Review of drug utilization patterns in NICUs worldwide

Krzyżaniak, N.; Pawłowska, I.; Bajorek, B.

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ABSTRACT

WHAT IS KNOWN AND OBJECTIVES: When considering acute care settings, such as the neonatal intensive care unit (NICU), the inappropriate use of medicines poses a great risk to vulnerable babies at the start of their lives. However, there is limited published literature that explores the current medication management practices in NICUs and where the main misuse issues lie. Therefore, the purpose of this review is to give an overview of medicine use in NICUs worldwide and identify therapeutic areas requiring more targeted pharmaceutical care. Specific objectives include: identifying the most commonly used medicines, comparing these to the A-PINCH (Anti-infectives, Potassium and other electrolytes, Insulin, Narcotics and sedatives, Chemotherapy agents, Heparin and other anticoagulants), high risk medicines list, and determining whether there are any differences in medicine use between countries.

METHOD: Quasi-systematic literature review

SEARCH STRATEGY: Google Scholar, Medline/PubMed, Scopus and Embase were searched utilising selected MeSH terms.

RESULTS: A total of 19 articles from 12 countries were reviewed. Medication use between countries was very similar with no discernible differences in types of medicines prescribed. The most commonly used medicines included gentamicin, ampicillin, caffeine, furosemide and vitamin K. The median number of medicines prescribed per patient ranged from 3 – 11, and an inverse relationship was identified between gestational age and the number of medications that were prescribed. Nine of the 20 most commonly used medicines were listed as A-PINCH medicines, and included antibiotics, fentanyl, morphine and heparin. Inappropriate prescribing, as well as the high use of off-label/unlicensed medicines, were highlighted as areas of practice that require consideration to improve medication safety and minimise the potential risk for medication errors.

WHAT IS NEW AND CONCLUSION: Overall, the types of medicines used in NICUs worldwide are similar, with consistent reports on the common use of antibiotics, caffeine and vitamins. However, it cannot be definitively stated that the findings of the review accurately depict current practice in NICUs, due to the limited amount of published literature available. There are several areas of concern that warrant further investigation to improve rational use of medicines in the neonatal populations, including high-use of antibiotics and off-label and unlicensed medicines.

KEY WORDS: Drug utilisation, Neonate, NICU, Prescription patterns

1. INTRODUCTION, WHAT IS KNOWN AND OBJECTIVES

The World Health Organisation (WHO) estimates that every year, 15 million babies are born prematurely, i.e. before 37 completed weeks of gestation, and 1 million newborns die because of complications of preterm birth. Many more preterm babies die in low-income countries than in their high-income counterparts.(1) To rescue their lives, various procedures in neonatal intensive care units (NICU) are applied in accordance with available guidelines and standards.(2-4) Without doubt, medicines play a pivotal role in the management of preterm babies. The medicines used in NICUs, including their formulations and doses, depends on their availability and accessibility in a particular country, as well as the international/national guidelines and local rules of each setting. Thus, the pattern of prescribing and the drug utilization at different NICUs is not uniform and may vary widely.

WHO has estimated that half of all medicines used worldwide are prescribed or dispensed inappropriately.(5) With consequences including increased patient morbidity, mortality, health care expenditures and wastage of resources, the irrational use of medicines is recognised as a major global problem.(5, 6) When considering acute care settings, such as the NICU, the inappropriate use of medicines poses a great risk to vulnerable babies at the start of their lives.(7, 8) The application of pharmacotherapy is complex in hospitalised newborns, with factors of vulnerability including developmental immaturity as well as a lack of licensed formulations and limited evidence based dosing information.(8, 9) NICU patients also have a high drug burden with a reported average of 8.6 medicines prescribed per patient.(10) As such, there is a need to implement a high-quality, safe and rational medicine use process in these patients to ensure optimal outcomes. However, there is limited published literature that explores the current medication management practices in NICUs and where the main misuse issues lie. There are no systematic reviews that comprehensively evaluate drug utilisation in NICUs. What reviews do exist, only give an insight into a subsection of total medicine use, for example, one class of medicines (antibiotics) or off-label/unlicensed use of medicines. (11-14) Ill newborns admitted to the NICU are therapeutic orphans, and where pharmacotherapy does exist, these patients are at high risk of dosing errors and adverse drug effects. Therefore, there is a need for such reviews to be extended to include the full spectrum of medicine use in the NICU and identify targets for the improvement of neonatal patient safety.

The aim of this review is to provide an overview of medicine use in NICUs worldwide. Specific objectives include: identifying the most commonly used medicines, comparing these medications with the A-PINCH high risk medicines list (Anti-infectives, Potassium and other electrolytes, Insulin, Narcotics and sedatives, Chemotherapy agents, Heparin and other anticoagulants), determining

whether there are any differences in medicine use between countries and highlighting any areas that require further attention to improve the rational use of medicines. The review does not focus on drug errors and adverse drug events, rather it seeks to provide better knowledge of the types of medicines prescribed in the NICU and the rates of off-label/unlicensed medicine use.

2. METHOD

A quasi-systematic review (a review that possesses some elements of a systematic review, including pre-defined selection criteria, however does not present a critical evaluation of the quality of studies and thus does not fulfill the criteria of comprehensiveness required from the systematic review method) extracted relevant publications pertaining to drug utilisation and prescription patterns in the NICU.(15-18) The literature was retrieved by searching the following electronic databases: Medline, Embase, Scopus and Google Scholar. The PRISMA guidelines provided a framework for the structure of this review.(19) In general, all active substances and their formulations which may be used in particular NICUs are included in drug formularies that are prepared by Hospital Therapeutic Committees.(20) Moreover, for a special need, other medicines may be used that are not enumerated in these formularies. However, these formularies are not commonly available, therefore only published studies could be a source of information on drug utilization within NICUs.

3. SEARCH STRATEGY

A comprehensive search was performed to find literature relevant to drug utilisation in the NICU using the MeSH terms *neonate, NICU, drug utilisation, prescription patterns*. Inclusion criteria for the searches restricted the content to the following: (i) neonatal patients, (ii) drug utilisation studies, (iii) providing information on drug use patterns, prescriptions patterns or drug consumption and (iv) written in the English language. We applied a date limit so that only recent articles published from the year 2000 or later, i.e. 2000 - 2016 were taken into account. Articles were excluded if they only focussed on evaluating the use of a single class of medications i.e. antibiotics. All full text articles were retrieved. Manual bibliographic searches were also performed to identify additional articles that were not found in the electronic searches. (Figure 1)

3.1 SCREENING PROCESS FOR INCLUSION

Articles were initially screened for inclusion in the review based on title, then abstract and full text article as necessary.

3.2 A-PINCH CRITERIA

The review sought to compare the most commonly used medications in the NICU using the A-PINCH high risk medicines list. Compiled by the Australian Clinical Excellence Commission, the list identifies types of medications that are universally considered to be high-risk and are represented by the acronym A-PINCH.(21) (Table 1) These medications are not necessarily those that have higher error rates or adverse events than other medications, however if misused can have the most severe consequences.(22, 23)

4. RESULTS

General Analysis

Overall, there is limited published literature comprehensively exploring current medication use in NICUs. A total of 19 articles met the inclusion criteria, the majority dated within the last 10 years, 2006 - 2016 (n = 17, 89%).(24-42) The patients enrolled in studies were mostly preterm babies (< 37 weeks) making up 40 – 85% of NICU patient groups, with term babies making up 24.6 – 51% of NICU admissions.(24, 25, 27-30, 33, 35-40) Male newborns comprised 43 – 62.5% of patient samples.(25, 27, 28, 30, 31, 33, 36, 40, 42) The mean gestational ages of patient groups ranged from 31 – 35 weeks, and the median birth weights ranged from 1560 – 2615g.(26, 27, 31-33, 36-39, 42) The mean duration of stay for the studied patients ranged from 15 – 21.1 days.(27, 28, 33, 36, 42)

The most common documented reason for patient admission into the NICU were respiratory distress followed by sepsis/infection, prematurity, neonatal jaundice, congenital malformations, birth asphyxia and seizures.(24, 25, 27, 28, 30, 32, 35, 38, 40)

Geographical distribution

Studies were conducted in 12 countries: USA (n = 4), Italy (n = 3), India (n = 2), Brazil (n = 2), UK, Australia, Estonia, Germany, Israel, Turkey, Ireland and France.

Methodology and Study Design

The majority of studies (n = 13, 68%) used a prospective study design, with the remaining six (32%) utilising a retrospective data extraction. The sample sizes in the studies ranged from 34 to 450,386 patients. This large variation in patient enrolment was attributed mainly to the duration of studies, which ranged from two weeks to nine years. Furthermore, some studies canvassed data from large databases, whilst others focussed their observations on one NICU. For example, two US based studies by Clark et.al. and Hsieh et.al. used retrospective reviews as the method for gathering data

for nine year and five year periods of time, respectively.(26, 31) This resulted in large sample sizes and large numbers of prescribed medicines. (Table 2)

The majority of studies (n = 12, 63%) investigated all medicines prescribed and used in the NICU.(24-29, 31, 32, 34, 36, 40, 41) However, the inclusion criteria of seven studies excluded the evaluation of certain products including: standard intravenous (IV) fluids (including electrolytes), oxygen, parenteral nutrition, blood and blood products, vaccinations, vitamin K, prophylactic ophthalmic ointment, phototherapy, expressed breast milk, milk formula, nutritional supplements and drugs used in clinical trials.(30, 33, 35, 37-39, 42)

The criteria for enrolling patients into studies were relatively uniform, and based simply on infant admission into the NICU.

Drug Use Profile

Types of medicines used

Overall, antibiotics (particularly aminoglycosides) including gentamicin as well as ampicillin were identified as the most frequently prescribed medicines in NICUs. This was followed by caffeine, furosemide, multivitamins and vitamin K. Figure 2 presents the 20 most commonly used medications in NICUs and highlights which of these medications are classified in the A-PINCH list. Nine of the 20 most commonly used medicines were listed as A-PINCH medicines, and included antibiotics, fentanyl, morphine and heparin. (Figure 2) Medications used between countries were very similar with no discernible differences in types of medicines prescribed.

The total number of different types of medications prescribed for the treatment of patients admitted to the NICU ranged from 23 – 409.(26-32, 34-39, 41) This large variation in different pharmacotherapeutic agents can again be attributed to the duration of studies, as some studies collected data over a period of several years which would potentially see the introduction of new active substances, drug formulations and regimens as well as the ceasing of older, less effective medicines.

Number of medicines used

The median number of medicines used per patient ranged from 3 – 11, with one German study by Neubert et.al. observing that two patients received as many as 40 medicines during their admission to the NICU.(27, 29, 32, 34-39) The prospective cohort study evaluating 183 patients by Neubert et.al. also reported that the high average medicine use per patient seen in their study was attributed to the fact that their NICU was a very specialised unit which experienced a higher intake of very

premature babies in comparison to other NICUs, leading to increased number of medicines per patient.(36) Overall, the most common route of administration was the IV route, (47 – 92.1% of products used), followed by the oral route (22 – 23.1%), topical (7.5 – 9%), intramuscular (IM) and endotracheal tube.(25, 28, 32, 33)

Patterns of use

In terms of patterns of use, three factors appear to impact on medication use. The first factor as identified in seven studies, is the inverse relationship between gestational age and the number of medications that were prescribed.(25, 27, 28, 33, 36, 38, 42) In an Indian based prospective study Chatterjee et.al. found that the average number of medicines prescribed in the NICU was 8.1 for preterm babies compared to 4.3 for term babies.(25) This is also supported by the Brazilian study, which reported a significant difference ($p < 0.001$) between average medication use in preterm and term neonates.(28) During their 6 month prospective observational study, de Souza Goncalves et.al. also reported a second relationship between average use of medicines and patient weight. The average number of medicines prescribed to very low birth weight (VLBW) babies (< 1000g) was approximately 3 times greater than the number prescribed to babies with birth weights of 2500g or more.(28) Third, de Souza et.al. found that the mortality rate was inversely proportional to the gestational age of infants in the NICU ($p > 0.05$).(27)

Considerations relating to medication use in the NICU

Off-label/Unlicensed Use

It was widely reported that a significant proportion of medicines have not been approved for use in neonates, and as such there is little to no information available relating to the efficacy and safety of these medicines in infants.(24, 27-39) The lack of information is reported as a major issue by one Brazilian study, identifying that only 20.5% of all medicines used had product information describing use of the medicine in neonates, and only 9.5% of medicines had available information for use in preterm babies.(28) Similarly, the German study by Neubert et.al. highlighted that 62% of all medicines used in their NICU had no information provided about their use in newborns.(36) Chatterjee et.al. reported that information in an Indian NICU was obtained from clinicians' standard neonatology textbooks as well as through online resources.(25)

Despite the lack of information, 22.7 – 63% and 5.7 – 28.8% of all medicines used in NICUs were classified as off-label and unlicensed medicines, respectively.(24, 25, 27, 29, 30, 32, 34, 36, 38, 39) Overall, it was reported that 71 – 100% of infants would receive at least one off-label or unlicensed medicine whilst admitted to a NICU.(24, 27, 32, 34-38) Premature infants were more likely to be

administered an off-label or unlicensed therapy in comparison to term babies.(27, 30, 34-36, 38) An Estonian study found that 100% of preterm babies admitted to their NICU received an unlicensed or off-label medicine.(35) This finding is supported by the Irish and German studies who both stated that 100% of preterm infants (<28 weeks gestation) would be administered at least one unlicensed or off-label medicine.(32, 36) Non-approved dosage, frequency of dosing, age, indication, treatment duration and route of administration as well as extemporaneous preparation of novel formulations by hospital pharmacy were identified as the main reasons for the use of medicines in alternative ways to those approved in the product information, rendering medicines off-label or unlicensed.(24, 27-39) Each of these reasons may have implications on the safety of neonates, with the potential for toxicity, adverse effects and ineffective treatment.(29)

The most commonly administered off-label medicines were reported as benzylpenicillin, furosemide, ranitidine, fentanyl, theophylline and gentamicin.(24, 27-30, 32-38) The most commonly used unlicensed medicines included folic acid, hydrocortisone, caffeine and parenteral nutrition, and were classified as unlicensed because they were specifically compounded by the hospital pharmacy.(24, 27-30, 32-38) (Table 3) An Italian study stated that caffeine is a well-known, effective and safe therapy frequently used for the treatment apnoea in prematurity, however it is not licensed for use in babies.(30) It must be noted that the aforementioned medicines are not classed as off-label/unlicensed in all instances of their use. This classification only applies to their use in certain indications, formulations, countries or as deemed by the definition of off-label/unlicensed in each respective study.

Irrational prescribing

In a study conducted in an Italian NICU, Dell'Aera et.al. drew attention to the prescribing of a number of medicines that were deemed inappropriate for neonatal patients, including: sulfadiazine (contraindicated in premature neonates due to the risk of inducing neonatal jaundice), meropenem (insufficient data on efficacy and tolerance in babies and not recommended in patients < 3 months of age), itraconazole (insufficient data to allow use in paediatric patients), flunisolide (contraindicated in children < 4 years of age), phenobarbital and prednisolone-neomycin (incorrectly administered – IV instead of IM, and intra-nasally instead of intra-ocularly).(29) In an Israeli NICU, Barr et.al. identified that out of a total of 525 prescriptions, 199 were given at a dosage that was unusually high and this included ampicillin, theophylline, amoxicillin, gentamicin, vancomycin and imipenem.(24) A further 25 courses were given in too low dosages and included gentamicin and cisapride.(24) Lass et.al. reported that five products contraindicated for use neonates were

prescribed in an Estonian NICU and included: diclofenac, drotaverine, metoclopramide, heparin sodium ointment and ursodeoxycholic acid tablets.(35)

5. DISCUSSION AND WHAT IS NEW

This review provides an insight into medicines use in NICUs worldwide. To our knowledge, this is the only review to explore DUE studies on a global scale. Overall, it appears that the types of medicines used in NICUs worldwide are similar, with high usage of aminoglycosides, penicillins, other antibiotics, caffeine and multivitamins. This is unsurprising as the majority of studies included in the review were from developed countries, and commonly treated the same patient pathologies, including sepsis, complications associated with prematurity and neonatal jaundice. However, there is variability in the average number of medicines used per patient, ranging from 3 – 11. This has been attributed to the specific characteristics of individual NICUs which may experience higher intakes of premature or very low birth weight patients that require longer hospitalisations and more medicines, affecting the overall mean. However, it cannot be definitively stated that the findings of the review accurately depict current practice in NICUs, due to the general lack of literature available. The 19 articles included in the review do not give a thorough account of global usage of medicines in NICUs.

There is a great need, from a pharmacy-based perspective, to promote the rational use of medicines to achieve positive and safe patient outcomes. The data from the drug use evaluation studies has highlighted several areas that should become the focus of neonatologists, pharmacologists and clinical pharmacists to improve efficacy and safety of medicines usage in NICUs:

- **High use of antibiotics:** The review drew attention to the high usage of antibiotics in NICUs. As severe infections are a main cause of neonatal mortality, accounting for more than one million neonatal deaths annually worldwide, the appropriate choice of antibiotic agents is essential to prevent serious consequences.(12) Antimicrobial stewardship programs should be established in NICUs to improve antimicrobial use, promote positive patient results and decrease antimicrobial resistance, adverse effects and excess costs.(43) The Priority Medicines for Europe and the World report by WHO highlighted the need to develop diagnostic tools tailored specifically for neonatal conditions to avoid the inappropriate use of antibiotics in the NICU.(44) Patel et.al. suggested several 'Get Smart' principles to optimize the safe use of antibiotics in the NICU. These included: accurately identifying patients who need antibiotic therapy, using local and regional antibiograms, avoiding prescribing therapies with overlapping activity, giving the right dose and interval of antibiotics,

reviewing culture results, monitoring for toxicity and stopping therapy promptly if indicated by culture results.(45)

- **Irrational Prescribing:** Incorrect choices of medicines, doses, routes of administration and dosing frequencies can be detrimental to neonatal outcomes.(46) Caffeine, for example, is commonly used in the NICU for the treatment of apnoea of prematurity and is well-known for being the safest option available.(47) However, there is still a high incidence of theophylline use, which is associated with higher rates of toxicity.(30, 47) Targeted guidelines are needed to ensure that the most appropriate medicines are being prescribed.
- **Polypharmacy:** Premature infants/very low birth weight babies receive larger numbers of prescribed medicines per patient in comparison to term babies.(25, 28) Consequently, there is an increased risk of duplicate therapies as well as drug interactions and adverse drug reactions.(48) There is a need for regular pharmacist interventions involving medication chart reviews and participation in multi-disciplinary ward rounds which may have an impact on decreasing the incidence duplicated therapies.
- **Use of narrow therapeutic index medicines:** All medicines need to be monitored to ensure that the doses administered are within their therapeutic range.(49) However, for medicines with a narrow therapeutic index, toxic concentrations can be reached quickly leading to adverse effects.(50) The review has highlighted that aminoglycosides and theophylline are commonly used in NICUs. Measures are needed to ensure proper therapeutic drug monitoring and accurate dosing to prevent the misuse of these medicines.
- **High use of A-PINCH medicines:** These medicines are those that have an increased risk of causing harm if they are misused or used in error. Neonates possess characteristics of vulnerability in relation to their pharmacologic capabilities, and given that 9 of the 20 most commonly used medicines found in the results are classified as high-risk medicines, there is a need to be highly vigilant to ensure the safety of neonates. In particular, appropriate guidelines or safety measures should be implemented when these medicines are prescribed to ensure appropriate and safe dosing for patients and the prevention of medication misuse.
- **High use of off-label/unlicensed medicines**: The review shows that the use of these types of medicines is common in NICUs worldwide because of a lack of information and availability of formulations. As such, there is a need to license medicines and for more clinical trials to be performed to provide reliable information to guide the use of medicines in neonates.(35, 39) However, in the interim, there is a need for a registry or practical guidelines on how to use these therapies based on the best available evidence and experience of health professionals.

- **Origin of dosing recommendations:** When considering the large range in the types of medicines prescribed (23 – 409) in the review, there is concern about the heterogeneity of drug recommendations within, and between, NICUs. A study by Leroux et.al. investigated antibiotic regimens in 45 NICUs in France and found approximately 9 different dosing protocols per drug.(51) This leads to considerable variability in the treatment of neonates, with differences in daily doses and dosing intervals potentially having a significant impact on patient outcomes. As such there is a need for robust evidence base to define pharmacokinetics, pharmacodynamics, safety and efficacy of pharmacotherapy in neonates in order to develop targeted guidelines.(52)
- **Modalities of drug prescription:** Differences in prescribing methods i.e. hand written versus computer physician order entry (CPOE) and clinical decision support (CDS) systems, may have an impact on rational drug use as well as medication error rates by addressing the accuracy of drug selection and dosing.(53) Kaushal et.al. found that most medication errors in paediatric and neonatal patients occurred at the point of prescribing, and identified that CPOE could have prevented 93% of those events occurring.(54) These decision support tools should be thoroughly considered in NICUs to promote uniform prescribing, decrease medication errors and improve the efficiency of resources.(55)

Whilst the use of medicines in neonates can have positive therapeutic effects on patients, when considering the aforementioned high-risk areas of medication use in the NICU, medication errors have a high risk of occurring in this patient population.(8, 56-58) The most commonly occurring medication errors comprise 10 to 100 fold dosing errors, patient misidentification, drug interactions, incorrect routes of administration and erroneous product dilutions.(56-58) Therefore, the inappropriate use of medicines can have a significant impact upon reducing the potential effectiveness of pharmacotherapy, causing negative effects for patients and producing costly economic outcomes. As such, there is great potential, particularly from the perspective of a clinical pharmacist, to improve medication management in the NICU, and the quality use of medicines should be made a priority to ensure the safety of this high risk population.

LIMITATIONS

Comparisons between countries were difficult due to differences in study methodologies. These included differences in the types and classes of medicines that were included for evaluation as well as differences in the definition of off-label and unlicensed medicines. For example, some studies classified medicines as off-label as those that were used in a manner different to that specified in the summary of product characteristics (SPC's), whereas other studies used a broader description and

defined off-label as medicines used in a manner different to that described in books, formularies, package inserts as well as manufacturer information.

6. CONCLUSION

Overall, it is apparent that the types of medicines used in NICUs worldwide are consistent, with the most commonly prescribed medicines including antibiotics, diuretics, caffeine and multivitamins. A-PINCH medicines made up nine of the 20 most commonly used medicines in NICUs and included fentanyl, morphine and heparin. The data available was collected from 12 countries and gave a good representation of drug use in NICUs, however 19 studies is not a substantial amount of data. Therefore, it cannot be definitively stated that the findings of the review accurately depict current practice in NICUs, due to the limited amount of published literature available. There are several areas of concern that warrant further investigation to improve rational use of medicines in the neonatal populations, including high-use of antibiotics and off-label and unlicensed medicines.

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TABLE 1 – A-PINCH MEDICINES LIST (21)

HIGH-RISK MEDICINE GROUPS	EXAMPLES OF MEDICINES
A: Anti-infective	Amphotericin Aminoglycosides
P: Potassium and other electrolytes	Injections of potassium, magnesium, calcium, hypertonic sodium chloride
I: Insulin	All insulins
N: Narcotics (opioids) and other sedatives	Hydromorphone, oxycodone, morphine Fentanyl, alfentanil, remifentanil and analgesic patches Benzodiazepines, for example, diazepam, midazolam Thiopentone, propofol and other short term anaesthetics
C: Chemotherapeutic agents	Vincristine Methotrexate Etoposide Azathioprine
H: Heparin and anticoagulants	Warfarin Enoxaparin Rivaroxaban, dabigatran, apixaban

Adapted from the New South Wales Clinical Excellence Commission, Australia website: High Risk Medicines. Clinical Excellence Commission. 2016. http://www.cec.health.nsw.gov.au/programs/high-risk-medicines/high-risk-medicines#eosm. Accessed 04/03/2016.

TABLE 2 – OVERVIEW OF THE STUDIES INCLUDED IN THE REVIEW

	Authors	Year	Country	Study Period	Number of Patients	Study Design
1	Barr J, et.al. (24)	2002	Israel	4 months	105	Prospective study
2	Chatterjee S, et.al. (25)	2007	India	6 months	176	Prospective study
3	Clark RH, et.al. (26)	2006	USA	9 years	253651	Retrospective review
4	De Souza AS, et.al.	2016	Brazil	6 months	192	Retrospective cohort study
5	de Souza Goncalves AC, et.al. (28)	2015	Brazil	6 months	187	Prospective observational study
6	Dell'Aera M, et.al. (29)	2007	Italy	2 months	34	Cross-sectional, prospective study
7	Dessi A, et.al. (30)	2010	Italy	1 month	38	Prospective study
8	Hsieh EM, et.al. (31)	2014	USA	5 years	450,386	Retrospective review
9	Kieran EA, et.al. (32)	2014	Ireland	2 months	110	Prospective observational study
10	Kumar P, et.al. (33)	2007	USA	3 years	2304	Retrospective review
11	Laforgia N, et.al. (34)	2014	Italy	1 month	126	Prospective observational study
12	Lass J, et.al. (35)	2011	Estonia	1 year	490	Prospective cohort study
13	Neubert A, et.al. (36)	2009	Germany	11 months	183	Prospective cohort study
14	Nguyen KA, et.al. (37)	2010	France	4 months	65	Prospective cross-sectional study
15	O'Donnell CP, et.al. (38)	2002	Australia	10 weeks	97	Prospective observational study
16	Oguz SS, et.al. (39)	2012	Turkey	24 hour period	464	Prospective observational study
17	Sharanappa M, et.al. (40)	2014	India	6 months	100	Retrospective review of case records
18	Turner MA, et.al. (41)	2009	UK	2 weeks	49 units	Prospective survey
19	Warrier I, et.al. (42)	2006	USA	7 years	6839	Retrospective data analysis

TABLE 3 – OVERVIEW OF MEDICATION USE IN EACH COUNTRY[1]

Country	Number of Drugs Used Per Patient	Most Commonly Used	How many patients will receive off-label med	Most common off-label/unlicensed meds
Australia	Median: 7	Gentamicin, Morphine, Vancomycin	80% of NICU patients and 93% of babies weighing <1000g received either an off-label or unlicensed medicine or both	Morphine (o), Theophylline (o), Aminophylline (o) sodium chloride (u), Dobutamine (o), paracetamol (o)
Brazil	Mean: 6.4 Median: 11	Fentanyl, Multivitamins, Gentamicin	99.5% of neonates will be exposed to an off-label medicine. Infants with gestational ages < 28 weeks have a higher exposure to unlicensed or off-label prescriptions	Heparin (o), Fentanyl (o), Multi-vitamins (o), injectable Alprostadil (u), Folic acid (u), Hydrocortisone (u)
Estonia	Median: 4	Gentamicin, Heparin, Simeticone	All preterm babies and 97% of term babies will receive at least one off-label or unlicensed medicine.	Furosemide IV (u), Ampicillin (o), Simeticone (O), Salbutamol (o)
France	Median: 4	Vitamin ADEC, Vitamin K, Calcium folinate	71% of babies will receive at least one off-label or unlicensed medicine	Calcium folinate (folic acid) u, Ferrous fumarate (o), Sodium chloride 10%, Benzylpenicillin (o), Amikacin (o),
Germany	Mean: 11.1	Vitamin K, Piperacillin, Tobramycin	70% of patients will receive at least one off-label or unlicensed medicine. 100% of preterm infants received at least one off-label or unlicensed medicine	100% of anaesthetics and analgesics had no info for use in neonates/preterm

[1] O = Off-label Medicine
U = Unlicensed Medicine

India	Mean: 4.8	Ceftriaxone, Amikacin, phenobarbital, Cefotaxime		
Ireland	Median: 4	Chlorhexidine, IM vitamin K, Gentamicin	91% and 94% of infants <32 weeks received an unlicensed and off-label medicine respectively, 100% of infants <28 weeks will receive an unlicensed and off-label medicine	Caffeine (U), benzyl penicillin (o), gentamicin (o)
Israel	N/A Between 1 - 13	Gentamicin, Ampicillin, Theophylline	93% of babies received at least one off-label or unlicensed medicine	Theophylline (u), cisapride (o)
Italy	Median: 3 – 5.5 Mean: 1.7	Amikacin, Ampicillin-Sulbactam, Parenteral nutrition infusions, Multivitamins, Aminophylline, caffeine, Gentamicin,	Preterm neonates received more unlicensed medicines compared to term newborns (14.5% vs 4.5%)	Parenteral nutrition infusions, amikacin, ranitidine, tobramycin, ofloxacin, caffeine, calcium levofolinate, sodium ferric gluconate complex Caffeine (u), furosemide (o), parenteral nutrition (u), phenobarbital (o), theophylline (o), ranitidine (o) caffeine (u), magnesium sulphate (u), ferrous sulphate (u), gentamicin (o), amoxicillin (o), miconazole (o), salbutamol (o),
Turkey	Median: 3	Ampicillin, Multi-vitamins, Amikacin		
UK	Median: 3.5	Gentamicin, Benzylpenicillin, Folic acid, vitamin K	90% of NICU patients received at least one off-label or unlicensed medicine	Benzylpenicillin (o), folic acid (o), caffeine (u), TPN (u - made in pharmacy), dalivit (o), vitamin k (o), Flucloxacillin (o) Caffeine (U), benzyl penicillin (o), gentamicin (o)
USA	Mean: 3.7 - 4	Ampicillin, Cefotaxime, Survanta, Gentamicin, caffeine citrate, supplemental sodium chloride, potassium chloride, Ferrous sulphate, heparin,		o - fentanyl, erythropoietin, dopamine, midazolam, hydrocortisone, dexamethasone, lorazepam, papaverine, ranitidine, milrinone Only 35% of meds are approved by FDA for use in NICU

FIGURE 1 – SEARCH STRATEGY

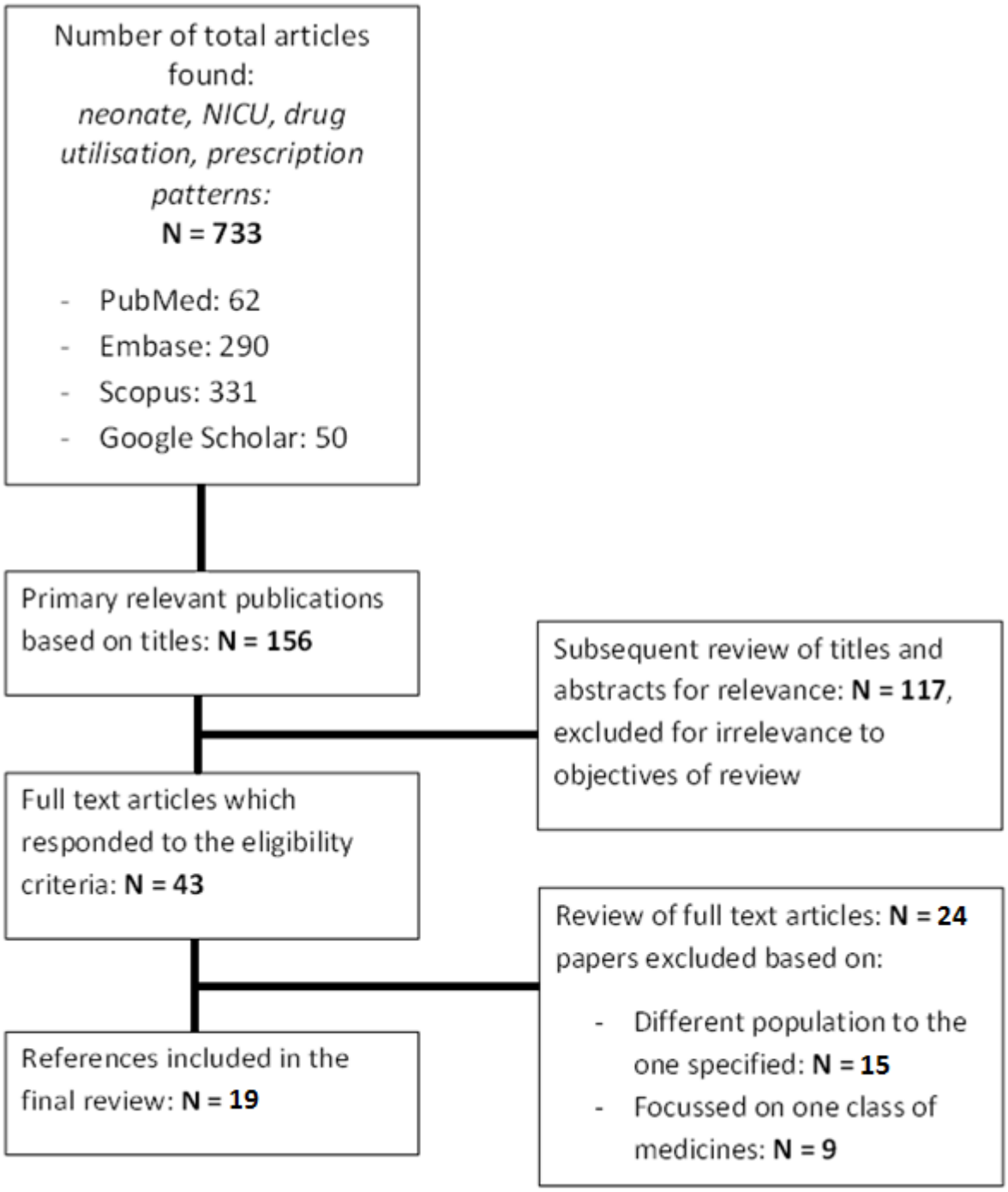

FIGURE 2 – MOST COMMONLY CITED MEDICINES USED IN NICUS WORLDWIDE