REVIEW ARTICLE

Drug Safety 2007; 30 (6): 503-513
0114-5916/07/0006-0503/$44.95/0

Incidence and Nature of Medication Errors in Neonatal Intensive Care with Strategies to Improve Safety

A Review of the Current Literature

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Contents

Abstract

Neonates are highly vulnerable to medication errors because of their extensive exposure to medications in the neonatal intensive care unit (NICU), the general lack of evidence on pharmacotherapeutic interventions in neonates and the lack of neonate-specific formulations. We searched PubMed and EMBASE to identify relevant original studies published in the English language. Eleven studies were identified on the frequency of medication errors in the NICU. The highest rate was 5.5 medication errors per 100 prescriptions; however, medication error rates varied widely between studies, partly due to differences in the definition of an error and the rigor of the method used to identify medication errors. Furthermore, studies were difficult to compare because medication error rates were calculated differently. Most studies did not assess the potential clinical impact of the errors. The majority of studies identified dose errors as the most common type of error. Computerised physician order entry and interventions by clinical pharmacists (e.g. the participation of pharmacists in ward rounds and review of patients'

prescriptions prior to dispensing) were the most common interventions suggested to improve medication safety in the NICU. However, only very limited data were available on evaluation of the effects of such interventions in NICUs. More research is needed to determine the frequency and types of medication errors in NICUs and to develop evidence-based interventions to improve medication safety in the NICU setting. Some of these research efforts need to be directed to the establishment of clear definitions of medication errors and agreement on the methods that should be used to measure medication error rates and their potential clinical impact.

The majority of studies on medication errors have been performed in adults and older children; thus, there is a lack of information regarding the epidemiology of medication errors in neonates in the neonatal intensive care unit (NICU). Neonates pose particular challenges to the system for prescribing, dispensing, administering and monitoring medications compared with older children and adults.[1-4] Most importantly, there is a lack of evidence to support much of the use of medications in neonates.[2,4-8] Prescribing decisions must be made on an individual patient basis, as neonates are not a homogeneous group. Neonates are born at different gestational ages. A neonate who is born preterm and weighs 500–700g at birth may spend from weeks to months in the NICU. During this time, pharmacokinetic and pharmacodynamic parameters change continuously due to changes in the neonate's weight and length, maturing enzyme systems and renal function.[2,8] This influences the ability to handle and tolerate medications and requires frequent adjustment of medication dosages and administration intervals.[2-4,7,9]

Medications are subject to licensing procedures to ensure their safety, effectiveness and quality. However, many medications used to treat neonates are either prescribed outside the terms of the product licence (off label) or are not licensed (unlicensed) for this age group.[5,6] On average, 45–60% of the medications prescribed in the NICU are used off label and 10–16% are used unlicensed in the UK,[6] Australia[10] and Israel.[11] Because of the lack of reference standards for doses of off-label and unlicensed medications, clinicians are often confronted with different published reference standards for a single medication. As a result of the limited range of licensed medications in appropriate dosage forms and the almost universal need for weight-based dose prescribing in neonates, more calculations and dilutions are involved prior to administration compared with those required in adults, leading to an increased number of opportunities for errors.

Given the complexity of medication use in the NICU, the high frequency at which neonates are exposed to medications and the potential for serious consequences of even small errors in this vulnerable patient group, medication safety is an important issue.[12-14] This article aims to review the literature on the frequencies and types of medication errors, as well as the evaluation of strategies to improve medication safety, in NICUs.

1. Literature Search Strategy

We searched the PubMed and EMBASE databases for articles published from 1975 through to May 2006. The search was restricted to original studies published in the English language. An experienced librarian assisted us with the search. We used the following MeSH search terms: medication errors, safety management (patient safety, medication safety), paediatrics and pharmacists. We narrowed the search with the MeSH terms infant, newborn, and intensive care, neonatal/intensive care units, neonatal. We reviewed this literature to identify additional studies.

The search strategy produced 116 references. The title, abstract or the full-text article was reviewed for relevance, and 102 references were excluded because they were not original studies on the

topics of interest. Two additional relevant studies were found, resulting in 16 references. Seven references were identified on the epidemiology of medication errors in neonates in the NICU. Five references were identified on strategies to improve medication safety in the NICU, of which four did not document activities in neonatal and paediatric units separately. Four references concerned both the epidemiology of medication errors and strategies to improve medication safety in the NICU.

2. Studies on the Frequency and Types of Medication Errors in the Neonatal Intensive Care Unit

Eleven studies were identified on the epidemiology of medication errors in neonates in the NICU (table I). Estimates of the rates of medication errors varied substantially between studies. Kaushal et al.[15] reported the highest error rate, using a combination of chart review and voluntary reporting. They found 5.5 medication errors per 100 prescriptions. Lower rates were reported by Simpson et al.[16] and Vincer et al.[17] using critical incident or spontaneous incident reporting methods. Results were difficult to compare between studies because rates were expressed differently. For example, Simpson et al.[16] reported rates per neonatal activity day, whereas Vincer et al.[17] and Myers et al.[18] reported the rate per patient-day and Larsen et al.[19] reported the rate per continuous medication infusion. Other studies only focussed on one type of error, such as documentation errors[20] or associated with continuous infusions.[19] Table I summarises studies on the frequency of medication errors.

The most common medication errors in the NICU concerned the dose (table I). Dose errors occurred because of incorrect recording of the patient's weight, incorrect recording of the dosage regimen, incorrect units (e.g. the interchange of milligrams and micrograms) and misplacement of decimal point when calculating the dose. Potentially very serious errors included 10- or 100-fold overdoses.[23,24,26] Kaushal et al.[15] reported that most dose errors occurred during physician ordering of medication and fewer errors occurred during preparation and administration of medications, whereas Vincer et al.[17] and Raju et al.[21] documented that dose errors were often due to mistakes in diluting medications from stock solutions primarily intended for use in adults. Vincer et al.,[17] Raju et al.[21] and Suresh et al.[22] documented administration errors as being the most common type of error. Other types included errors in the route of administration and errors involving enteral nutrition.[13,16,22] Several studies demonstrated that intravenous medications were particularly prone to errors in neonates.[15,24] Patient misidentification was also involved in serious medication errors.[16,22] Furthermore, Carroll et al.[20] found a high frequency of documentation discrepancies in medical notes involving medications, which increased with extended length of stay and when the patient had more indwelling lines and received more medications. Examples of such discrepancies included not recording a medication the patient had received or recording a medication the patient did not receive.

3. Studies on Strategies to Improve Medication Safety

3.1 Computerised Physician Order Entry (CPOE) and Other Technologies

Three studies were found that evaluated selected aspects of using computerised physician order entry (CPOE) in neonatology. Cordero et al.[25] found that post-CPOE, gentamicin administration errors were eliminated and the timeliness of caffeine administration was improved (table I). Myers et al.[18] reported a reduction in medication errors from 3.2 (pre-intervention period) to 0.6 errors per 1000 patient-days (post-intervention period) following the use of CPOE with administration guidelines that consisted of indication documentation, formulation and dose regimen information, and administration instructions (table I). Lucas[27] reviewed staff satisfaction with CPOE in a NICU: 87% (20 members) of the neonatology staff believed that the changes had improved medication safety; 65% (15 members) believed that the changes increased their comfort level in the provision of patient care with respect to medi-

Table I. Studies on the frequencies and types of medication errors in neonates in the neonatal intensive care unit (NICU)

Study	Country and year(s) of study	Setting	Study period	Study method	Outcome	Most common type of error
Kaushal et al.[15]	US, 1999	Nine wards, including one NICU, in two teaching hospitals[a]	6wk	Prospective identification of medication errors, potential ADEs and ADEs through clinical staff reports, and review of medication order sheets, medication administration records and patient charts	5.5 medication errors per 100 NICU prescriptions 91 (n = 49) medication errors per 100 admissions in neonates in the NICU 50 (n = 65) medication errors per 100 admissions in neonates who were not in the NICU 46 (n = 25) potential ADEs per 100 admissions in neonates in the NICU 9 (n = 12) potential ADEs per 100 admissions in neonates who were not in the NICU[b]	Incorrect dose
Simpson et al.[16]	UK, 2002–3	NICU in a maternity hospital	1y	Prospective identification of medication errors by critical incident reporting. The interventions (a daily review of medication orders and parenteral fluid prescriptions for each infant) were made after a 4-month, pharmacy-led education programme for each new member of pharmacy, nursing or medical staff	105 medication errors 24.1 medication errors per 1000 neonatal activity days in the pre-intervention period and 5.1 per 1000 neonatal activity days in the post-intervention period 12.2 medication errors per 1000 neonatal activity days after change over of junior medical staff	Incorrect dose
Vincer et al.[17]	Canada, 1986–7	NICU in a maternity hospital	2y	Prospective analysis of reports of medication errors and incidents	13.4 incidents per 1000 patient-days	Administration error
Raju et al.[21]	US, 1985–8	NICU and PICU in a university hospital	4y	Prospective review of written incident reports	15 (n = 315) medication-related errors per 100 admissions	Incorrect time of administration
Suresh et al.[22]	US, 2000–3	54 hospitals, all containing a NICU	27mo	Prospective analysis of voluntary anonymous reports of medical errors, near-miss errors, and adverse events to a secure internet site	47% of all reported events (n = 1230) were related to medications, nutritional agents or blood products	Administration error
Ross et al.[23]	UK, 1994–9	Different wards, including a NICU, in a paediatric hospital[a]	65mo	Retrospective review of all reported medication errors and the associated investigations	Medication errors occurred in 0.15% (n = 195) of all admissions and 0.98% (n = 33) of all admissions to the NICU (17% of all medication errors)	Incorrect IV infusion rate

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Table I. Contd

Study	Country and year(s) of study	Setting	Study period	Study method	Outcome	Most common type of error
Larsen et al.[19]	US, 2002–3	Paediatric hospital, including a NICU[a]	Two 12-mo periods	Retrospective comparison of reported continuous medication infusion errors pre- and post-intervention. The intervention involved medication preparation by the pharmacy department and smart pump technology	Pre-intervention: 3.5 continuous medication infusion errors per 1000 doses; post-intervention: 1.4 continuous medication infusion errors per 1000 doses	One type of error studied
Myers et al.[18]	US, 1993–6	Academic NICU	4y (data collection)	Retrospective analysis of medication errors through adverse drug reaction reports and reported errors in written orders and dosage formulation, preparation, and administration. Birth weight-specific neonatal survival rates were measured using standard methods. The intervention was CPOE supported by guidelines	Pre-intervention: 3.2 medication errors per 1000 patient-days; post-intervention: 0.6 medication errors per 1000 patient-days	Not mentioned
Chappell and Newman[24]	UK, 2001	Neonatal unit in a university hospital	6wk	Prospective comparison of the prescribed intravenous doses with the lowest available strength vial of that medication for the potential for 10- or 100-fold errors if prepared (potential errors)	31% (n = 104) of the total number of prescriptions were potential 10-fold overdoses 5% (n = 16) of the total number of prescriptions were potential 100-fold overdoses	Overdosing (potential)
Cordero et al.[25]	US, 2001–2	Nursing units and a NICU in a university hospital	Two 6-mo periods	Retrospective comparison of the number of prescription medication errors for gentamicin, pre- and post-CPOE	13% (n = 14) of all prescriptions for gentamicin contained prescription dosage errors pre- CPOE; 0% (n = 0) of all prescriptions for gentamicin contained prescription dosage errors post-CPOE	Underdosing
Carroll et al.[20]	US, 2000–1	NICU in a university hospital	4mo	Retrospective analysis of documentation discrepancies using the number of discrepancies per entry in the patient's notes	62% (n = 209) of all included junior doctors' patient notes contained discrepancies	Vascular lines documented in patient's notes, but not present in patient

a In studies that included wards other than NICUs, only data involving neonates were included.

b Calculations are based on the numbers of events and patients in the respective categories in the publication.

ADEs = adverse drug events; **CPOE** = computerised physician order entry; **IV** = intravenous; **PICU** = paediatric intensive care unit.

cations; and 30% (7 members) believed that the timeliness of pharmaceutical services had improved. However, they also found that CPOE may contribute to new types of medication errors, such as the selection of an incorrect product when multiple strengths of medication were available.[27]

Larsen et al.[19] evaluated the use of standard medication concentrations prepared by the pharmacy department, smart-pump technology and user-friendly labels on preparations (table I). There was a reduction of reported medication errors from 3.5 (pre-intervention period) to 1.4 per 1000 doses (post-intervention period) regarding continuous medication infusions in the NICU. In total, preparation errors involving both paediatric patients and patients in the NICU that occurred in the pharmacy department decreased from 0.66 to 0.16 per 1000 doses, and 10-fold errors in dosage decreased from 0.41 to 0.08 per 1000 doses.[19]

3.2 Interventions by Clinical Pharmacists

Only one study was identified that specifically investigated the role of the clinical pharmacist in reducing medication errors in neonates[16] (table II). The pharmacist reviewed medication orders daily on the ward. This intervention led to a significant reduction in the frequency of medication errors. An additional four studies on clinical pharmacy services in the paediatric setting were identified, which also included activities in NICUs, but results relating to NICU were not reported separately.

Two studies investigated the impact of pharmacists routinely reviewing the individual medication orders of paediatric patients in the pharmacy department prior to dispensing the medications (table II). In a 3-month study, Blum et al.[28] reported that pharmacists found that 2.7% of medication orders contained errors, of which 90% were confirmed by physicians. During a 6-month period, Folli et al.[29] reported that pharmacists found errors in 0.5% of medication orders.

Two other studies investigated the impact of pharmacists reviewing medication orders during rounds (table II). Both studies also included cost analyses. Condren et al.[30] reported on the activities of a paediatric pharmacy team consisting of paediatric specialty residents, pharmacotherapy residents, pharmacy practice residents and students caring for patients in general paediatrics, paediatric intensive care, neonatal intensive care and ambulatory clinics. The main clinical activities of the pharmacists included recommendations of changes in medication therapy (e.g. add/stop medications, change doses/dosage forms, interval adjustments, intravenous to oral switches), pharmacokinetic monitoring and providing general medication information, as well as taking medication histories and carrying out patient counselling. Interventions were most commonly made in patients with infectious (39.6%) and respiratory (23.3%) diseases. More interventions were performed in patients who had underlying chronic diseases than those who had acute diseases. Physicians accepted recommendations completely in 91% of cases and partially in 4% of cases. A total of 4605 interventions were made for 3978 patients. The estimated cost savings from medication error prevention or detection were $US459 000 for the study period of 1 year (2002 values). Krupicka et al.[31] performed a 6-month study in a paediatric intensive care unit of a children's hospital. A pharmacist participated in ward rounds with the paediatric intensive care unit team approximately twice a week and reviewed medication lists daily. There were, on average, 35 recommendations per 100 patient-days (or 172 recommendations for 77 patients). The most common interventions concerned dosage changes (28%), medication information (26%) and other information (22%). The total cost savings for the 6-month study period were $US1977. The authors extrapolated that cost savings per year would be $US9135 (1996–7 values) [if a full-time pharmacist was employed for that purpose].

4. Discussion

4.1 Frequency and Types of Medication Errors

Although exact numbers of medication errors in the NICU are not known, errors occur frequently. Most likely, differences amongst reported error rates

Table II. Studies on the pharmacist's role in prevention of medication errors in children

Study	Country and year(s) of study	Setting	Study period	Study method	Role of the pharmacist	Outcome	Most common intervention
Simpson et al.[16]	UK, 2002–3	NICU in a maternity hospital	1y	Prospective identification of medication errors by critical incident reporting. The interventions (a daily review of medication orders and parenteral fluid prescriptions for each infant by the pharmacist) were made after a 4-month, pharmacy-led education programme for each new member of pharmacy, nursing or medical staff	Pre-intervention: analysis of critical incident forms. Post-intervention: a daily cot side, pharmacist-led review of medication orders	105 medication errors 24.1 medication errors per 1000 neonatal activity days in the pre-intervention period and 5.1 per 1000 neonatal activity days in the post-intervention period 12.2 medication errors per 1000 neonatal activity days after change over of junior medical staff	Correction of dosage
Blum et al.[28]	US, 1986–7	Paediatric and adult wards in a university and a children's hospital	3mo	Prospective, daily collection of medication orders	Review of erroneous medication orders	2.7% (n = 1277) of the total amount of medication orders from the children's hospital contained errors 1.3% (n = 1012) of the total number of medication orders from the university hospital contained errors 90% of the orders questioned by the pharmacists were confirmed by the physicians as being in error	Correction of dosage
Folli et al.[29]	US 1985	Different types of wards in two children's hospitals	6mo	Prospective review of all medication orders	Review of erroneous medication orders	0.5% (n = 479) of the total number of medication orders contained errors	Correction of overdosage
Condren et al.[30]	US 2002	Paediatric wards at two campuses of one university, including a NICU	1y	Prospective recording and analyses of all clinical interventions	Making recommendations to the practitioner and review of interventions	4605 interventions were performed 91% of all recommendations were completely accepted by the physician, whereas 4% were accepted partially	Changing medication therapy (especially adding and stopping medications)
Krupicka et al.[31]	US, 1996–7	Paediatric intensive care unit in a academic children's hospital	24wk	Prospective documentation of all interventions undertaken by a pharmacist during a shift	Making recommendations on rounds or during private discussion with physicians	172 recommendations were made (35 recommendations per 100 patient days)	Correction of dosage

NICU = neonatal intensive care unit.

are due to differences in settings and research methods, including the definition of a medication error and the rigor of the study method to identify the frequency and different types of errors. Studies using critical incident reporting or spontaneous incident reporting are known to detect only a fraction of medication errors.[32] Not surprisingly, studies using these methods[16,17] reported lower error rates than Kaushal et al.,[15] which used more intensive methods of data collection. Based on the available data, it also remains unknown whether or not neonates experience medication errors more frequently than older children or adults. Studies directly comparing error rates are inconclusive. Comparing different wards in two children's hospitals, Folli et al.[29] found the lowest error rates in the NICU compared with other types of wards. Kaushal et al.[15] found similar medication error rates across all different types of wards in a children's hospital. However, in the NICU a significantly higher rate of potential and preventable adverse drug events (ADEs) was observed. In this study, potential ADEs were defined as medication errors with the potential to injure patients and ADEs were defined as medication errors that injured the patients.

As in studies performed in older children,[33] most studies performed in the NICU reported dose errors as being the most common type of medication error. Studies provided conflicting results as to whether dose errors occurred more frequently during the prescribing or the administration stage. However, this may also depend on the methods used for the detection of medication errors. Chart review is a method that is better for detecting prescribing errors than other types of errors.[15] Furthermore, the studies reviewed did not assess actual or potential harm of errors systematically. Therefore, it cannot be judged which errors are clinically most important. Such data are needed to target preventive strategies to the most vulnerable step in the process.

4.2 CPOE and Other Technologies

There are few studies that have evaluated strategies to prevent medication errors in the NICU. Extrapolating results from studies performed in adults and older children, CPOE and pharmacist participation in ward rounds may improve medication safety. Although experience with CPOE in adult[34,35] and paediatric populations[36,37] is increasing, little is known about its influence on clinical practices in the NICU.[38] However, several authors have suggested that CPOE may dramatically improve medication safety in neonatology.[18,25] In the paediatric setting, Fortescue et al.[39] estimated that CPOE with basic clinical decision support could prevent 66% of medication errors, whereas more advanced decision support could prevent 73%. Kaushal et al.[15] judged that 93% of the potential ADEs were potentially preventable by CPOE with clinical decision support and 94% by ward-based clinical pharmacists. Studies evaluating CPOE in practice have shown considerable reductions in medication-related incidents. Potts et al.[36] found rates of potential ADEs and medication prescribing errors of 2.2 and 30.1 per 100 orders, respectively, in a paediatric critical care unit before the implementation of CPOE. After implementation of CPOE, the rate of potential ADEs was reduced to 1.3 per 100 orders and the rate of medication prescribing errors was reduced to 0.2 per 100 orders. King et al.[37] compared two paediatric medical wards using CPOE with one medical and two surgical paediatric wards that were not using CPOE. Before implementation of CPOE, the medication error rate in the intervention versus the control wards was equal. After implementation, the error rate on the intervention wards was 40% lower than on the control wards. In contrast, in a study using univariate analysis, an increase in mortality rate was reported after introduction of CPOE in a children's hospital.[40] Delays in the administration of time-sensitive medication and an increased need for physicians to be away from the bedside because of computer-related activities were noticed. A limitation of this study might be that there was only a relatively short post-CPOE observation period, which means that these results may reflect the fine-tuning period that follows a major change. Furthermore, the fact that the pre- and post-CPOE observation periods did not occur at the same time of year might have introduced confounding from seasonal variability of illness.

The type of CPOE and the extent to which additional technology was used may influence medication safety.[38] The assignment of barcodes to medications and patients may prevent errors of misidentification. The use of smart intravenous devices may reduce the chance of error through simplified programming and computerised checks.[19,39] Intravenous or enteral route mistakes may be prevented by adopting administration systems with specialised functions that prevent feeding pumps and syringes from being attached to intravenous lines.[13,41] Again, there is a lack of studies evaluating the impact of these technologies on medication errors in neonates.

The scarcity of data on CPOE in the NICU can be explained by the fact that the development of CPOE and clinical decision support systems are more complicated for neonates than adults and older children. This is partly due to a lack of evidence-based data on pharmacotherapy, which we have already highlighted. In addition, computer applications need to allow easy updating of a patient's weight, as most dose determination in neonates is weight dependent.[38] Economic reasons may prevent development of such software, since opportunities for marketing are limited.

4.3 Interventions by Clinical Pharmacists

Only one study was identified that specifically investigated the role of the clinical pharmacist in reducing medication errors in neonates[16] (table II). Medication errors were identified by critical incident reporting which, as highlighted above, only detects a fraction of medication errors. Additional studies were identified from paediatric settings; however, results for neonates were not reported separately. Furthermore, the studies were descriptive in nature (e.g. lacking a control group). Two studies[30,31] from the paediatric and neonatal settings reported cost savings, but results differed considerably between these two studies. This was possibly because Krupicka et al.[31] based their analysis on the cost of the pharmacist's time spent on the ward (0.73 hours/day) and the money saved due to discontinued medications, whereas Condren et al.[30] based their cost analysis on costs saved by preventing possible adverse clinical events as a consequence of medication errors. Furthermore, Condren et al.[30] derived estimated costs for ADEs from data obtained in adult patients and it is unknown if these findings are applicable to a paediatric population.

The reviewed studies evaluated the impact of pharmacist's activities at an individual patient level. In most studies, the activities of pharmacists were not described in detail. The activities included the review of the appropriateness of medication orders (dosage, incompatibilities, interactions, administration route) by pharmacists, taking into account allergies, possible adverse drug reactions and laboratory values, as well as the possible effects of medications given to the mother during pregnancy, labour and delivery.[42,43] This also involved pharmacokinetic monitoring of medications.[4,7] Although the choice of medication for an indication is a clinical specialty of the neonatologist, verification of the appropriateness of the medication-indication matching may be of additional value to drug safety. Furthermore, activities of pharmacists may also include coordination of discharge planning regarding medications.[44]

There are other activities by pharmacists suggested in the literature that have not been part of evaluation studies that included activities on an organisational level and teaching responsibilities. At an organisational level it is suggested that pharmacists participate in multidisciplinary teams to develop a formulary, including administration guidelines. Pharmacists may particularly contribute to information on reconstitution and dilution of medications, the compatibility of intravenous medications and the administration and rates of infusion for medications, as well as to information on parenteral nutrition.[4,44] Pharmacists should also be involved in the development and implementation of information technology in medication management, such as CPOE with decision support systems. Other services that they may facilitate could include a unit dose medication distribution system.[45,46] The latter may also be able to provide all intravenous doses ready for administration as part of a central intravenous admixture service.[45,46] Pharmacists should be actively in-

volved in medication error reporting systems. This includes contributing to the creation of a 'no blame' culture for medication error reporting and improved communication between nursing, medical and pharmacy staff.[44] Pharmacists should be involved in teaching pharmacists, nurses and physicians.[16,27] For example, as recommended by Dean et al.,[47] pharmacists should be involved in teaching junior doctors the principles of medication administration and the importance of prescribing accurately and legibly. Another important area concerns teaching nurses the pharmaceutical aspects of medication preparation and administration.[48] However, the impact of such activities on medication safety has not been formally evaluated.

5. Conclusion

More research is needed to determine the frequency and types of medication errors in NICUs and to develop evidence-based interventions to improve medication safety in this setting. Part of these research efforts need to be focussed on establishing clear definitions of medication errors, agreement on methods to measure the rates of these errors and determining the potential clinical impacts of medication errors, in order to compare the results of studies across different settings and countries.

Acknowledgements

No sources of funding were used in the preparation of this article. The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

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