ORIGINAL ARTICLE

Use of a systematic risk analysis method to improve safety in the production of paediatric parenteral nutrition solutions

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Background: Until recently, the preparation of paediatric parenteral nutrition formulations in our institution included re-transcription and manual compounding of the mixture. Although no significant clinical problems have occurred, re-engineering of this high risk activity was undertaken to improve its safety. Several changes have been implemented including new prescription software, direct recording on a server, automatic printing of the labels, and creation of a file used to pilot a BAXA MM 12 automatic compounder. The objectives of this study were to compare the risks associated with the old and new processes, to quantify the improved safety with the new process, and to identify the major residual risks.
Methods: A failure modes, effects, and criticality analysis (FMECA) was performed by a multidisciplinary team. A cause-effect diagram was built, the failure modes were defined, and the criticality index (CI) was determined for each of them on the basis of the likelihood of occurrence, the severity of the potential effect, and the detection probability. The CIs for each failure mode were compared for the old and new processes and the risk reduction was quantified.
Results: The sum of the CIs of all 18 identified failure modes was 3415 for the old process and 1397 for the new (reduction of 59%). The new process reduced the CIs of the different failure modes by a mean factor of 7. The CI was smaller with the new process for 15 failure modes, unchanged for two, and slightly increased for one. The greatest reduction (by a factor of 36) concerned re-transcription errors, followed by readability problems (by a factor of 30) and chemical cross contamination (by a factor of 10). The most critical steps in the new process were labelling mistakes (CI 315, maximum 810), failure to detect a dosage or product mistake (CI 288), failure to detect a typing error during the prescription (CI 175), and microbial contamination (CI 126).
Conclusions: Modification of the process resulted in a significant risk reduction as shown by risk analysis. Residual failure opportunities were also quantified, allowing additional actions to be taken to reduce the risk of labelling mistakes. This study illustrates the usefulness of prospective risk analysis methods in healthcare processes. More systematic use of risk analysis is needed to guide continuous safety improvement of high risk activities.

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The compounding of paediatric parenteral nutrition solutions is a complex combination of high risk activities which closely link the quality of the prescription with the accuracy of production. As the consequences of errors may be dramatic, optimising the reliability of the process is of paramount importance.

Parenteral nutrition is frequently prescribed at our institution when enteral feeds are inaccessible or are not tolerated at a level sufficient to maintain or improve nutritional status. As recently described in a national survey,[1] adult parenteral nutrition is mostly administered in the form of commercial multi-compartment bags but, for children, the pharmacy department compounds parenteral nutrition solutions individually. In our hospital about 2500 bags are prepared each year, mainly for the neonatal and paediatric intensive care units but also for oncology patients and following surgery.

Parenteral nutrition solutions are complex, containing almost 50 ingredients prepared by the mixing of more than 10 different solutions. There is a high risk of error and microbiological contamination during the compounding. Potentially dramatic complications may result, especially in small children. Since the 1970s the methods of compounding parenteral nutrition solutions have changed dramatically. Initially, intravenous nutrition was directly administered to the patient from source containers of nutrient solutions (glucose, amino acids and lipids) using an arrangement of parallel intravenous lines. Electrolytes were added to the

glucose solution by the nursing staff on the ward before starting the infusion and the incidence of line infections was high, sometimes exceeding 20%.[2] In an attempt to reduce the risk of infection from contamination during mixing, it was recommended that parenteral nutrition solutions should be manufactured by specialised pharmacy staff within a dedicated aseptic preparation unit in a laminar airflow hood.[3][4] Observational studies have reported a high risk of errors during the compounding of parenteral nutrition solutions in hospital pharmacies, especially with manual preparation.[5] To reduce the risk and to optimise the workload, several automated compounding devices delivering the finished mixture into a final container using a volumetric pumping system have been developed over a number of years.[6–10] Studies comparing their performance with manual preparation have shown that they save time, reduce costs, and improve safety.[11][12]

The prescription of nutrition mixtures is complex and, without specific guidance, is associated with a high incidence of errors[13] that may lead to potentially severe healthcare accidents. Standardised prescription forms,[13][14] handheld programmable calculators,[15] and computer software[16–21]—recently even associated with artificial intelligence[22]—have been developed to help physicians in this intricate task, with the aim of eliminating calculation errors and proposing recommended values for each prescribed constituent of the parenteral solution.

To analyse reliability problems, root cause analysis is a useful retrospective method when the frequency of incidents is high but its use is not appropriate when the failure frequency is very low or unknown. For critical processes it is not acceptable to wait for an accident to happen before deciding what safety improvements are needed, especially when the potential outcome may be dramatic for the patient. There has been a growing awareness and acceptance that more proactive risk analysis approaches—used in a number of high risk areas such as aviation, aerospace, nuclear power, and the food industry—need to be applied to high risk areas in health care. These techniques assume that, no matter how knowledgeable or careful we are, there will always be situations in which human error or mechanical failure are possible. In the United States the Joint Commission on Accreditation of Health Organizations (JCAHO) has, since 1 July 2001, required each accredited hospital to conduct at least one proactive risk assessment annually.[23] The Institute of Medicine (IOM) in its report ''Patient safety: a new standard of care'' recommended research on the application of proactive hazard and risk analysis approaches.[24]

A number of tools are available to improve the safety of health care, including Six Sigma, hazard analysis and critical control points (HACCP), failure modes and effects analysis/ healthcare failure modes and effects analysis (FMEA/ HFMEA), failure modes, effects, and criticality analysis (FMECA), probabilistic risk assessment (PRA), Toyota production system (TPS), hazard and operability studies (HAZOP), and total quality management/continuous quality improvement (TQM/CQI).[25] Each of these approaches has its champions and can be applied in the healthcare setting. There are more similarities than differences between them. FMEA and FMECA are two well described methods that assess systematically a process or product and enable determination of the location and mechanism of potential failures. They dissect a given process, identify possible or likely errors (''failure mode''), and gauge what their effect will be, even before they take place.[26] Although the two methods are often confused in the literature, FMECA goes one step further than FMEA and includes a quantitative evaluation of the criticality of each failure mode, whereas FMEA is only a qualitative method. Criticality indexes are calculated by multiplying three components—occurrence, severity and detection—determined from reference scales on the basis of known or estimated data for each failure mode. FMECA classifies the failure modes and identifies the top critical events, which is very helpful for deciding and prioritising actions to be taken to eliminate the possibility or reduce the frequency of errors and to improve their detection before they occur.

Probabilistic risk assessment (PRA) is especially useful for modelling equipment failures, human error, and recovery opportunities through the use of fault trees.[27] Its main interest is in assessing the impact of a combination of failures leading to a specific outcome. In particular, it allows an accurate determination of occurrences when probability estimates exist for the basic events. However, in practice, most healthcare issues do not have up to date risk rates for the underlying events. The method is based mainly on the probability of occurrence without taking into consideration either the severity or the possibilities of detection.

To date, prospective risk analyses are uncommon in health care, except in the field of blood transfusion.[28–31] Only a few other processes—such as drug prescription,[32] drug distribution systems,[33] and the use of medical devices[34]—have occasionally been analysed by these techniques. However, we predict their more widespread use in the future because of the development of systematic approaches to medication error prevention in hospitals and the promotion of these tools by some authors.[35–38]

To the best of our knowledge, there has been no published description of the application of a structured risk analysis to the process of preparing parenteral nutrition solutions from prescription to compounding. This may be because the main objective of most studies on compounding parenteral nutrition solutions has been to reduce costs and time, rather than to study the risk of the different steps in the process.

As the production of paediatric parenteral nutrition solutions was identified as one of the high risk activities in our pharmacy, some major improvements in both the prescription and the compounding methods, as well as in the connection between these two major steps, were initiated in 2001. We have performed a comparative risk analysis of the old and new processes to provide a quantitative evaluation of safety improvements and to identify the remaining risks which may need further improvement.

METHODS
System used in our institution
Prescriptions for paediatric parenteral nutrition solutions are transmitted by the physician to the central pharmacy before 13.00 hours, 7 days a week. All prescriptions are specific and individualised. The compounding of the solutions is performed in a class A horizontal laminar airflow cabinet placed in a class B grade room. The main steps involved in the old and new processes are described in box 1 and are summarised in table 1.

Risk analysis
A comparative risk analysis of the old and new processes was performed by the quality assurance pharmacist in collaboration with other pharmacists and technicians, several of whom were not involved in the paediatric parenteral nutrition process. The analysis was not used to set up the new system but to quantify the improvements after its implementation and to examine whether further improvements were necessary. The method chosen was FMECA because of its ease of use and the quantification of failures by a criticality index (CI) which takes into account the likelihood of occurrence, the severity of the potential

Table 1 Summary of old and new processes of production of paediatric parenteral nutrition solutions

	Old process	New process
Prescription	DOS based software Printing of prescription and compounding protocol	Access software Step by step guide
Transmission to pharmacy	Fax	Saved on a server Fax for medicolegal purposes only
Pharmacist validation	Comparison with previous days	Comparison with previous days and with predefined limits
Label production	Printing after re-transcription in Windows based software	Directly printed from the server
Compounding	Manual non-sterile reconstitution of the mixture Aseptic filling by filtration in an HLAC	Direct creation of an electronic compounding file Automatic filling with a BAXA MM 12 compounder in an HLAC Written SOP
Quality control	Analysis of sodium, potassium, glucose content	Analysis of control bags to detect inversion of raw materials

HLAC, horizontal laminar airflow cabinet; SOP, standard operating procedure.

Box 1 Description of old and new processes

Old process

DOS based software was used to prescribe a nutrient mixture based on different solutions available as well as to print the compounding protocol. The prescription and the protocol were then transmitted to the pharmacy by fax and validated there by comparison with prescriptions of previous days. Labels were printed after re-transcription of the parenteral nutrition formulation into a second Windows based software. The parenteral solutions were then prepared in two steps: (1) non-sterile reconstitution of the mixture by manually measuring the volumes of the 11 constituents; and (2) aseptic filling of EVA bags by filtration in a horizontal laminar airflow cabinet. The sodium, potassium, and glucose contents were analysed from an aliquot of each mixture before release on 5 days each week.

New process

Integrated Access software was developed to guide, help and give safety boundaries to the prescribing physician according to the weight and age of the child and to connect the prescription process directly to the production process including pharmaceutical validation, labelling, and compounding.[40] The prescribed formulations are saved on a server and a printed summary is signed by the prescribing physician and faxed to the pharmacy for medicolegal purposes. The pharmacist then accesses the prescribed parenteral formulation on the server, validates it, directly prints the labels, and automatically creates an electronic support (floppy disk) containing the coded compounding information to pilot a BAXA MM 12 compounder based on a detailed written standard operating procedure. The prescribed parenteral nutrition solutions are then automatically produced in a laminar airflow cabinet. Physical and bacteriological validation of the BAXA MM 12 production cascade was performed before its regular clinical use.[41] Several control steps are included to avoid inversion of raw materials on the compounder. In addition, a control bag is manufactured at the beginning and end of every session for chemical and bacteriological analysis. These new developments have abolished re-transcriptions and manual volume measurements.

Table 2 FMECA occurrence, severity and detection ranking[39]

	Probability	Ranking
Occurrence		
Remote	1 in 10 000	1
No known occurrence		
Low	1 in 5000	2–4
Possible but no known data		
Moderate	1 in 200	5–6
Documented but infrequent		
High	1 in 100	7
Documented and frequent	1 in 50	8
Very high	1 in 20	9
Documented, almost certain error	1 in 10	10
Severity		
Slight annoyance		1
May affect the system		
Moderate system problem		2–3
May affect the patient		
Major system problem		4–5
May affect the patient		
Minor injury		6
Major injury		7
Terminal injury or death		8–9
Detection		
Very high	9 of 10	1
System will always detect error		
High	7 of 10	2–3
Error likely to be detected before		
product reaches patient		
Moderate	5 of 10	4–6
Moderate likelihood of detection	4 of 10	
before error reaches patient		
Low	2 of 10	7–8
Low likelihood that error will be	1 of 10	
detected before product/service		
reaches patient		
Remote	0 of 10	9
Detection not possible at any point		
within system		

outcome, and the possibility of detecting failure before it occurs. These elements can be particularly useful for deciding which specific failure mode needs to be improved and the impact of process adjustments. The analysis was performed according to the methodology previously described.[39]

A multidisciplinary team including several pharmacists (head of quality assurance, head of production, head of quality control, clinical pharmacist specialised in nutrition) and technicians was formed for the analysis. They were required to meet as many times as was necessary to complete the analysis. The main steps of the old and new production processes were identified and defined by the group. A brainstorming session was organised to determine the ways in which the process could fail at each step. The team had to answer the following question: ''What could possibly go wrong with this process step?'' An Ishikawa cause-effect diagram was constructed and the failure modes were determined in order to define the same failure modes for the two methods to be able to compare them.

Criticality analysis

The likelihood of occurrence (incidence) for each failure mode was classified from 1 to 10, the severity of the potential effect from 1 to 9, and the chance to detect the failure from 1 to 9. Estimations were obtained by consensual quotations in the group on the basis of explicit criteria defined by Williams[39] (table 2).

The CI of each failure mode was calculated by multiplying the frequency, effect and detection scores (CI 1–810) and the results were summarised in a table comparing the CIs for each mode of failure in the old and new processes. The CIs for the new process were classified from the highest to the lowest value.

Data analysis

The table of CIs was analysed by the multidisciplinary team to compare risks associated with the old and new processes, to quantify the safety improvement, and to identify remaining risks that may be the target of further actions. The sum of the CIs for the old and new processes was compared to determine the global improvement in process safety and the potential impact on patient outcome. For each mode of failure the evolution of the CI was discussed and the acceptability of the residual risk evaluated. When it was not considered acceptable, additional improvements were planned and their effect on the CI quantified.

RESULTS

The analysis was performed between October 2002 and January 2003 during four meetings each lasting approximately 2 hours.

The process was split into six major steps: prescription, transmission to the pharmacy, pharmacist validation, label
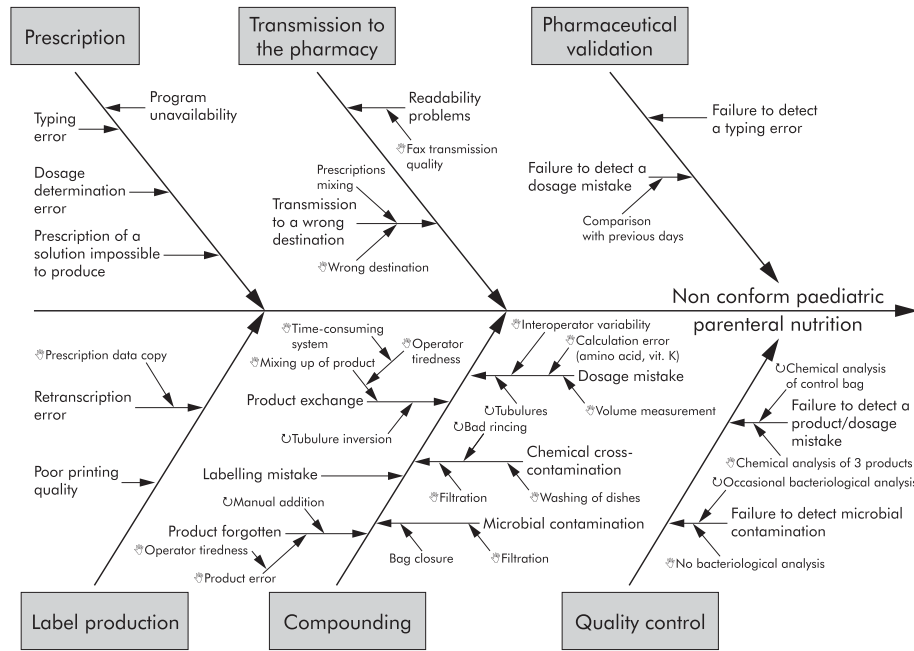
Figure 1   Ishikawa cause-effect diagram for the process of producing paediatric parenteral nutrition formulations.

production, compounding, and quality control. During the brainstorming session more than 40 potential problems were identified and they were summarised on an Ishikawa cause-effect diagram divided into six parts relating to each step of the process (fig 1). Problems leading to the same outcome were grouped together and 18 failure modes were finally identified for risk analysis.

The CIs calculated from the defined frequency, severity, and detection scores for each of the 18 failure modes are shown in table 3. The total CI was 3415 for the old process and 1397 for the new process, a reduction of 59%. Individual CIs were reduced by a mean factor of 7. For 15 of the 18 failure modes the CI was smaller in the new process, it was unchanged for two, and slightly increased for one. The two unchanged failure modes were associated with labelling mistakes (CI 315) and failure to detect a typing error during prescription (CI 175). The only increased failure mode was the potential risk of programme unavailability (by a factor of 2), but the criticality remained very low (CI 20). The greatest risk reduction (by a factor of 36) concerned the re-transcription error followed by prescription reading problems (by a factor of 30) and chemical cross contamination (by a factor of 10).

The highest risks in the old process were computed for dosage errors (CI 512), product exchange (CI 384), failure to detect a dosage/product error (CI 360), and product omission (CI 336). In the new process the most critical steps were labelling mistakes (CI 315), failure to detect a dosage/product mistake (CI 288), failure to detect a typing error during the prescription (CI 175), and microbial contamination (CI 126).

Analyses of the global impact concluded that the new process significantly increased the safety for patients by reducing the risk in administering a solution with a dosage error. The largest improvement in safety was obtained by elimination of the fax transmission and re-transcription, and by automation of the compounding procedure. The risk of microbial contamination, on the other hand, was only slightly reduced and this type of failure remained relatively critical in the new process. The highest risks identified in the new process were the inversion of the raw solutions on the BAXA MM 12 leading to dosage errors and the inversion of

labels on the final product leading to a potentially harmful injection of a wrong solution to two distinct patients. The first of these two risks was considered acceptable because of the strict procedure in force to control the daily set up of the pump. The risk of label inversion, however, was considered unacceptable and additional safety improvements were therefore considered. As it was considered difficult to significantly reduce the likely occurrence of this event, efforts were focused on detecting a possible failure. As each prescription is individual in composition and volume, a weight control of the bags was added at the end of the compounding procedure to test for agreement between the predicted (calculated from the prescription) and the real (measured) weight for each bag of parenteral solution. This additional control markedly improved the error detection ability (detection ranking from 7 to 2) and consequently the CI of this failure mode was reduced by a factor of 3.5 (from 315 to 90). The residual risk of this failure mode was considered acceptable.

DISCUSSION

Proactive risk analyses are generally used during the development of a new process before its implementation. In this study we performed an analysis to confirm and quantify the risk reduction we hoped we had achieved by modifying our process and, above all, to identify residual risks that may require further actions.

The FMECA method confirmed that re-engineering the process of paediatric parenteral nutrition production had resulted in a significant risk reduction. There was a reduction in the criticality associated with almost all the failure modes, with a mean reduction of nearly one log. This analysis allowed quantification of the improvement in safety achieved with the new process. Even though such a process obviously cannot avoid all errors, the risk for the patient of receiving a solution with a wrong dosage has been markedly reduced. Furthermore, the analysis identified and classified the residual risks, so the investigators had to decide whether to accept the determined level of risk or to further improve the safety of the process, usually at an increased cost. In the current analysis the most critical steps in the new process

Table 3 Failure modes and comparative criticality indexes (CIs) for the old and new processes

Process steps	Failure modes	Criticality index		Reduction factor (new/old)
		Old process	New process	
Prescription	Typing error	105	28	3.8
	Dosage determination error	175	28	6.3
	Programme unavailability	9	20	0.5
	Prescription of a solution impossible to produce	18	5	3.6
Transmission to pharmacy	Readability problems	210	7	30.0
	Transmission to wrong destination	45	9	5.0
Pharmaceutical validation	Failure to detect a typing error during prescription	175	175	1.0
	Failure to detect a dosage error	210	105	2.0
Label production	Re-transcription error	72	2	36.0
	Poor printing quality	10	4	2.5
Compounding	Product exchange	384	48	8.0
	Product omission	336	112	3.0
	Dosage error	512	64	8.0
	Microbial contamination	189	126	1.5
	Chemical cross-contamination	210	21	10.0
	Labelling error	315	315	1.0
Quality control	Failure to detect a dosage/product error	360	288	1.3
	Failure to detect a microbial contamination	80	40	2.0
	Sum	**3415**	**1397**	
	Mean			**7**

were considerably lower than in the old process, but several failure modes remained subject to further improvement. The risk of labelling errors at the end of compounding became the most critical step and illustrates how risk analysis methods allow a dynamic improvement in processes (in the present example by the use of weighing as an economic but efficient way of detecting parenteral nutrition differences).

Although the results of our study may not be directly applicable to other organisations, they nevertheless show that some general principles such as eliminating re-transcription procedures and automation of compounding may reduce the risk of errors significantly. These findings should encourage other institutions to re-engineer their high risk processes, guided by risk analysis methodology. This study illustrates the value of a prospective risk analysis method as an accompanying tool in a process review, and should stimulate a more widespread use of these techniques in the future. At our institution we have started to apply the same methodology to other high risk processes such as the use of cytotoxic drugs from their prescription to administration.

Key messages

- Proactive risk analysis methods are useful for analysing and improving the safety of high risk processes, especially when it is difficult to directly measure an outcome because of its very low incidence.
- Failure modes, effects, and criticality analysis (FMECA) allows classification of the criticality of failure possibilities on the basis of three important criteria: likelihood of occurrence, severity of the potential outcome, and the possibility of detecting failure before it occurs.
- This study confirmed a major risk reduction in our paediatric parenteral nutrition process following re-engineering of the process, particularly by eliminating re-transcription and by automation of compounding.
- More widespread use of similar risk analyses may be used in the future to prioritise safety improvements in high risk healthcare activities.

The major limitation of FMECA is the unavoidable subjectivity in the selection of failure modes and the determination of the CIs by brainstorming. The team should therefore be sufficiently large and multidisciplinary to reduce this bias, and should include several neutral investigators. The moderator should obtain consensual quotations to guarantee the best possible objectivity. Moreover, to reduce judgement variability, it is recommended that the frequency, severity, and ability to detect a failure mode is determined on the basis of explicit criteria such as those proposed by Williams[39] and used in our study. However, it is important to note that the specific number defined for a failure mode is not essential. Indeed, as the main goal is to classify risk stages and to determine orders of magnitude, the method allows for some imprecision.

A further limitation of FMECA, in contrast to the probabilistic risk assessment method, is that it is impossible to assess the impact of a combination of multiple failures on a specific outcome. However, the separate analysis of each failure mode is also an advantage as it gives in depth understanding and visualisation of the risk associated with each step and therefore allows implementation of specific improvements. Finally, the simplicity of the method contributes to the easy use of the reported risk analysis.

In conclusion, our study confirmed a major risk reduction by re-engineering our paediatric parenteral nutrition process. It also identified and classified the residual failure possibilities and led to additional improvements. The study demonstrates the usefulness of the risk analysis method in healthcare processes. A more systematic use of this tool in future may help researchers to prioritise the use of continuous safety improvement for high risk activities.

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