med, 2014;40:458–459.
19. Neubert A, Wong IC, Bonifazi A et al. Defning off-label and unlicensed use of medicines for children: results of a Delphi survey. Pharmacol Res, 2008;58:316–322.
20. Maat B. Optimization of electronic prescribing in pediatric patients. 09/ 25/ 2014. https:// www.google.com/ search?q=optimization+ of+electronic+prescribing+Barbara+Maat& ie=u tf-8&oe=utf-8 (verifed 02/ 10/ 2016)
21. Leroux S, Zhao W, Bellaïeux P, Pladys P, Saliba E, Jacqz-Aigrain E, French Society of Neonatology. Therapeutic guidelines for prescribing antibiotics in neonates should be evidence-based: a French national survey. Arch Dis Child, 2015;100: 394–398.