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NeoCheck: a prescription-screening tool to optimise pharmacotherapy for hospitalised neonates

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Summary

AIMS OF THE STUDY: To develop a screening tool to optimise neonatal drug prescription, which is often based on low-quality evidence.

METHODS: Neonatal pharmacotherapy recommendations were identified by literature review and synthesised into NeoCheck tool statements. In a two-round modified Delphi process, experts from Swiss neonatal intensive care units (NICUs) rated their agreement with individual statements using a five-point Likert scale (5 = totally agree). Statements with >65% scores ≥4 in round 1 and >75% scores ≥4 in round 2 were selected.

RESULTS: We identified 1375 clinical guidelines via literature review. After synthesis, 158 statements were submitted to 23 experts (1 clinical pharmacist, 22 neonatologists; 65% with >10 years neonatology practice) from 10 Swiss NICUs. Nineteen items did not reach the agreement threshold and were eliminated in the second Delphi round. The final NeoCheck tool comprises 141 statements in 11 medical domains concerning 49 neonatal diseases. Most (79%) statements concern all neonates, 13% concern preterm (<37 weeks gestational age) infants and 3% concern very preterm (<32 weeks gestational age) infants

CONCLUSIONS: NeoCheck is the first prescription-screening tool developed to optimise neonatal pharmacotherapy. In a future prospective study, its effect on NICU prescription optimisation and the quality of care will be assessed.

Introduction

Drug prescription in neonatology is challenging. For hospitalised neonates, it is based largely on low-quality pharmacotherapeutic evidence from small clinical studies, and off-label drug use occurs in >85% of cases [1–5]. Widely accepted guidelines are rare, leading to great variability in practice [6].

Medication errors occur more frequently for hospitalised neonates, particularly those born preterm, than for older children and adults, with reported error rates of 15–90% [7–9]. A significant portion of these errors occurs during prescription [7]. Neonates are more susceptible than older patients to adverse drug reactions, and serious adverse drug reactions occur in approximatively 10% of medication error cases [8]. In a multicentre prospective cohort study, adverse drug events were more prevalent in neonatal than in paediatric wards [10]. The most vulnerable neonatal patients – those with the lowest weights and youngest gestational ages – receive the largest number of drugs and are thus most subject to medication error [7, 9].

Prescription-screening tools (PSTs) are checklists that effectively optimise and secure pharmacotherapy, allowing healthcare professionals to review patients' ongoing treatments and identify unsuitable drugs, suboptimal dosages and missing treatments that would provide additional benefits [11, 12]. They aim to lead prescribers to the best available treatments in specific situations based on up-to-date knowledge, thereby contributing to care quality improvement. Most PSTs were developed in geriatric settings, but some have been created for other populations (e.g., the potentially inappropriate medication (PIM)-Check tool for adult internal medicine and the POPI (paediatrics: omission of prescriptions and inappropriate prescriptions) tool for general paediatrics) [13, 14]. In these settings, PSTs are

ABBREVIATIONS

CI	confidence interval
GOR	grade of recommendation
NICU	neonatal intensive care unit
PIM	potentially inappropriate medication
POPI	Omission of Prescription and Inappropriate Prescription
PST	prescription-screening tool
STOPP-START	Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert doctors to the Right Treatment

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effective for the detection of PIMs, which are risk factors for adverse drug events. Use of the "screening tool of older persons' potentially inappropriate prescriptions/screening tool to alert doctors to the right treatment" (STOPP-START) criteria has been associated with reduced adverse drug events and hospitalisation duration [11, 12, 15, 16]. PSTs are also used to train young physicians and pharmacists and to standardise practices. To our knowledge, no PST has been developed for hospitalised neonates; our aim was to develop a such a tool.

Material and methods

PST development committee

According to Swiss law, this study did not require ethical approval, as it did not directly involve patients, patients' data, human tissue or animals. For PST development, a steering committee comprising two clinical pharmacists (TR, CFC) and two senior neonatologists (RDL, RP) from the Neonatology Unit of the Geneva University Hospitals was formed. This committee defined the themes and subthemes the tool needed to address based on the index of a neonatology textbook [17]. These themes covered basic management issues and pathologies of hospitalised neonates.

Literature review

A semi-structured literature review was conducted to identify recent clinical recommendations in the literature. The steering committee compiled a list of sources that were reviewed (table 1). Guidelines from scientific societies, hospitals, governments, textbooks and manufacturers were included. When data from these sources was insufficient to form recommendations, key-word searches of the PubMed, Embase and/or Google Scholar databases were performed. Studies and clinical guidelines addressing pharmacotherapy for hospitalised neonates (corrected age ≤28 days after term), with no restriction on gestational age or weight, were included. The date of publication was not restricted, but the most recent publications were prioritised.

The themes on which recommendations were sought are listed in table 2 and appendix 1.

Table 1: Sources consulted in the literature review.

Systematic search		
Neonatology documents and protocols		
Geneva University Hospitals (HUG) (local guidelines)	Local neonatal guidelines HUG	Internal website
Foreign hospitals (structured and open access hospital guidelines commonly used by the authors)	Royal Children Hospital Melbourne, AU	http://www.rch.org.au
	Victoria State Government, AU	http://www.health.vic.gov.au
	Auckland District Health Board – drug monograph, NZ	http://www.adhb.govt.nz
	Auckland District Health Board – clinical guideline, NZ	http://www.adhb.govt.nz
	Canterbury District Health Board - drug monograph, NZ	https://www.cdhb.health.nz
	Christchurch Women's Hospital – Neonatology institutionnal textbook, NZ	Mckie J, Lynn A, Meeks M. Neonatal Unit Handbook. Christchurch Women's Hosp. 2015;(November):1–152.
Guidelines from scientific societies (main societies from Switzerland, Europe and America)	Swiss Society of Neonatology, CH	http://www.neonet.ch
	American Academy of Pediatrics, US	Google scholar and Google search: "Neonate + theme + guideline/recommendation + american academy of pediatrics" and "neonatal + theme + guideline/recommendation + american academy of paediatrics".
	American Academy of Pediatrics, US	http://pediatrics.aappublications.org/
	Canadian Paediatric Society	Google scholar and Google search: "Neonate + theme + guideline/recommendation + canadian paediatric society" and "neonatal + theme + guideline/recommendation + canadian paediatric society".
	Canadian Paediatric Society	www.cps.ca
	Royal College of Paediatrician and Child Health, UK	http://www.rcpch.ac.uk
	National Institute for Health and Care Excellence, UK	https://www.nice.org.uk
	European Society of Neonatology, EU	Google scholar and Google search: "Neonate + theme + guideline/recommendation + european society of neonatology" and "neonatal + theme + guideline/recommendation + european society of neonatology"
	European Society of Neonatology, EU	http://esn.espr.info/
	Other recommendations	Google scholar and Google search: "Neonate + theme + guideline/recommendation" and "neonatal + theme + guideline/recommendation"
	Geneva Foundation for medical research, INTL	http://www.gfmer.ch
Research groups, textbooks		
	Cochrane Neonatal, INTL	http://neonatal.cochrane.org
	Neonatal Formulary, UK	http://www.neonatalformulary.com
Complementary search (only if systematic search deemed insufficient)		
	PubMed	"Neonate + theme or drug" and "Neonatal + theme or drug + guideline/recommendation"
	Embase	
	Uptodate	"Theme + neonates" or "theme"
	Referent senior neonatologist	Senior neonatologist from the steering committee

Recommendation formulation and grading

Recommendations identified via the literature review were grouped by theme, and those on the same subjects were merged. From these materials, recommendations and definitions were selected and optimised through individual interviews with sub-specialists (a paediatric infectiologist for infectious diseases, a paediatric nephrologist for nephrology, a clinical pharmacist for pharmacological issues and a neonatologist for all others). The steering committee then reduced the expert-approved recommendations to address only the most relevant topics.

The selected recommendations were reformulated as simple "main statements" on neonatal drug therapy starting with active, directive verbs (start, stop, do not use, administer, check, reassess, consider, do not provide). Additional information was added to provide context or include relevant details, and the recommendation grade and key references were provided (appendix 2).

The grade of recommendation (GOR), collected from relevant publications, was assessed for each item using the scale of the Scottish Intercollegiate Guidelines Network [18]. Available GORs determined using this or an equivalent scale were retained. When no such GOR was provided, the type of study or recommendation was recorded. For each item based on several references, an overall GOR was determined according to, in order of priority, the GOR given in the reference on which the item was most directly based or the highest GOR among those provided.

Delphi-based selection

A modified Delphi method was used in two rounds (June 2016–September 2017 and May–September 2018) to select items with strong consensus among Swiss experts. Paediatricians working or having recently worked in Swiss neonatal intensive care units (NICUs) with Neonatology subspecialty titles or equivalent foreign qualifications and clinical pharmacists who had worked for several years in a Swiss neonatology centre were invited to participate in the Delphi rounds. The recommendation items were submitted to the experts via questionnaire on the SurveyMonkey website (surveymonkey.com; SurveyMonkey Inc., San Mateo, CA, USA; appendix 2). In the first round, the complete items were accompanied by multiple-choice questions about the experts' level of agreement and item usefulness. Free text fields were provided for experts to add comments and/or propose the addition of references. In the second round, experts were asked only to indicate their level of agreement with the recommendations. In addition to the questionnaire, each expert received a table indicating his or her level of agreement in the first round and the median level of agreement of the expert group for each item. When these two values differed, the expert was asked to accept the group rating or to maintain his or her position, and explain why. Respondents indicated their level of agreement with the main statements using a five-point Likert scale (1, strongly disagree; 5, totally agree; 0, no opinion). They could also provide comments related to their responses. Item scores ≥4 were considered to indicate expert agreement. Items on which >65% of experts agreed in the first round were selected for the second round; all other items were eliminated. The process was then repeated, and items on which >75% of experts agreed in the second round were validated and included in the final tool. Items were revised between rounds when one or more experts suggested improved wording and when several experts had similar dissenting opinions in the first round, and the overall level of agreement was insufficient for validation.

Table 2: Themes included in the literature review.

Themes	Examples of subthemes
Basic managment	Nutritional management, vaccination
Cardiology	Congenital heart disease, patent ductus arteriosus
Haematology	Anaemia, Rh incompatibility
Pneumology	Apnoea, bronchopulmonary dysplasia
Nephrology	Renal failure (acute)
Gastroenterology	Direct hyperbilirubinaemia, necrotising enterocolitis
Neurology	Intracranial haemorrhage, seizures in the neonate
Pain and analgesia	Sedation and analgesia in a neonate
Infectiology	Sepsis, respiratory syncytial virus
Endocrinology and metabolism	Thyroid disorders, hyperglyacemia
Ophthalmology	Eye disorders of the newborn, retinopathy of prematurity
Pharmacology and toxicology	Drug interactions, drug breast-feeding compatibility
Electrolyte disorders	Calcium disorders, hyperkalaemia
Dermatology	Rash and dermatological problems

Usefulness assessment

The experts evaluated recommendation usefulness at the time of the first Delphi round, classifying items as (1) essential for neonatology practice,(2) useful especially for the training of young physicians or pharmacists or (3) useless. Items classified as "useless" by a majority of experts were eliminated.

Statistical analysis

Descriptive statistics were calculated for the Delphi data using the Excel® software (version 15.0.5189.1000; Microsoft Corporation, Redmond, WA, USA). For each main statement, the median agreement rating, percentage of experts conferring ratings ≥4 and number of responses were determined.

Results

Recommendation identification and selection

Through the literature review, we identified 1375 recommendations covering 12 themes and 56 sub-themes. Infectiology (29.5%), basic management (11.4%), pneumology and gastroenterology (10.8% each) were the most prevalent themes. The combination of recommendations covering the same subjects yielded a set of 328 recommendations. Ninety-seven of these recommendations were excluded based on interviews with experts, due mainly to irrelevance or incorrect interpretation (74.76%) and moderate usefulness (33.34%). The steering committee eliminated another 73 recommendations, resulting in a final set of 158 recommendations (fig. 1).

GORs

Fourteen items had associated GORs (A, n = 5; B, n = 3; D, n = 6). Fifty-seven of the other items were national guidelines, 17 were international guidelines and 15 were institu-

tional guidelines. Table 3 shows GORs and study types for the items included in the modified Delphi process.

Delphi results

The first Delphi round was conducted from June 2016 to September 2017, the second round from May to September 2018. Twenty-three experts (22 neonatologists from 10 of 25 Swiss NICUs, 1 clinical pharmacist) filled out questionnaires in the two Delphi rounds. Most (65%) of the experts had >10 years neonatology experience (table 4).

For each item in the first round, the mean response rate was 94% (95% confidence interval [CI] 93–95%] and the smallest number of responses was 15. Thirteen (8%) items were eliminated after this round (appendix 3). Two items that did not reach the agreement threshold were modified according to experts' comments and included in the second round (appendix 4). For each item in the second round, the mean response rate was 98% (95% CI 97–98%) and the smallest number of responses was 19. Four additional items were eliminated after the second round (appendix 3).

The final PST, named NeoCheck, comprises 141 items on 11 major themes and 49 subthemes (table 5, appendix 5; www.NeoCheck.ch). Ophthalmology themes were eliminated because none of the recommendations was retained. Most (79%) statements concern all neonates, 13% concern only preterm infants and 3% concern only very preterm infants. Some statements contain other age or weight restrictions (appendix 6).

Figure 1: Flow of recommendation selection.

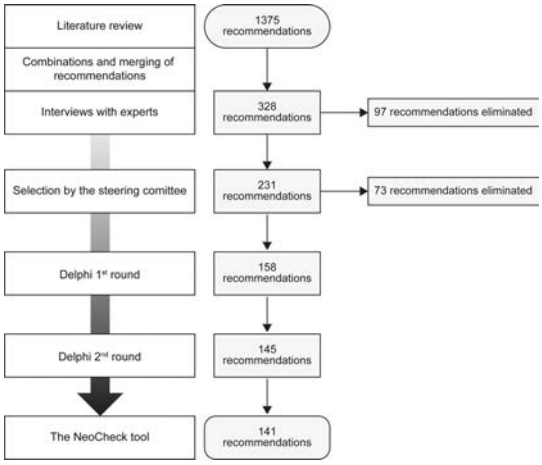

Table 3: Distribution of grades of recommendation (GORs) and source types for retained items.

GOR/source	n (%)
GOR identified	**14 (10)**
A	5 (4)
B	3 (2)
C	0 (0)
D	6 (4)
GOR not identified	**127 (90)**
Further research needed	9 (6)
Systematic review/meta-analysis	2 (1)
Randomised controlled trial	2 (1)
Cohort study	1 (1)
Case-control study	0 (0)
Descriptive study (case report, case series, cross-sectional, survey)	0 (0)
Review	12 (9)
National guidelines	57 (40)
International guidelines	17 (12)
Institutional guidelines	15 (11)
Textbook	7 (5)
Manufacturer	2 (1)
No reference	3 (2)
Total	**141 (100)**

Recommendation usefulness

The mean response rate for item usefulness was 94% (95% CI 93–95%). No item was deemed to be useless by a majority of experts. On average, the items were deemed essential by 52% of experts, useful by 42% and useless by 6% of experts.

Discussion

We developed the first PST adapted for neonates. It consists of 141 simple, precise recommendations for the management of typical neonatal situations.

The development of the NeoCheck tool was based on a modified Delphi technique, similar to the methods used for the development of comparable validated tools used in routine practice for other populations, such as the STOPP-START, PIM-Check and POPI criteria [13, 19, 20]. The Delphi method is used commonly for consensus building in healthcare research, including for PST development. The two-round modified Delphi approach used in this study, with a final consensus level of >75% and participation of 23 experts, was comparable to the methods used in most similar studies [21].

Direct comparison of NeoCheck content with that of other PSTs seems irrelevant, given significant differences in targeted populations. Considering practical aspects, NeoCheck appears to be adequate, as it contains a similar number of statements and themes as the PIM-Check tool, but more than the STOPP-START and POPI tools. The as-

Table 4: Characteristics of participating Swiss experts.

Expert characteristic	n (%)
Total	23 (100)
Sex: female/male	16 (70) / 7 (30)
Profession	
MD neonatologist	22 (96)
Clinical pharmacist	1 (4)
City	
Geneva	8 (35)
Bern	1 (4)
Aarau	4 (17)
Chur	1 (4)
Luzern	2 (9)
Wintherthur	2 (9)
Lausanne	2 (9)
St Gallen	2 (9)
Zurich	1 (4)
Years of experience in neonatology	
<5	4 (17)
5–10	4 (17)
>10	15 (65)

Table 5: The NeoCheck validated statements.

No.	Main statement
Basic management	
Body care	
1	Do not use routinely topical ointments in preterm neonates.
2	Stop the use of antiseptics for the daily care of the uncomplicated umbilical cord in healthy hospitalised term neonates.
Vaccination	
3	Administer a dose of DTPa-IPV/Hib ± HBV and of pneumococcal vaccine at 60, 90 and 120 days of postnatal life to all hospitalised preterm neonates.
4	Recommend BCG vaccine at discharge to neonates at high risk of tuberculosis exposure in the first year of life.
5	Check/administer pertussis vaccination to close contacts of neonates.
6	Check status and recommend or administer vaccination to close contacts of neonates.
Parenteral nutrition	
7	Start parenteral nutrition shortly after birth in all preterm neonates when it is clear that enteral feeds will not be tolerated soon.
8	Start reducing the percentage of parenteral nutrition as quickly as possible by the introduction of enteral nutrition until enteral nutrition finally replaces completely parenteral nutrition in order to minimise any side effects from exposure to parenteral nutrition.
9	Start continuous parenteral glucose administration in preterm infants needing parenteral nutrition.
10	Start amino acid supply in the first day of life in preterm infant needing parenteral nutrition.
11	Start continuous lipid emulsion infusion within the first 24–48 hours of life in preterm infant needing parenteral nutrition.
12	Do not administer parenteral lipid emulsion at a dose higher than 3–4 g/kg/day in neonates.
13	Check that a sufficient quantity of linoleic acid is administered in all neonates on parenteral nutrition.
14	Start electrolytes supplementation with parenteral nutrition after onset of diuresis.
15	Start vitamins and trace element supplementation in neonates receiving parenteral nutrition.
16	Start vitamin D supplementation from the first days of life in all neonates.
Cardiology	
Congenital heart disease	
17	Start alprostadil (prostaglandin E1) as an initial continuous intravenous infusion at 0.01 µg/kg/min until a definitive diagnosis is made in an infant suspected of having ductus-dependant heart disease.
18	Reassess the indication of alprostadil treatment.
19	Stop ibuprofen, indomethacin and paracetamol in patients with duct dependent congenital heart disease.
Patent ductus arteriosus	
20	Consider pharmacological closure of confirmed patent ductus arteriosus in preterm neonates after 2 weeks of life, with ibuprofen as first-line treatment.
21	Reassess the indication of ibuprofen, indomethacin and paracetamol in preterm neonates <2 weeks of life with confirmed or unconfirmed patent ductus arteriosus.
22	Reassess the indication of ibuprofen, indomethacin and paracetamol in term neonates with patent ductus arteriosus.
23	Do not use paracetamol as first-line treatment for patent ductus arteriosus closure. Consider a switch to ibuprofen.
Hypotension	
24	Do not use volume expansion as first-line treatment in very low birthweight infants (birthweight <1500g) with hypotension.
25	Consider a conservative approach (permissive hypotension) for the managment of very low birthweight infants (birthweight <1500g) if the clinical examination is satisfactory in the face of apparent hypotension
Haematology	
Anaemia	
No.	**Main statement**
Basic management	
26	Do not use routinely erythropoietin to limit exposure to blood transfusions in preterm neonates. The indication of treatment should be reassessed.
27	Start iron supplement of 2–3 mg/kg/day in all preterm infants fed human milk once full oral feeds have been achieved.
Coagulation disorders	
28	Start oral vitamin K in neonates breastfed by a mother treated with phenprocoumon.
29	Check in all neonates that complete vitamin K prophylaxis has been given at birth.
Thrombocytopenia and platelet dysfunction	
30	Consider platelet transfusion even in the absence of bleeding in all neonates with a platelet count of $<30 \times 10^9$/l.
31	Consider platelet transfusion in neonates with a platelet count of $30–49 \times 10^9$/l and minor bleeding or those at risk for major bleeding.
32	Consider platelet transfusion in neonates with a platelet of count $50–99 \times 10^9$/l only if bleeding is present.
33	Do not transfuse neonates with mild thrombocytopenia (platelet count $100–150 \times 10^9$/l) even if bleeding.
34	Start intravenous immunoglobulin only in case of severe thrombocytopenia (platelet count of $<50 \times 10^9$/l) or if bleeding persists despite compatible platelet transfusion or in combination with unmatched platelets transfusion in neonates with neonatal allo-immune thrombocytopenia.
35	Start intravenous immunoglobulin as first-line treatment in neonates with neonatal auto-immune thrombocytopenia and born to mothers who have idiopathic thrombocytopenic purpura, when the platelet count is $<30 \times 10^9$/l or clinical bleeding is present.
Vasospasms and thromboembolism	
36	Start unfractionned heparin or low molecular weight heparin in neonates with a first event venous thromboembolism and continue for at least 5 days.
37	Start alteplase or urokinase only in the case of major vessel occlusion causing critical compromise of organs or limbs in infants with venous thromboembolism.
Pneumology	
Pneumothorax	
38	Do not routinely use supplemental oxygen in infants with spontaneous pneumothorax.
Apnoea of prematurity	
39	Start caffeine citrate in patients with apnoea of prematurity (loading dose 20 mg/kg; maintenance dose 5 mg/kg/day). Dose may be increased to 10 mg/kg/day if apnoea persists.
40	Reassess the need for caffeine citrate treatment.
41	Reassess the indication of anti-gastro-oesophageal reflux therapy in neonates with apnoea.
Bronchopulmonary dysplasia (BPD)	
42	Do not use dexamethasone in the prevention or the treatment of bronchopulmonary dysplasia.
43	Do not use loop diuretics for prevention of BPD in preterm neonates.
44	Do not use thiazid diuretics for prevention of BPD in preterm neonates. Use them judiciously for treatment of BPD in preterm neonates.
Respiratory distress syndrome (hyaline membrane disease)	
45	Start surfactant therapy in infants born <26 weeks of gestational age who need fraction of inspired oxygen (FiO_2) >0.30.
46	Start surfactant therapy in infants born ≥26 weeks of gestational age who need FiO_2 >0.40.
Meconium aspiration syndrome	
47	Consider inhaled nitric oxide in neonates with hypoxic respiratory failure due to meconium aspiration syndrome.
48	Reassess the indication for antibiotics in patients with meconium aspiration syndromealone.
49	Administer a bolus instillation of surfactant in intubated infants with meconium aspiration syndromerequiring more than 50% oxygen.
Persistent pulmonary hypertension of the newborn (PPHN)	

No.	Main statement
Basic management	
50	Start inhaled nitric oxide in neonates who have severe PPHN.
51	Do not use sildenafil as initial therapy for PPHN.
Nephrology	
Acute kidney injury	
52	Do not use nephrotoxic drugs in neonates if possible, especially in preterm infants.
53	Stop all nephrotoxic drugs when possible in neonates with acute kidney injury (stage 1–3).
54	Consider dosage adjustement for drugs highly excreted by renal elimination in neonates with acute kidney injury (stage 1–3). When needed, refer to a specialist.
Gastroenterology	
Direct hyperbilirubinaemia (conjugated hyperbilirubinaemia)	
55	Decrease or stop intravenous soybean-based lipid emulsion in neonates with marked progressive cholestasis associated with parenteral nutrition.
56	Administer adequate protein intake of 2–3 g/kg/day to neonates with direct hyperbilirubinAemia.
57	Start fat-soluble vitamins (ADEK) in neonates with cholestasis.
58	Consider ursodeoxycholic acid in neonates with direct hyperbilirubinaemia.
Indirect hyperbilirubinaemia (unconjugated hyperbilirubinaemia)	
59	Administer intravenous immunoglobulin to neonates with a positive direct Coombs test and severe hyperbilirubinaemia, or to those progressing to severe hyperbilirubinaemia despite initial treatment.
Necrotising enterocolitis	
60	Start probiotics in preterm neonates at high risk of developing necrotising enterocolitis.
61	Stop all enteral medications in neonates suspected to have necrotising enterocolitis.
62	Do not use enteral antibiotics for the prevention of necrotising enterocolitis.
63	Start broad spectrum antibiotic promptly after blood cultures have been drawn in neonates with any stage of necrotising enterocolitis.
Gastrointestinal bleeding from the upper tract	
64	Check that vitamin K prophylaxis was administered postdelivery in neonates with upper gastrointestinal bleeding, to guide diagnosis.
Gastro-oesophageal reflux	
65	Consider proton pump inhibitors or H2-blockers only in neonates with severe cases of acid gastro-oesophageal reflux disease, when nonpharmacological measures (including milk thickeners) have failed.
66	Do not use metoclopramide, domperidone or erythromycin to treat gastro-oesophageal reflux or gastro-oesophageal reflux disease.
Neurology	
Seizures	
67	Start phenobarbital as the first-line agent in neonates with either EEG-diagnosed or clinically apparent seizures when prolonged or frequent.
68	Consider phenytoin or a benzodiazepine or lidocaine in neonates with persistant seizures despite adequate phenobarbital treatment.
69	Stop antiepileptic drugs if seizure-free for >72 hours in neonates with normal neurological examination and/or normal electroencephalography.
70	Consider pyridoxine only in neonates with recurrent seizures with no obvious cause.
Pain, analgesia and sedation	
71	Start pain management in neonates with nonpharmacological techniques (including sucrose) if aproppriate.
72	Start paracetamol in neonates who are still in pain despite adequate nonpharmacological interventions.
73	Do not use nonsteroidal anti-inflamatory agents as analgesics.
74	Start morphine as first-line treatment for pain relief in neonates who are still in pain despite adequate nonpharmacological techniques and paracetamol treatment.

No.	Main statement
Basic management	
75	Start opioids as first-line treatment for postoperative analgesia, and use them as long as pain assessment scales deem necessary.
76	Reassess the indication of morphine or fentanyl in chronically ventilated preterm neonates without pain.
77	Do not use ketamine treatment for routine management of pain.
Neonatal abstinence syndrome	
78	Consider non-pharmacological interventions for the initial management of all infants suspected of having or at risk of developing neonatal abstinence syndrome. This may mitigate the need for medication.
79	Start morphine as the first-line pharmacological treatment for neonatal abstinence syndromewhen opioids are used by the mother and supportive measures have failed.
80	Start weaning of morphine as soon as Modified Finnegan scores are <8 for 24–48 hours in neonates with neonatal abstinence syndrome.
81	Do not use morphine in neonates with neonatal abstinence syndromewhen the drugs used by the mother are not opioids.
Infectiology	
Meningitis	
82	Start empirical antibiotic treatment with high dose amoxicillin and gentamicin in neonates with diagnosed or strongly suspected meningitis.
83	Check results of cerebrospinal fluid culture as soon as they are available in order to reassess the need for treatment or the choice of antibiotics in neonates with suspected meningitis treated with empirical antibiotics.
84	Do not use corticosteroids for the treatment of neonates with suspected or confirmed bacterial meningitis. Reassess the corticosteroid indication.
Sepsis	
85	Do not use empirical antibiotic therapy for asymptomatic neonates with a single risk factor of infection (including mother with suspected chorioamnionitis or unexplained premature delivery).
86	Start empirical antibiotic treatment after blood cultures have been drawn in all newborn infants with suggestive signs of neonatal infection.
87	Reassess the need for antibiotics after 48 hours in neonates treated empirically with antibiotics for suspected sepsis.
88	Do not use cephalosporins as first-line treatment in infants with suspected neonatal infection, because of the high risk of developing resistance. Use is restricted to special cases
89	Do not use intravenous immunoglobulin in the treatment of suspected or proven neonatal sepsis.
90	Do not use vancomycin as prophylaxis against sepsis in preterm neonates.
Hepatitis	
91	Administer an initial dose of hepatitis B vaccine within 12 hours of birth in infants born to HBsAg-positive mothers, including infants weighing <2000g. Administer hepatitis B immune globulin 200 IU concurrently but at a different anatomical site.
92	Do not use early hepatitis B vaccine in infants born to mothers whose HBsAg and HBeAg status is negative but with positive anti-HBs status (prior infection or at risk of infection).
Human immunodeficiency virus (HIV)	
93	Start HIV prophylaxis with zidovudine as close to birth as possible for at least 4 weeks or consider tritherapy in neonates born to HIV-infected mothers who did not follow proper antenatal treatment or have detectable viraemia.
94	Start tritherapy immediately in the neonate aged <72 hours if the mother is diagnosed postpartum with HIV infection.
Respiratory syncytial virus	
95	Start respiratory syncytial virus prophylaxis with palivizumab in neonates with severe bronchopulmonary dysplasia.
96	Start respiratory syncytial virus prophylaxis with palivizumab in neonates with haemodynamically significant congenital heart disease AND other associated risk factors.
97	Dot not use respiratory syncytial virus prophylaxis with palivizumab routinely in preterm neonates.

No.	Main statement
Basic management	
98	Do not use palivizumab for the treatment of respiratory syncytial virus infection. Stop the treatment, even if it was given before the infection.
Toxoplasmosis	
99	Administer a combination of pyrimethamine-sulfadiazine-folinic acid during the first year of life to neonates in whom a diagnosis of congenital toxoplasmosis is confirmed or probable.
100	Do not use spiramycin in neonates. Stop treatment and screen for potential QT interval prolongation.
Cytomegalovirus	
101	Start antiviral treatment as soon as virologic testing is confirmed and within the first 30 days of life in symptomatic cytomegalovirus-infected newborns with central nervous system involvement or if life threatening.
102	Stop antiviral treatment in neonates with asymptomatic cytomegalovirus infection.
Herpes simplex virus	
103	Start aciclovir IV in neonates with herpes simplex virus disease, regardless of maternal history or pending laboratory confirmation or exclusion of herpes simplex virus.
104	Start a topical antiviral treatment in combination with aciclovir IV in neonates with herpes simplex virus disease with ocular involvment.
Varicella-zoster virus	
105	Start varicella-zoster immune globulin 125 IU IM as soon as exposure is known and within a 72-hour period, independent of maternal history of varicella, in neonates born at <28 weeks of gestational age or who weighed <1000g at birth who have been significantly exposed to varicella-zoster virus.
106	Start varicella-zoster immune globulin 125IU IM in neonates ≥28 weeks gestational age or ≥1000 g birthweight who have been significantly exposed postnatally to varicella-zoster virus, only if born to mother who has no or unkown history of varicella.
107	Start varicella-zoster immune globulin 125IU IM as soon as possible, after birth or with onset of maternal illness, in term or late preterm neonates whose mother had varicella disease 5 days prior to or 2 days after delivery.
108	Start aciclovir IV in neonates who develop systemic symptoms or severe cutaneous varicella-zoster disease, or who are at high risk of infection.
109	Stop varicella-zoster immune globulin if neonatal chickenpox has developed.
Chlamydia	
110	Do not use prophylactic antibiotic treatment in neonates at high risk of chlamydial infection (born to mothers who have untreated chlamydia).
111	Start erythromycin orally for 14 days in neonates with chlamydial conjunctivitis or with suspected or confirmed chlamydial pneumonia.
112	Start azithromycin as second-line treatment when erythromycin is not avaliable in neonates with chlamydial conjunctivitis or with suspected or confirmed chlamydial pneumonia.
113	Stop topical antibiotics for the treatment of chlamydial conjunctivitis in neonates.
Gonorrhoea	
114	Administer one dose of ceftriaxone IV or IM in all neonates born to mothers who have untreated gonorrhoea.
115	Administer one dose of ceftriaxone IV or IM in neonates with suspected or confirmed gonococcal ophtalmia neonatorum or other localised gonococcal infection.
116	Stop topical antibiotics in neonates with suspected or confirmed gonococcal ophtalmia neonatorum.
117	Start ceftriaxone IV or IM in neonates with disseminated gonococcal infection.
Methicillin-resistant *Staphylococcus aureus* infections	
118	Start vancomycin IV until bacteraemia is excluded for localised methicillin-resistant *Staphylococcus aureus* disease in preterm or very low-birthweight neonates or in more extensive forms of the disease involving multiple sites in full-term neonates.
Syphilis	
119	Administer benzylpenicillin G IV, OR procaine penicillin to neonates with confirmed or presumed congenital syphilis, or
	born to syphilis-infected mothers who have not been treated with penicillin at least 4 weeks prior to delivery.
120	Administer one dose of benzathine penicillin G IM in neonates with normal examination, born to syphilis infected mothers who have been adequately treated during pregnancy more than 4 weeks prior to delivery.
Ureaplasma urealyticum infection	
121	Reassess the use of macrolides or other antibiotics for the treatment of *Ureaplasma urealyticum* in neonates.
Urinary tract infection	
122	Start empirical antibiotics after urine samples and cultures are collected in neonates with fever when urinary tract infection is suspected.
123	Consider antibiotic prophylaxis after an urinary tract infection only in neonates with grade IV–V vesico-ureteric reflux.
Pertussis	
124	Start azithromycin oral daily for 5 days in neonates with suspected or confirmed pertussis infection, or in those in close contact with confirmed and contagious cases of pertussis.
Tuberculosis	
125	Start isoniazid prophylaxis orally in neonates born to mothers with tuberculosis, or those in close contact with people with smear-positive pulmonary or laryngeal tuberculosis who have not had at least 2 weeks of anti-tuberculosis treatment.
126	Start anti-tuberculosis treatment in neonates with congenital tuberculosis or postnatal primary pulmonary tuberculosis.
Endocrinology	
Metabolic bone disorder	
127	Administer calcium, phosphate and vitamin D in preterm infants <32 weeks of gestational age or <1500g or infants at risk of metabolic bone disorders.
128	Administer the maximum recommended doses of calcium, phosphate and vitamin D to prevent fractures in neonates with biochemical features of metabolic bone disease.
129	Stop steroids and furosemide as soon as possible in neonates at risk of metabolic bone disorder.
Thyroid disorders (or hypothyroidism)	
130	Start levothyroxine immediately in neonates with a thyroid function test that results in either a free T4 a concentration below normal for age or a venous thyroid stimulating hormone concentration >20 mIU/l.
Hyperglycaemia	
131	Decrease glucose intake if necessary and decrease or stop drugs that worsen hyperglycaemia, in neonates with hyperglycaemia.
132	Start insulin only in patients with persistent hyperglycaemia when other methods of glucose control have failed.
133	Do not provide high glucose infusion rates to prevent hypoglycaemia in neonates receiving parenteral nutrition.
134	Do not use early insulin therapy in neonates at risk of hyperglycaemia.
Hypoglycaemia	
135	Start IV glucose infusion in asymptomatic neonates with serum glucose level of <2.6 mmol/l if increased enteral caloric intake is not effective.
136	Start IV glucose infusion immediately in symptomatic neonates with glucose levels <2.6 mmol/l.
Pharmacology	
Drugs and breast feeding	
137	Check the possible milk transfer of drugs taken by mothers to breastfed neonates, and monitor for potential adverse drug effects.
Drug-drug interactions	
138	Check changes in drug effect when initiating strong inhibitors or inducers of cytochrome P450 and/or p-glycoprotein.
Various	
139	Do not use ceftriaxone in neonates who are being, or who have recently been given any IV fluids that contain calcium (such as TPN or Ringer lactate)
140	Do not use trimethoprim–sulfamethoxazole in neonates.

No.	Main statement
Basic management	
141	Check excipients contained in prescribed drug formulations administered orally or parenterally since they can be harmful and responsible for adverse events in neonates, due to immature metabolism.

sessment of user satisfaction and the average time required for patient treatment review with NeoCheck would be of use to better understand the practicability of NeoCheck use.

The representation in NeoCheck of key research and resources for neonatology practice is a very important aspect of the tool. NeoCheck development was based on expert opinion, which is very low-quality evidence according to the principles of evidence-based medicine [22]. Thus, underlying references and GORs are systematically included in NeoCheck recommendations to increase the tool's value for users. However, many published guidelines do not include GORs, and the interpretation of those given was sometimes difficult in this study due to pronounced variability among evidence grading scales. Grading guidelines are particularly complex for the interpretation of inconclusive evidence [23]. A main difficulty specific to neonatal research is in long-term morbidity, particularly delay of development and learning ability at school age. The difficulties in targeting relevant short-term and unbiased outcomes certainly have contributed to the limited availability of GORs in this medical speciality (and consequently in NeoCheck). However, the types of studies underlying recommendations are provided and updated systematically in NeoCheck to help users understand recommendation origins and appreciate their clinical weights. A working-group assessment of the GORs using a standard scale, as done for the Beers geriatric PST [24], could be part of NeoCheck updating. All NeoCheck items were judged to be "useful" to "essential" by at least half of the participating experts, supporting the quality of the recommendation selection process and the final tool.

We believe that NeoCheck is useful for the optimisation of drug use in neonatal care, for the training of young physicians and pharmacists, and as a basis for institutional guideline development. In a future prospective study, we will assess the effect of NeoCheck use by a clinical pharmacist in a level-3 NICU on prescription optimisation, as well as user satisfaction. Additional studies are needed to assess the impact of NeoCheck use in the training of young physicians and pharmacists, and its role as a tool for continuous quality of care improvement should be assessed.

This study has some limitations. NeoCheck was developed with experts working in Switzerland; although some of these experts had extensive work experience in other countries, the tool may not be fully suitable for application outside of the Swiss context. This limitation may apply particularly to infectious pathologies, for which antibiotic treatments are adapted according to regional resistance profiles. Immunisation recommendations in NeoCheck were based on Swiss references when available; recommendations for all other themes were generally based on North American sources, as few national guidelines for neonatal clinical management have been published in Switzerland. The scientific societies and hospital guidelines systematically consulted were selected to ensure representation of local, national and international practices. Internationally, North American scientific societies have been selected for their wide range of recommendations, and Australian and New Zealand hospitals because they were structured open-access guidelines commonly used by the authors. The search for recommendations was not limited to these sources, and guidelines from other scientific societies and hospitals were included during the literature review. We believe that the NeoCheck tool is suitable for use in most high-income countries. As NeoCheck was based on scientific knowledge that was current in 2016, it needs to be regularly updated to maintain relevance. A literature review every 5-6 years is planned in order to identify any new recommendation or changes in the current recommendations. Modifications can also be made to the items in the event of a significant change in the literature. Any change or creation of an item would be validated with the same modified Delphi method described above.

The NeoCheck tool provides possible attitudes drawn from existing recommendations and deemed correct by a panel of experts. This tool should not be considered as a textbook, presenting national or international recommendations.

NeoCheck is the first PST developed to optimise neonatal prescription. It contains 141 recommendations that should help young physicians and clinical pharmacists review patient treatments in daily practice based on up-to-date medical knowledge. Because of the complexity of neonatal drug prescription, NeoCheck use could improve neonatal pharmacotherapy and care quality.

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Appendix

Appendix 1: Themes and subthemes included in the literature review

TABLE A1-1 Themes and subthemes included in the literature review

BASIC MANAGMENT	Temperature Regulation
	Respiratory Management
	Fluid and Electrolytes
	Nutritional Management
	Management of the Extremely Low Birthweight Infant During the First Week of Life
	Management of the Late Preterm
	Vaccination
	Is the Infant Ready for Discharge?
CARDIOLOGY	Congenital Heart Disease
	Patent Ductus Arteriosus
	Arrythmia
HEMATOLOGY	Blood Component Therapy
	ABO Incompatibility
	Anemia
	Coagulation disorders
	Hematuria
	Rh Incompatibility
	Thrombocytopenia and Platelet Dysfunction
	Polycythemia and Hyperviscosity
	Vasospasms and Thromboembolism
PNEUMOLOGY	Extracorporeal Life Support in the Neonate
	Air Leak Syndromes (Pneumoperitoneum, Pneumothorax)
	Apnea
	Bronchopulmonary Dysplasia
	Hyaline Membrane Disease (Respiratory Distress Syndrome)
	Meconium Aspiration
	Perinatal Asphyxia
	Persistent Pulmonary Hypertension of the Newborn
	Transient Tachypnea of the Newborn
	Pulmonary Hemorrhage
NEPHROLOGY	Renal Failure (Acute)

GASTROENTEROLOGY	Air Leak Syndromes
	Hyperbilirubinemia, Direct (Conjugated Hyperbilirubinemia)
	Hyperbilirubinemia, Indirect (Unconjugated Hyperbilirubinemia)
	Necrotizing Enterocolitis and Spontaneous Intestinal Perforation
	Gastrointestinal Bleeding from the Upper Tract
	No Stool in 48 Hours
NEUROLOGY	Hydrocephalus and Ventriculomegaly
	Intracranial Hemorrhage
	Neural Tube Defects
	Transient Neonatal Myasthenia Gravis
	Seizures in the Neonate
PAIN and ANALGESIA	Sedation and Analgesia in a Neonate
	Pain in the Neonate
INFECTIOLOGY	Chlamydial Infection
	Enteroviruses and Perochoviruses
	Gonorrhea
	Hepatitis
	Human Immunodeficiency Virus (HIV)
	Lyme Disease and Pregnancy
	Meningitis
	Methicillin-Resistant Staphylococcal Aureus (MRSA) Infections
	Parvovirus B19 Infection
	Respiratory Syncytial Virus (RSV)
	Sepsis
	Syphilis
	TORCH Infections (Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes Simplex Virus)
	Ureaplasma Urealyticum Infection
	Urinary Tract Infection
	Varicella-Zoster Infections
	Pertussis
	Tuberculosis
	Postdelivery Antibiotics
ENDOCRINOLOGY AND METABOLISM	Disorders of Sex Development
	Infant of a Diabetic Mother
	Osteopenia of Prematurity
	Thyroid Disorders
	Hyperglycemia
	Hypoglycemia
	Inborn Errors of Metabolism with Acute Neonatal Onset
OPHTHALMOLOGY	Eye Disorders of the Newborn and Retinopathy of Prematurity
	Eye Discharge (Conjunctivitis)

PHARMACOLOGY AND TOXICOLOGY	Drug Interactions
	Infant of a Drug-Abusing Mother
	Drug Pharmacokinetics in the neonate
	Drug Breast-Feeding Compatibility

ELECTROLYTE DISORDERS	Calcium Disorders
	Magnesium Disorders
	Hyperkalemia
	Hypokalemia
	Hyponatremia

DERMATOLOGY	Rash and Dermatologic Problems

Appendix 2: Questionnaire design

The recommendation items were submitted to the experts via online questionnaires on the SurveyMonkey website (http://surveymonkey.com). In the first round, the complete items were accompanied by multiple-choice questions about the experts' level of agreement and item usefulness. Free text fields were provided for experts to add comments and/or propose the addition of references.
In the second round, experts were asked only to indicate their level of agreement with the recommendations. Item modifications made after the first round were identified. In addition to the questionnaire, each expert received a table indicating his or her level of agreement in the first round and the median level of agreement of the expert group for each item. When these two values differed, the expert was asked to accept the group rating or to maintain his or her position, and explain why.

Explicative text provided to the experts in the 1st round of Delphi:

Why this survey?

Prescribing drugs to a neonate is challenging, especially for young doctors.
Research in neonatal pharmacotherapy being limited by many obstacles, widely accepted guidelines are rare and most medicines used in the newborn are off label.

Our project aims to create a modular medication-review tool which could help young doctors and clinical pharmacists in their practice.

What does an item look like?

Based on literature review, items with statements about basic management of neonates and items about drug therapy were elaborated for the most common clinical situations in neonatal care.

We ask you to evaluate the main statement of the items on 3 points:
- Your institutional practice
- The usefulness of the item

You may add comments or references after each item.

What does an item look like?

Each item is structured with:
- A main statement on basic management or drug therapy in neonate;
- Complementary informations on the statement (rational basis);
- Grade of recommendation for the statement based on methodological quality of literature;
- References used to elaborate the statement.

If useful, a definition of the disease has been added in front of the items.

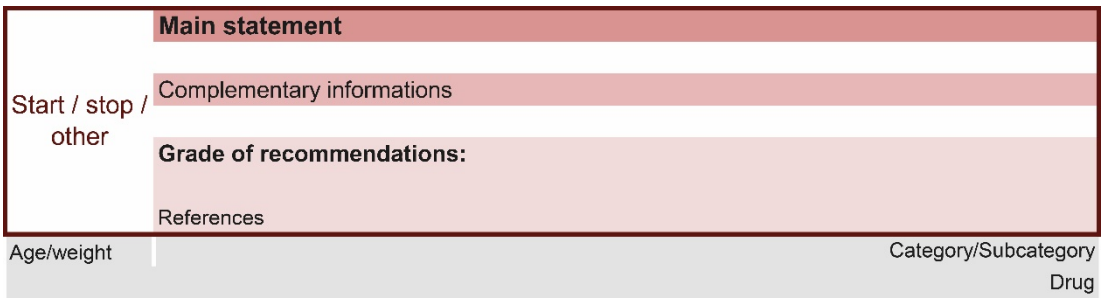


FIGURE A2-1 Item layout

Below each item, you will find links to the studies of the references list.
For exemple:
Links to references: Cleminson 2016 Erdemir 2015 Raboni 2014 Campbell 2000

How is the survey organized?

The survey is divided in categories. Each category is presented in a new page and contains a set of items.

You will have to evaluate the main statement of each item by answering two mandatory questions.

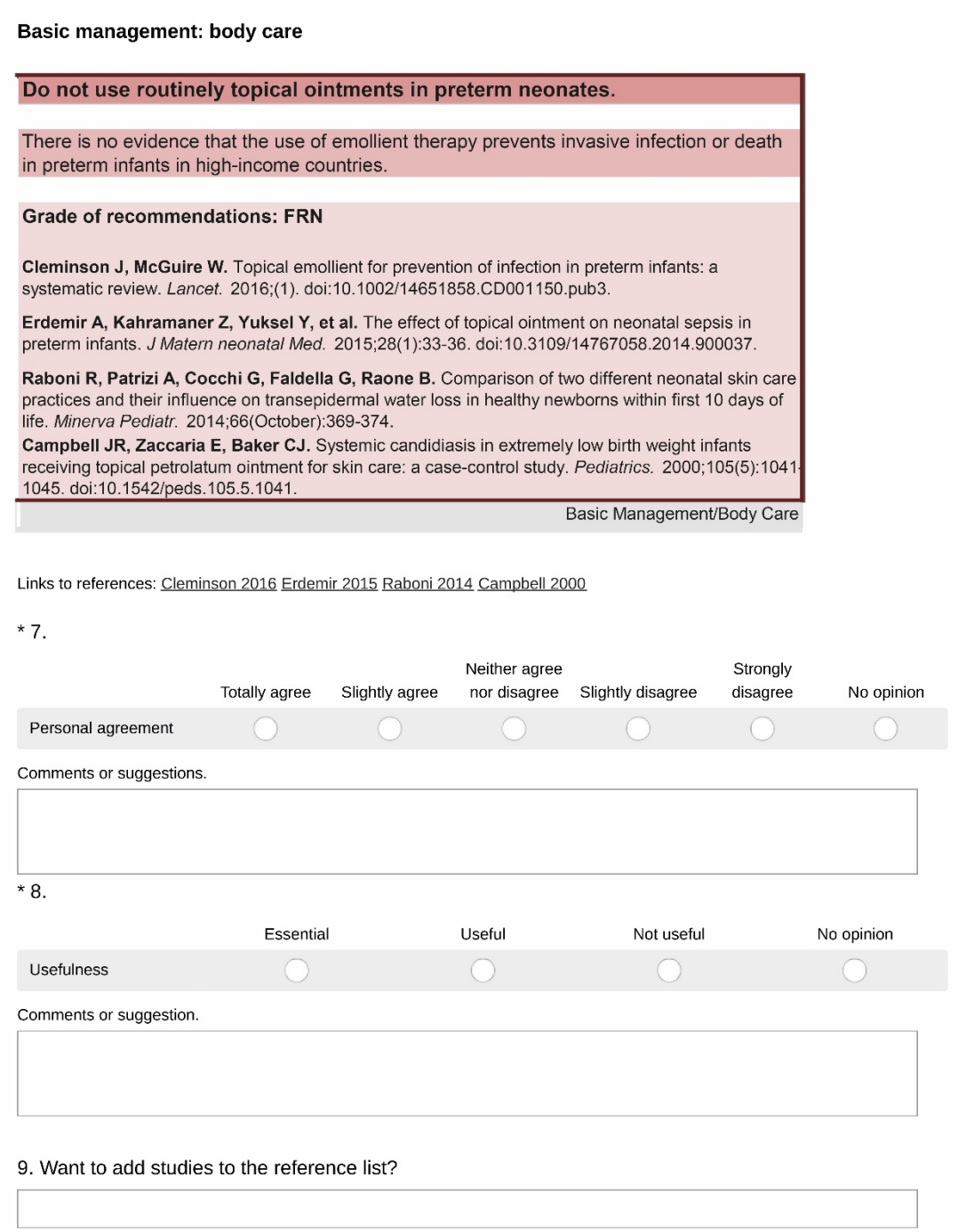
1. Your level of personal agreement with the statement:
   - I would recommend this practice (= totally agree);
   - I find this practice acceptable (= slightly agree);
   - I neither agree nor disagree with this practice (= neither agree nor disagree);
   - I would rather not see this practice applied in my ward (= slightly disagree);
   - I would recommend against this practice (= strongly disagree);
   - I do not know (= no opinion).
2. The usefulness of the item :
   - This item is essential for the basic practice of neonatology (= essential);
   - This item is not essential but can be helpful for the junior staff (= useful);
   - This item is not useful (= not useful).

Please note that we ask you to evaluate the main statement only. The complementary information adds details which may help understand the main statement but this should not be considered when judging your level of agreement with the item or its correspondence with your institutional practice. For example, for an item recommending to start a treatment, recommended doses may be added in the complementary information for a further development of the tool. In this case, if you would recommand the statement but using a different dose, your answer should be "totally agree".

You may add free comments or references at the end of each page. If you want to add a study, please write its references in the field as formated citation (any journal format).

Finally, when it was found that certain terms or pathology used in the items needed to be defined, definitions were added. These will not be evaluated in this survey.

Design of a question of the 1st round of Delphi:



Basic management: body care

Do not use routinely topical ointments in preterm neonates.

There is no evidence that the use of emollient therapy prevents invasive infection or death in preterm infants in high-income countries.

Grade of recommendations: FRN

Cleminson J, McGuire W. Topical emollient for prevention of infection in preterm infants: a systematic review. *Lancet.* 2016;(1). doi:10.1002/14651858.CD001150.pub3.

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Basic Management/Body Care

Links to references: Cleminson 2016 Erdemir 2015 Raboni 2014 Campbell 2000

* 7.

	Totally agree	Slightly agree	Neither agree nor disagree	Slightly disagree	Strongly disagree	No opinion
Personal agreement	○	○	○	○	○	○

Comments or suggestions.

* 8.

	Essential	Useful	Not useful	No opinion
Usefulness	○	○	○	○

Comments or suggestion.

9. Want to add studies to the reference list?

FIGURE A2-2 Layout of a question in the 1st round of Delphi

Explicative text provided to the experts in the 2nd round of Delphi:

What was done after the 1st round of Delphi?

After the first round of Delphi, items were selected based on experts' opinion (23 experts). The items on which at least 65% of the experts either totally agreed with or slightly agreed with were selected for 2nd round. A total of 145 of the 158 items were selected for the 2nd round or Delphi. Comments made on the main statements of items were used to modify some of them. Other comments will be taken into account and answers at the end of the Delphi process.

What should you do in this 2nd round?

This is the final step for the validation of the 145 items.

You have received by email:

- A recapitulative table with the level of agreement of the experts group and your level of agreement for each item with the main statement. Modified items appear in orange. This should allow you to quickly identify items for which your opinion was greatly different to the one of the group.
- A document with the list of items for the 2nd round of Delphi. Modifications are highlighted in yellow and suppressed items appear in red. Under each item, you will find the median level of agreement with the main statement of the experts group and your personal level of agreement.

Both documents should help you to reevaluate your level of agreement for each item in regards to experts group value. If your personal level of agreement greatly differs from the median value, we would like you to either change your level of agreement to join the group or to maintain your evaluation and briefly tell us why.

Quotation of the level of agreement on the main statement of the item:

5 = totally agree = I would recommend this practice ;
4 = slightly agree = I find this practice acceptable ;
3 = neither agree nor disagree = I neither agree nor disagree with this practice ;
2 = slightly disagree = I would rather not see this practice applied in my ward ;
1 = strongly disagree = I would recommend against this practice ;
NO = no opinion

Quotation of each item has to be performed in the SurveyMonkey survey. Remember that we ask your level of agreement with the main statement and not the complementary information. Complementary information is presented only to help you understand the main statement.

Design of a question of the 2nd round of Delphi:

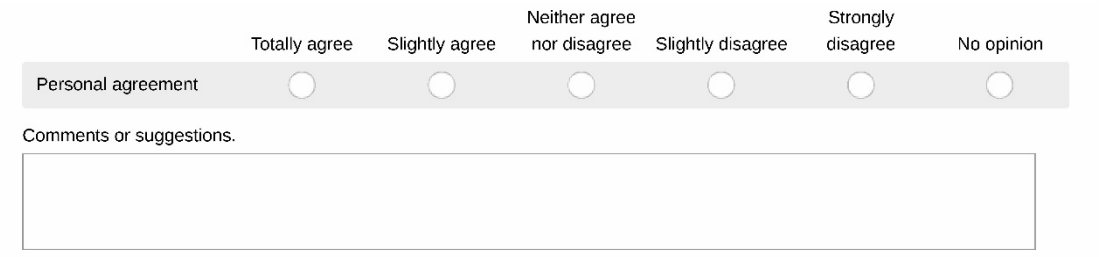

FIGURE A2-2 Layout of a question in the 2nd round of Delphi

Excerpt of a table provided to an expert during the 2nd round of Delphi with the level of agreement he noted during 1st round and the median agreement level of the expert group. This table also showed modifications of items:

BASIC MANAGEMENT	
Body Care	
1	**Do not use routinely topical ointments in preterm neonates.** Group median: 5 (Totally agree) Your evaluation: 4 (Slightly agree)
2	**Stop the use of antiseptics on the uncomplicated umbilical cord in hospitalized neonates.** **BECOMES:** **Stop the use of antiseptics for the daily care of the uncomplicated umbilical cord in healthy hospitalized term neonates.** Group median: 5 (Totally agree) Your evaluation: 4 (Slightly agree)
Vaccination	
3	**Give a dose of DTPa-IPV/Hib ± HBV and of pneumococcal vaccine at 60, 90 and 120 days of postnatal life to all hospitalized preterm neonates.** Group median: 5 (Totally agree)

Your evaluation: 5 (Totally agree)

Parenteral Nutrition (PN)

14 **Monitor serum triglyceride concentrations and consider a reduction of parenteral lipid dosage in patients with severe unexplained thrombocytopenia.**

ITEM ELIMINATED

Group median: 2 (Slightly agree)

Your evaluation: 1 (Totally agree)

Appendix 3: Items eliminated in the first and second Delphi rounds

TABLE A3-1 Items eliminated in the first and second Delphi rounds

Theme and subtheme	Main statement	Round of elimination	% of agreement
Basic management : Parenteral nutrition	Monitor serum triglyceride concentrations and consider a reduction of parenteral lipid dosage in patients with severe unexplained thrombocytopenia.	1	60%
Cardiology : Patent ductus arteriosus	Start digoxin and furosemide in patients < 5 kg with large patent ductus arteriosus (PDA) and symptomatic left-to-right shunt resulting in heart failure.	1	21%
Hematology : Vasospasms and thromboembolism	Start continuous infusion of low dose unfractionned heparin (UFH) in neonates with central venous access devices (CVAD), umbilical arterial catheter (UAC) or arterial catheters to prevent occlusion.	2	74%
Hematology : Vasospasms and thromboembolism	Consider alteplase or urokinase to restore catheter permeability only after appropriate clinical assessment of neonates with central venous catheter occlusion.	1	45%
Pneumology : Apnea of prematurity	Reassess the indication of caffeine citrate in neonates >28 weeks of gestational age who do not require positive pressure support. Await the occurrence of apnea before initiating therapy.	2	65%
Pneumology : Apnea of prematurity	Reassess the indication of doxapram treatment.	1	63%
Pneumology : Bronchopulmonary displasia	Consider Vitamin A treatement intramuscularly in all infants <1000 grams.	1	40%
Pneumology : Bronchopulmonary displasia	Start prophylactic low-dose of hydrocortisone in the first week of life in extremely preterm infants (<28w GA).	2	65%
Pneumology : PPHN	Start dobutamine in neonates with PPHN.	2	74%
Pneumology : PPHN	Do not use milrinone in the management of PPHN.	1	52%
Gastroenterology : Direct hyperbilirubinemia	Give a caloric intake of approximately 125% more of the recommended dietary intake in neonates with cholestasis.	1	50%
Gastroenterology : Direct hyperbilirubinemia	Consider erythromycin in preterm neonates on parenteral nutrition who fail to establish adequate enteral nutrition.	1	24%
Gastroenterology : Direct hyperbilirubinemia	Consider measuring ammonia levels and trace elements levels (Zn, Cr, Cu) in infants who develop conjugated hyperbilirubinemia while on Total Parenteral Nutrition (TPN).	1	30%

Gastroenterology : Indirect hyperbilirubinemia	Give supplemental fluids only in infants receiving intensive phototherapy.	1	52%
Pain, sedation & NAS : NAS	Start phenobarbital as the first line pharmacological treatment for NAS when non-opioids, multiple or unknown consumption are used by the mother and supportive measures failed.	1	50%
Infectiology : HIV	Stop antiretroviral treatment in neonates born to HIV-infected mothers who have received antiretroviral therapy since the second trimester at the latest and are stable (undetectable viremia).	1	63%
Infectiology : Urinary tract infection	Do not use antibiotics for the treatment of neonates with asymptomatic bacteriuria.	1	58%

% of agreement = % of experts who slightly agreed or strongly agreed with the statement. PPHN = persistant pulmonary hypertension of the newborn. NAS = neonatal abstinence syndrome. HIV = human immunodeficiency virus.

Appendix 4: Items modified after the first Delphi round according to experts' comments

TABLE A4-2 Items modified after the first Delphi round according to experts' comments

Theme and subtheme	Main statement before modification	% of agreement at round 1	Main statement after modification	% of agreement at round 2
Cardiology : Hypotension	Consider dopamin as first line treatment in VLBW infant (BW <1500g) with hypotension of unknown cause.	52%	Consider a conservative approach (permissive hypotension) for the managment of VLBW infants (BW <1500g) if the clinical examination is satisfactory in the face of apparent hypotension.	83%
Hematology : Anemia	Start iron supplement of 2-3 mg/kg/day in all preterm infants fed human milk at 2 months of life.	61%	Start iron supplement of 2-3 mg/kg/day in all preterm infants fed human milk once full oral feeds have been achieved.	91%

% of agreement = % of experts who slightly agreed or strongly agreed with the statement. VLBW = very low birthweight.

Appendix 5: Validated NeoCheck items

01. BASIC MANAGEMENT
Body Care

Item 1

Do not use routinely topical ointments in preterm neonates.

There is no evidence that the use of emollient therapy prevents invasive infection or death in preterm infants in high-income countries.

Grade of recommendations: FRN

Stop

Cleminson J, McGuire W. Topical emollient for prevention of infection in preterm infants: a systematic review. *Lancet.* 2016;(1). doi:10.1002/14651858.CD001150.pub3.

Erdemir A, Kahramaner Z, Yuksel Y, et al. The effect of topical ointment on neonatal sepsis in preterm infants. *J Matern neonatal Med.* 2015;28(1):33-36. doi:10.3109/14767058.2014.900037.

Raboni R, Patrizi A, Cocchi G, Faldella G, Raone B. Comparison of two different neonatal skin care practices and their influence on transepidermal water loss in healthy newborns within first 10 days of life. *Minerva Pediatr.* 2014;66(October):369-374.

Campbell JR, Zaccaria E, Baker CJ. Systemic candidiasis in extremely low birth weight infants receiving topical petrolatum ointment for skin care: a case-control study. *Pediatrics.* 2000;105(5):1041-1045. doi:10.1542/peds.105.5.1041.

< 37w GA

Basic Management/Body Care

Ointments

Item 2

Stop the use of antiseptics for the daily care of the uncomplicated umbilical cord in healthy hospitalized term neonates.

In high-income settings, there is limited research which has not shown an advantage of antibiotics or antiseptics over simply keeping the cord clean. Antimicrobial agent may actually delay the time to cord separation. On the contrary, there is high-quality evidence that chlorhexidine skin or cord care in the community setting results in reduction of the incidence of omphalitis and neonatal mortality.

Grade of recommendations: FRN

Stop

Medves JM, O'Brien BAC. Cleaning solutions and bacterial colonization in promoting healing and early separation of the umbilical cord in healthy newborns. *Can J Public Heal.* 1997;88(6):380-382. doi:9458563.

Sinha A, Sazawal S, Pradhan A, et al. Chlorhexidine skin or cord care for prevention of mortality and infections in neonates. *Cochrane database Syst Rev.* 2015;3(3):CD007835. doi:10.1002/14651858.CD007835.pub2.

Zupan J, Garner P, Aaa O. Topical umbilical cord care at birth. *Cochrane database Syst Rev.* 2004;(3). doi:10.1002/14651858.CD001057.

Imdad A, Bautista RMM, Senen KAA, et al. Umbilical cord antiseptics for preventing sepsis and death among newborns. *Cochrane database Syst Rev.* 2013;(5). doi:10.1002/14651858.CD008635.pub2.

All

Basic Management/Body Care

Antiseptics

Vaccination

Item 3

	Administer a dose of DTPa-IPV/Hib ± HBV and of pneumococcal vaccine at 60, 90 and 120 days of postnatal life to all hospitalized preterm neonates.
Start	Hospitalized preterm infants should receive immunisation against diphtheria, tetanus, pertussis (whooping cough), polio, Haemophilus influenzae type b and pneumococcal at 2, 3 and 4 months of postnatal age. Use the combined vaccine. Cardiorespiratory function should be monitored in unstable preterm infants for 48 hours following immunisation. In preterm neonates <33 weeks of gestational age who will be discharged before their 60th day of postnatal age, the first dose of DTPa-IPV/Hib and of pneumococcal vaccine should be advanced. In this case, the immunisation can be administered from the 50th day of postnatal life, followed by booster vaccination 1 and 2 month later.
	Grade of recommendations: National Guidelines
	Département de l'enfant et de l'adolescent - HUG. Cahier de l'interne. *Hôpitaux Univ Genève.* 2015;(Décembre). **Office fédéral de la santé publique, Commission fédérale pour les vaccinations, Société suisse de néonatologie, Société suisse de pédiatrie.** Vaccinations des enfants nés prématurément. *Directives et recommandations.* 2009. **Office fédéral de la santé publique, Commission fédérale pour les vaccinations.** Plan de vaccination suisse 2016. *Directives et recommandations.* 2016.
<37w GA	Basic Management/Vaccination

Item 4

	Recommend BCG vaccine at discharge to neonates at high risk of tuberculosis exposure in the first year of life.
Start	BCG vaccine is recommended only to newborns at risk of developing disseminated tuberculosis. Infants at risk are those who come from AND will return definitely to regions with high prevalence of tuberculosis (Africa, Asia, Latine America, Eastern Europe) before the age of 1 year of postnatal life. Short stays (vacation) in those regions are not an indication for immunisation.
	Grade of recommendations: National Guidelines
	Office fédéral de la santé publique, Commission fédérale pour les vaccinations, Société suisse de néonatologie, Société suisse de pédiatrie. Vaccinations des enfants nés prématurément. *Directives et recommandations.* 2009. **Office fédéral de la santé publique, Commission fédérale pour les vaccinations.** Plan de vaccination suisse 2016. *Directives et recommandations.* 2016.
All	Basic Management/Vaccination

Item 5

	Check / administer Pertussis vaccination to close contacts of neonates.
Start	Preterm infants are at high risks of pertussis. Booster vaccination is recommended to the mother (unless immunized during pregnancy), the father (unless the last booster dates less than 10 years), the siblings (unless up-to-date), the grand-parents and/or all those who will be in close contact to the neonate before the age of 4 months (i.e. reception of 2 vaccine doses).
	Grade of recommendations: National Guidelines
	Office fédéral de la santé publique, Commission fédérale pour les vaccinations. Plan de vaccination suisse 2016. *Directives et recommandations.* 2016.
All	Basic Management/Vaccination

Item 6

	Check status and recommend or administer vaccination to close contacts of neonates.
Start	**Pertussis:** booster vaccination is recommended to the mother (unless immunized during pregnancy), the father (unless the last booster dates less than 10 years), the siblings (unless up-to-date), the grand-parents and/or all those who will be in close contact to the neonate before the age of 4 months (i.e. reception of 2 vaccine doses). **Haemophilus inflenzae type b:** catch-up vaccination to brothers and sisters <5 years old. **Pneumococcal:** catch-up vaccination to brothers and sisters <5 years old. **Influenza:** immunisation for all members of the family circle during the two first winters. **ROR:** catch-up vaccination for all members of the family circle. **Varicella:** catch-up vaccination for all members of the family circle.
	Grade of recommendations: National Guidelines
	Office fédéral de la santé publique, Commission fédérale pour les vaccinations, Société suisse de néonatologie, Société suisse de pédiatrie. Vaccinations des enfants nés prématurément. *Directives et recommandations.* 2009.
	Office fédéral de la santé publique, Commission fédérale pour les vaccinations. Plan de vaccination suisse 2016. *Directives et recommandations.* 2016.
All	Basic Management/Vaccination

Parenteral Nutrition (PN)

Item 7

Start parenteral nutrition shortly after birth in all preterm neonates when it is clear that enteral feeds will not be tolerated soon.

Start

In the small preterm infant, starvation for just one day may be detrimental. Recommended volumes of parenteral nutrition:
<1500g BW (ml/kg/day) :
Day 1: Fluid 80-90 ml/kg/day
Day 2: Fluid 100-110 ml/kg/day
Day 3: Fluid 120-130 ml/kg/day
Day 4: Fluid 130-150 ml/kg/day
Day 5: Fluid 140-160 ml/kg/day
Day 6: Fluid 160-180 ml/kg/day
>1500g BW (ml/kg/day) :
Day 1: Fluid 60-80 ml/kg/day
Day 2: Fluid 80-100 ml/kg/day
Day 3: Fluid 100-120 ml/kg/day
Day 4: Fluid 120-150 ml/kg/day
Day 5: Fluid 140-160 ml/kg/day
Day 6: Fluid 140-160 ml/kg/day
Target parenteral energy intake (including protein) of stable patients may be roughly estimated as 110-120 kcal/kg for preterm infants. Energy intake should be adapted in patients with disease states that increase resting energy expenditure, such as pulmonary and cardiac disorders but should not be increased after uncomplicated surgery.

Grade of recommendations: International Guidelines

Koletzko B, Goulet O, Hunt J, et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr.* 2005;41(Suppl 2):S1-S4. doi:10.1097/01.mpg.0000181841.07090.f4.

Moyses HE, Johnson MJ, Leaf AA, Cornelius VR. Early parenteral nutrition and growth outcomes in preterm infants: A systematic review and meta-analysis. *Am J Clin Nutr.* 2013;97(4):816-826. doi:10.3945/ajcn.112.042028.

Ehrenkranz RA. Early, Aggressive Nutritional Management for Very Low Birth Weight Infants: What Is the Evidence? *Semin Perinatol.* 2007;31(2):48-55. doi:10.1053/j.semperi.2007.02.001.

<37w GA

Basic Management/Nutrition

Item 8

Start reducing the percentage of parenteral nutrition as quickly as possible by the introduction of enteral nutrition until enteral nutrition finally replaces completely PN in order to minimise any side-effects from exposure to PN.

Stop

Aim to reach full enteral feeding by about two weeks in babies weighing <1000 g at birth and by about one week in babies weighing 1000–1500g as clinically feasible.

Grade of recommendations: National Guidelines

Fusch C, Bauer K, Böhles HJ, et al. Neonatology/Paediatrics - Guidelines on Parenteral Nutrition, Chapter 13. *Ger Med Sci.* 2009;7:1-23. doi:10.3205/000074.

Dutta S, Singh B, Chessell L, et al. Guidelines for Feeding Very Low Birth Weight Infants. *Nutrients.* 2015;7:423-442. doi:10.3390/nu7010423.

<37w GA

Basic Management/Nutrition

Parenteral nutrition

Item 9

Start continuous parenteral glucose administration in preterm infants needing parenteral nutrition.

Start

An early start of parenteral glucose together with amino acids from the very first day onwards contributes to preventing hyperglycemia in premature infants. The recommended starting dose of glucose is 4-8 mg/kg/min (5.8-11.5 g/kg/day).
Recommended parenteral glucose supply in parenteral nutrition:
Neonates up to 3 kg : Day 1: 7 mg/kg/min (10 g/kg/day), Day 2: 9.7 mg/kg/min (14 g/kg/day), Day 3: 11.1 mg/kg/min (16 g/kg/day), Day 4: 12.5 mg/kg/min (18 g/kg/day).
Glucose intake should usually cover 60–75% of non-protein calories. These recommendations need to be adapted to the clinical situation to oral and/or enteral energy intake and to the required weight gain for normal or catch up growth. It is important, especially when prescribing PN for infants, to accurately evaluate the carbohydrate load provided by concurrent infusion therapy. An excessively high carbohydrate intake can result in net lipogenesis with hepatic fat deposition and steatosis of the liver.

Grade of recommendations: International Guidelines

Fusch C, Bauer K, Böhles HJ, et al. Neonatology/Paediatrics - Guidelines on Parenteral Nutrition, Chapter 13. *Ger Med Sci.* 2009;7:1-23. doi:10.3205/000074.

Koletzko B, Goulet O, Hunt J, et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr.* 2005;41(Suppl 2):S1-S4. doi:10.1097/01.mpg.0000181841.07090.f4.

Cai W. CSPEN guidelines for nutrition support in neonates. *Asia Pac J Clin Nutr.* 2013;22(4):655-663. doi:10.6133/apjcn.2013.22.4.21.

<37w GA

Basic Management/Nutrition

Parenteral nutrition

Item 10

	Start amino acid supply in the first day of life in preterm infant needing parenteral nutrition.
	Start with 1.5-2 g/kg/day and increase up to 3.5-4 g/kg/day. Amino acid imbalances can result in toxic organ damage and may be involved in the development of PN-associated cholestasis. Achieving an adequate energy to protein ratio is as important as providing adequate energy intake. Recommended non-protein energy to protein ratio depends on neonate age and weight and varies between 25 and 40 kcal/g of protein (≈150-250 kcal/g of nitrogen). If energy intake is insufficient, protein is used as an energy source, and the nitrogen balance becomes less positive. Increasing the caloric intake will spare the protein loss and improve nitrogen retention, but with limited protein intake, the protein retention reaches a plateau, and the energy excess is used solely for fat deposition.
Start	**Grade of recommendations: B**
	Cai W. CSPEN guidelines for nutrition support in neonates. *Asia Pac J Clin Nutr.* 2013;22(4):655-663. doi:10.6133/apjcn.2013.22.4.21.
	Koletzko B, Goulet O, Hunt J, et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr.* 2005;41(Suppl 2):S1-S4. doi:10.1097/01.mpg.0000181841.07090.f4.
	Fusch C, Bauer K, Böhles HJ, et al. Neonatology/Paediatrics - Guidelines on Parenteral Nutrition, Chapter 13. *Ger Med Sci.* 2009;7:1-23. doi:10.3205/000074.
	Ziegler EE. Meeting the nutritional needs of the low-birth-weight infant. *Ann Nutr Metab.* 2011;58(SUPPL. 1):8-18. doi:10.1159/000323381.
	Agostoni C, Buonocore G, Carnielli VP, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr.* 2010;50(1):85-91. doi:10.1097/MPG.0b013e3181adaee0.
	Rigo J, Senterre J. Nutritional needs of premature infants: Current Issues. *J Pediatr.* 2006;149(5):80-88. doi:10.1016/j.jpeds.2006.06.057.
	Tudehope D, Vento M, Bhutta Z, Pachi P. Nutritional requirements and feeding recommendations for small for gestational age infants. *J Pediatr.* 2013;162(3 SUPPL.):S81-S89. doi:10.1016/j.jpeds.2012.11.057.
<37w GA	Basic Management/Nutrition Parenteral nutrition

Item 11

Start continuous lipid emulsion infusion within the first 24-48 hours of life in preterm infant needing parenteral nutrition,

The initiation of lipids within the first 2 days of life in VLBW infants appears to be safe and well tolerated; however, beneficial effects on growth could not be shown for this treatment. Lipid intake should usually provide 25–40% of non-protein calories in fully parenterally fed patients. The recommended starting dose of lipid emulsions is 1-2 g/kg/day and is increased by 0.5-1.0 g/kg/day, up to 3 g/kg/day. No difference have been shown between the different lipid emulsion formulations. Reduction of the dosage of lipid emulsions should be considered if serum or plasma triglyceride concentrations during infusion exceed 250 mg/dL. In critically ill or infected patients receiving lipid emulsions, more frequent monitoring of plasma triglyceride concentration and dose adjustment in case of hyperlipidaemia are recommended. Lipid emulsions should be protected by validated light-protected tubing during phototherapy to decrease the formation of hydroperoxides.

Start

Grade of recommendations: B

Vlaardingerbroek H, Veldhorst MAB, Spronk S, et al. Parenteral lipid administration to very-low-birth-weight infants - Early introduction of lipids and use of new lipid emulsions: A systematic review and meta-analysis. *Am J Clin Nutr.* 2012;96(2):255-268. doi:10.3945/ajcn.112.040717.

Drenckpohl D, McConnell C, Gaffney S, et al. Randomized Trial of Very Low Birth Weight Infants Receiving Higher Rates of Infusion of Intravenous Fat Emulsions During the First Week of Life. *Pediatrics.* 2008;122(4):743-751. doi:10.1542/peds.2007-2282.

Cai W. CSPEN guidelines for nutrition support in neonates. *Asia Pac J Clin Nutr.* 2013;22(4):655-663. doi:10.6133/apjcn.2013.22.4.21.

Koletzko B, Goulet O, Hunt J, et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr.* 2005;41(Suppl 2):S1-S4. doi:10.1097/01.mpg.0000181841.07090.f4.

Hojsak I, Colomb V, Braegger C, et al. ESPGHAN Committee on Nutrition Position Paper. Intravenous Lipid Emulsions and Risk of Hepatotoxicity in Infants and Children: a Systematic Review and Meta-analysis. *J Pediatr Gastroenterol Nutr.* 2016;62(5):776-792. doi:10.1097/MPG.0000000000001121.

<37w GA

Basic Management/Nutrition

Parenteral nutrition

Item 12

Do not administer parenteral lipid emulsion at a dose higher than 3-4 g/kg/day in neonates.

Maximum lipid oxidation of 4 g/kg/day is reached in full-term neonates with a glucose intake below 18 g/kg/day. An increase in the concentration of plasma triglycerides is to be expected if the infusion speed of the lipid emulsions exceeds the speed of hydrolysis of the triglycerides.

Other

Grade of recommendations: B

Koletzko B, Goulet O, Hunt J, et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr.* 2005;41(Suppl 2):S1-S4. doi:10.1097/01.mpg.0000181841.07090.f4.

Fusch C, Bauer K, Böhles HJ, et al. Neonatology/Paediatrics - Guidelines on Parenteral Nutrition, Chapter 13. *Ger Med Sci.* 2009;7:1-23. doi:10.3205/000074.

All

Basic Management/Nutrition

Parenteral nutrition

Item 13

Check that a sufficient quantity of linoleic acid is administered in all neonates on parenteral nutrition.

In order to prevent Essential Fatty Acids (EFA) deficiency a minimum linoleic acid intake of 0.25 g/kg per day should be given to preterm infants and 0.1 g/kg per day to term neonates. Linoleic acid is contained in vegetal oils: soy oil (54%) and olive oil (10%). The appoximate linoleic acid content in existing lipid solutions on the swiss market are:
Lipofundin®: 29% of total lipids
Lipoplus®: 24% of total lipids
Omegaven®: 4% of total lipids
SMOFlipid®: 19% of total lipids.

Start

Grade of recommendations: D

Koletzko B, Goulet O, Hunt J, et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr.* 2005;41(Suppl 2):S1-S4. doi:10.1097/01.mpg.0000181841.07090.f4.

Fusch C, Bauer K, Böhles HJ, et al. Neonatology/Paediatrics - Guidelines on Parenteral Nutrition, Chapter 13. *Ger Med Sci.* 2009;7:1-23. doi:10.3205/000074.

Vlaardingerbroek H, Veldhorst MAB, Spronk S, et al. Parenteral lipid administration to very-low-birth-weight infants - Early introduction of lipids and use of new lipid emulsions: A systematic review and meta-analysis. *Am J Clin Nutr.* 2012;96(2):255-268. doi:10.3945/ajcn.112.040717.

All

Basic Management/Nutrition

Parenteral nutrition

Item 14

	Start electrolytes supplementation with parenteral nutrition after onset of diuresis.
	Recommended starting dose is sodium 2-3 mmol/kg/day, potassium 1-2 mmol/kg/day, calcium 0.6-0.8 mmol/kg/day, phosphates 1.0-1.2 mmol/kg/day and magnesium 0.3-0.4 mmol/kg/day.
Start	**Grade of recommendations: D**
	Cai W. CSPEN guidelines for nutrition support in neonates. *Asia Pac J Clin Nutr.* 2013;22(4):655-663. doi:10.6133/apjcn.2013.22.4.21.
	Koletzko B, Goulet O, Hunt J, et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr.* 2005;41(Suppl 2):S1-S4. doi:10.1097/01.mpg.0000181841.07090.f4.
All	Basic Management/Nutrition Parenteral nutrition

Item 15

	Start vitamins and trace elements supplementation in neonates receiving parenteral nutrition.
	The optimum time to begin with trace element supplementation in premature infants <1500 g birth weight is not clear. It is proposed to start supplementation on the 5th day of life to coincide with an increase in body weight. Vitamin preparations should, if possible, be administered together with the lipid emulsion in order to limit light-induced lipid peroxidation and vitamin loss. Parenteral zinc supply is recommended in daily dosages of 450–500 mg/kg per day for premature infants.
Start	
	Grade of recommendations: D
	Koletzko B, Goulet O, Hunt J, et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr.* 2005;41(Suppl 2):S1-S4. doi:10.1097/01.mpg.0000181841.07090.f4.
	Fusch C, Bauer K, Böhles HJ, et al. Neonatology/Paediatrics - Guidelines on Parenteral Nutrition, Chapter 13. *Ger Med Sci.* 2009;7:1-23. doi:10.3205/000074.
All	Basic Management/Nutrition Parenteral nutrition

Item 16

Start	**Start vitamin D supplementation from the first days of life in all neonates.** Recommended dose is 400 IU once daily during the first year of life and 600 IU once daily during the two next years. **Grade of recommendations: National Guidelines** **L'Allemand D, Neuhaus TJ, Janner M, et al.** Recommandations de l' Office fédéral de la santé publique concernant l ' apport en vitamine D en Suisse – quelle signification pour le pédiatre? *Paediatrica.* 2012;23(4):22-24.
All	Basic Management/Nutrition Parenteral nutrition

2. CARDIOLOGY
Congenital Heart Disease

Item 17

Start	**Start prostaglandin E1 (alprostadil) as an initial continuous intravenous infusion at 0.01 mcg/kg/min, until a definitive diagnosis is made in an infant suspected of having ductus-dependant heart disease.** **Grade of recommendations: A** **Donofrio MT, Moon-Grady AJ, Hornberger LK, et al.** Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. *Circulation*. 2014;129(21):2183-2242. doi:10.1161/01.cir.0000437597.44550.5d. **Eichenwald EC, Kim MS, Weisman LE.** Overview of cyanosis in the newborn. *UpToDate.com.* http://www.uptodate.com/contents/overview-of-cyanosis-in-the-newborn. Published 2014. Accessed March 10, 2016.
All	Cardiology/Congenital Heart Disease

Item 18

Stop	**Reassess the indication of prostaglandin E1 (PGE1) treatment.** Infants with Non Duct Dependent Lesions (Ventricular septal defect and others such as Atrioventricular canal defect) do not require PGE1 infusion. **Grade of recommendations: Institutional Guidelines** **Clinical Practice Committee.** Antenatally Diagnosed Major Congenital Heart Disease Management at Delivery and in NICU. *Newborn Services Clinical Guideline - Auckland District Health Board.* http://www.adhb.govt.nz/newborn/Guidelines/Cardiac/AntenatallyDiagnosedCHD.htm. Published 2013. Accessed March 3, 2016.
All	Cardiology/Congenital Heart Disease Prostaglandin E1 (PGE1)

Item 19

Stop	**Stop ibuprofen, indomethacin and paracetamol in patients with duct dependent congenital heart disease.** Ibuprofen, indomethacin or paracetamol must not be used in patients with congenital heart disease in whom patency of the ductus arteriosus is necessary for satisfactory pulmonary or systemic blood flow (e.g. pulmonary atresia, severe tetralogy of Fallot, severe coarctation of the aorta). **Grade of recommendations: Manufacturer** **Ovation Pharmaceuticals.** Product Information: Neoprofen(R) IV injection. *Micromedex - Truven Health Analytics Inc.* http://www.micromedexsolutions.com/. Published 2006. Accessed September 15, 2016. **Fresenius Kabi USA.** Product Information: Indomethacin IV injection. *Micromedex - Truven Health Analytics Inc.* http://www.micromedexsolutions.com/. Published 2014. Accessed September 15, 2016.
All	Cardiology/Congenital Heart Disease Ibuprofen, indomethacin, paracetamol

Patent Ductus Arteriosus (PDA)

Definition	**Confirmed patent ductus arteriorus (PDA)** Substantial ductal shunting may be associated with an increased ratio of left atrial to aortic root dimensions ≥1.5:1, ductal diameter ≥1.5 mm, left ventricular volume and pressure loading, and reversal of diastolic flow in the descending aorta or in cerebral or renal arteries. **Benitz WE.** Patent Ductus Arteriosus in Preterm Infants. *Pediatrics.* 2016;137(1):1-6.

Item 20

Start	**Consider pharmacological closure of confirmed patent ductus arteriosus (PDA) in preterm neonates after 2 weeks of life, with ibuprofen as first-line treatment.** Ibuprofen is as effective as indomethacin in closing a PDA and currently appears to be the drug of choice. Ibuprofen reduces the risk of NEC and transient renal insufficiency. Recommended dose is 10 mg/kg as the initial dose followed by 5 mg/kg 24 and 48 hours later. When possible, choose the enteral route for the administration of ibuprofen. **Grade of recommendations: FRN** **Ohlsson A, Walia R, Shah Sachin S.** Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. *Cochrane Database Syst Rev.* 2015;(2). doi:10.1002/14651858.CD003481.pub6. **Benitz WE.** Patent Ductus Arteriosus in Preterm Infants. *Pediatrics.* 2016;137(1):1-6.
<37w GA or <2500g BW	Cardiology/PDA

Item 21

Stop	**Reassess the indication of ibuprofen, indomethacin and paracetamol in preterm neonates <2 weeks of life with confirmed or unconfirmed patent ductus arteriosus (PDA).**
	The cumulative evidence supports the conclusion that early (in the first 2 weeks after birth), routine (as prophylaxis or for infants with echocardiographic confirmation of ductal patency with or without clinical signs) treatment to close the ductus arteriosus does not improve long-term outcomes for preterm infants.
	Grade of recommendations: National Guidelines
	Benitz WE. Patent Ductus Arteriosus in Preterm Infants. *Pediatrics.* 2016;137(1):1-6.
<37w GA	Cardiology/PDA Ibuprofen, indomethacin, paracetamol

Item 22

Stop	**Reassess the indication of ibuprofen, indomethacin and paracetamol in term neonates with patent ductus arteriosus (PDA).**
	In term neonates, inhibitors of prostaglandin synthesis are not effective for PDA closure, and thus are not recommended.
	Grade of recommendations: Textbook
	Doyle T, Kavanaugh-McHugh A, Soslow J, Hill K. Management of patent ductus arteriosus. *UpToDate.com.* http://www.uptodate.com/contents/management-of-patent-ductus-arteriosus. Published 2016. Accessed March 14, 2016.
>37w GA	Cardiology/PDA Ibuprofen, indomethacin, paracetamol

Item 23

Stop	**Do not use paracetamol as first-line treatment for patent ductus arteriosus (PDA) closure. Consider a switch to ibuprofen.**
	Paracetamol appears to be a promising new alternative to indomethacin and ibuprofen for the closure of a PDA with potentially fewer adverse effects. Additional studies testing this intervention with long-term follow-up are needed before paracetamol can be recommended as standard treatment for a PDA in preterm infants.
	Grade of recommendations: FRN
	Ohlsson A, Shah PS. Paracetamol (acetaminophen) for prevention or treatment of pain in newborns. *Cochrane Database Syst Rev.* 2015;(6). doi:10.1002/14651858.CD011219.pub2.
<34w GA or <2500g	Cardiology/PDA Paracetamol

Hypotension

Definition	**Hypotension** Hypotension is defined as a mean blood pressure (MBP) <30 mmHg or, during the first 3 days of postnatal life, a MBP with a number lower than the infant's gestational age in weeks. **Vargo L, Seri I.** The management of hypotension in the very-low-birth-weight infant: guideline for practice. *National Association of Neonatal Nurses.* 2011. **Subhedar Nimish V, Shaw NJ.** Dopamine versus dobutamine for hypotensive preterm infants. *Cochrane Database Syst Rev.* 2003;(3). doi:10.1002/14651858.CD001242.

Item 24

Stop	**Do not use volume expansion as first line treatment in VLBW infants (BW <1500g) with hypotension.** Hypotension in VLBW infants should be treated on the basis of the etiology of the hypotension, when an etiology is known. In general, the early use of volume expansion with normal saline solution, fresh frozen plasma, albumin, plasma substitute, or blood in VLBW infants with hypotension is not recommended. Evidence that VLBW infants with hypotension benefit from volume expansion is insufficent, as is the evidence to determine what type of volume expansion should be used in VLBW infants.The majority of VLBW infants who are hypotensive are not hypovolemic and have normal circulating blood volume. **Grade of recommendations: National Guidelines** **Dempsey, E. M.** Challenges in Treating Low Blood Pressure in Preterm Infants. *Children.* 2015;2(2), 272–288. doi:10.3390/children2020272 **Vargo L, Seri I.** The management of hypotension in the very-low-birth-weight infant: guideline for practice. *National Association of Neonatal Nurses.* 2011.
<1500g BW	Cardiology/hypotension Normal saline, fresh frozen plasma, albumin, plasma substitute, blood

Item 25

Start / Stop	**Consider a conservative approach (permissive hypotension) for the managment of VLBW infants (BW <1500g) if the clinical examination is satisfactory in the face of apparent hypotension** A careful clinical and biochemical assessment of a potentially hypotensive infant is an essential first step towards management. This should include: heart rate, capillary refill time, urine output, serum lactate concentration, pH, base excess and haemoglobin. If a pharmacological treatment is considered, dopamine can be a valid option for the sole treatment of hypotension. Hydrocortisone may be as effective as dopamine when used as a primary treatment for hypotension. Clinical trials are underway and could provide stronger recommendations in the near future to guide clinicians in the management of the hypotension of the VLBW neonate. **Grade of recommendations: FRN** **Dempsey, E. M.** Challenges in Treating Low Blood Pressure in Preterm Infants. *Children.* 2015;2(2), 272–288. doi:10.3390/children2020272 **Ibrahim H, Sinha IP, Subhedar NV.** Corticosteroids for treating hypotension in preterm infants. *Cochrane Database Syst. Rev.* 2011;12. doi:10.1002/14651858.CD003662.pub4. **Subhedar Nimish V, Shaw NJ.** Dopamine versus dobutamine for hypotensive preterm infants. *Cochrane Database Syst Rev.* 2003;(3). doi:10.1002/14651858.CD001242. **Paradisis M, Osborn DA.** Adrenaline for prevention of morbidity and mortality in preterm infants with cardiovascular compromise. *Cochrane Database Syst Rev.* 2004;1. doi:10.1002/14651858.CD003958.pub2. **Vargo L, Seri I.** The management of hypotension in the very-low-birth-weight infant: guideline for practice. *National Association of Neonatal Nurses.* 2011.
<1500g BW	Cardiology/hypotension

03. HEMATOLOGY

Anemia

Item 26

	Do not use routinely erythropoietin to limit exposure to blood transfusions in preterm neonates. The indication of treatment should be reassessed.
	Aside from research about its possible neuroprotective potential (EPO appears to be a promising drug in many conditions where neonatal brain injury occurs), there is little current justification for the use of erythropoietin in neonatal medicine, except in a few limited situations (for example to respect the views of parents who are Jehovah's witnesses).
Stop	**Grade of recommendations: A** **Ohlsson A, Sm A.** Early erythropoietin for preventing red blood cell transfusion in preterm and / or low birth weight infants (Review). *Cochrane Database Syst Rev.* 2014;(4). doi:10.1002/14651858.CD004863.pub4. **Sm A, Ohlsson A.** Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. *Cochrane Database Syst Rev.* 2014;(4). doi:10.1002/14651858.CD004868.pub4. **Canadian Paediatric Society Fetus and Newborn Committee, Lemyre B, Sample M, Lacaze-Masmonteil T.** Minimizing blood loss and the need for transfusions in very premature infants. *Paediatr Child Heal.* 2015;20(8):451-456. **Neonatal Formulary.** Erythropoietin. *Neonatal Formulary.* http://www.neonatalformulary.com/pdfs/commentary/ERYTHROPOIETIN-(commentary).pdf. Published 2014. Accessed July 12, 2016.
<37w GA	Hematology/Anemia OR Prevention/Anemia Erythropoietin (EPO)

Item 27

Start	**Start iron supplement of 2-3 mg/kg/day in all preterm infants fed human milk once full oral feeds have been achieved.** This is the amount of iron supplied by iron-fortified formulas and infant fed with preterm formula do not need supplementation. Preterm infants fed human milk should receive an iron supplement of 2-3 mg/kg/day starting once full enteral feed have been achieved and continued until the infant is weaned to iron-fortified formula or begins eating complementary foods that supply the 2 mg/kg of iron. An exception to this practice would include infants who have received an iron load from multiple transfusions of packed red blood cells. Term healthy infants have sufficient iron for at least the first 4 months of life and should not receive iron supplementation. Supplementation with 4-6 mg/kg/day can be considered in newborns who are iron deficient. The available data suggest that infants who receive iron supplementation have a slightly higher haemoglobin level, improved iron stores and a lower risk of developing iron deficiency anaemia when compared with those who are unsupplemented. However, it is unclear whether iron supplementation in preterm and low birth weight infants has long term benefits in terms of neurodevelopmental outcome and growth. **Grade of recommendations: National Guidelines** **Baker RD, Greer FR, American Academy of Pediatrics.** Diagnosis and Prevention of Iron Deficiency and Iron-Deficiency Anemia in Infants and Young Children (0−3 Years of Age). *Pediatrics.* 2010;126(5):1040-1050. doi:10.1542/peds.2010-2576. **Mills RJ, Davies MW.** Enteral iron supplementation in preterm and low birth weight infants. *Cochrane Database Syst Rev.* 2012;(3):CD005095. doi:10.1002/14651858.CD005095.pub2. **Canadian Paediatric Society Fetus and Newborn Committee, Lemyre B, Sample M, Lacaze-Masmonteil T.** Minimizing blood loss and the need for transfusions in very premature infants. *Paediatr Child Heal.* 2015;20(8):451-456.
<37w GA	Hematology/Anemia OR Prevention/Anemia

Coagulation disorders

Item 28

Start	**Start oral Vitamin K in neonates breastfed by a mother treated with phenprocoumone.** Breastfed infants from mothers treated with phenprocoumone should receive oral vitamin K (phytomenadione) 1mg once a week. This doesn't apply if the mother is treated with acenocoumarol because of the short elimination half life of this drug. **Grade of recommendations: National Guidelines** **Schubiger G, Laubscher B, Bänziger O, Société Suisse de Néonatologie, Commission de nutrition de la Société suisse de pédiatrie, Société suisse de gynécologie et obstétrique.** Prophylaxie à la vitamine K chez le nouveau-né : nouvelles recommandations. *Swiss Soc Neonatol.* 2003.
All	Hematology/Coagulation disorders

Item 29

	Check in all neonates that a complete Vitamin K prophylaxis has been given at birth.
Start	Adequate prophylaxis depends on clinical context and gestational age: healthy neonates >34 weeks of gestational age; >2000g birthweight: 4 hours after birth: 2 mg of oral phytomenadione 4 days after birth: 2 mg of oral phytomenadione 4 weeks after birth: 2 mg of oral phytomenadione ill neonates / preterms with infusion / nil by mouth neonates: 4 hours after birth: 0.5 mg of IV/IM phytomenadione 4 weeks after birth: 2 mg of oral phytomenadione
	Grade of recommendations: National Guidelines **Schubiger G, Laubscher B, Bänziger O, Société Suisse de Néonatologie, Commission de nutrition de la Société suisse de pédiatrie, Société suisse de gynécologie et obstétrique.** Prophylaxie à la vitamine K chez le nouveau-né : nouvelles recommandations. *Swiss Soc Neonatol.* 2003.
All	Hematology/Coagulation disorders OR Prevention/Coagulation disorders

Thrombocytopenia and Platelet Dysfunction

Definition	**Risk factors for major bleeding in infant with thrombocytopenia:** - <1000g and <7 days - Clinically unstable (e.g. fluctuating BP) - Previous major bleeding (e.g. Grade 3-4 IVH, pulmonary haemorrhage) - Current minor bleeding - Concurrent coagulopathy - Requiring surgery or exchange transfusion **Roberts I, Murray N.** Neonatal thrombocytopenia: causes and management. *Arch Dis Child - Fetal Neonatal Ed.* 2003;88(5):359F-364. doi:10.1136/fn.88.5.F359. **Clinical Practice Committee.** Neonatal Thrombocytopenia. *Newborn Services Clinical Guideline - Auckland District Health Board.* http://www.adhb.govt.nz/newborn/Guidelines/Blood/Platelets/NeonatalThrombocytopenia.htm. Published 2016. Accessed July 15, 2016.

Item 30

Consider platelets transfusion even in the absence of bleeding in all neonates with a platelet count of <30x10^9/L.

The recommended volume of platelets to be transfused is 10-20 mL/kg. Transfuse over 30 minutes and monitor platelet count one hour post transfusion.
In neonates receiving platelet transfusion, the administered platelet type should be:
- Human platelet antigen (HPA) compatible platelets for neonates with neonatal allo-immune thrombocytopenia (NAIT), except in emergency situations in order to avoid delays to platelet transfusion; in that case, consider IV immunoglobulin (IVIG) (1-2 g/kg) in combination with the unmatched platelets.
- Blood group-compatible, cytomegalovirus (CMV) negative for all other infants.
- Irradiation of platelets is not routinely required but consider for babies with definite or suspected immunodeficiency or those who have undergone intrauterine transfusions.

Start

Grade of recommendations: Institutional Guidelines

Roberts I, Murray N. Neonatal thrombocytopenia: causes and management. *Arch Dis Child - Fetal Neonatal Ed.* 2003;88(5):359F-364. doi:10.1136/fn.88.5.F359.

Clinical Practice Committee. Neonatal Thrombocytopenia. *Newborn Services Clinical Guideline - Auckland District Health Board.* http://www.adhb.govt.nz/newborn/Guidelines/Blood/Platelets/NeonatalThrombocytopenia.htm. Published 2016. Accessed July 15, 2016.

The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network. Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.

All

Hematology/Thrombocytopenia and Platelet Dysfunction

Item 31

Consider platelets transfusion in neonates with a platelet count of 30-49x10^9/L and minor bleeding or those at risk for major bleeding.

The recommended volume of platelets to be transfused is 10-20 mL/kg. Transfuse over 30 minutes and monitor platelet count one hour post transfusion.
In neonates receiving platelet transfusion, the administered platelet type should be:
- Human platelet antigen (HPA) compatible platelets for neonates with neonatal allo-immune thrombocytopenia (NAIT), except in emergency situations in order to avoid delays to platelet transfusion; in that case, consider IV immunoglobulin (IVIG) (1-2 g/kg) in combination with the unmatched platelets.
- Blood group-compatible, cytomegalovirus (CMV) negative for all other infants.
- Irradiation of platelets is not routinely required but consider for babies with definite or suspected immunodeficiency or those who have undergone intrauterine transfusions.

Start

Grade of recommendations: Institutional Guidelines

Roberts I, Murray N. Neonatal thrombocytopenia: causes and management. *Arch Dis Child - Fetal Neonatal Ed.* 2003;88(5):359F-364. doi:10.1136/fn.88.5.F359.

Clinical Practice Committee. Neonatal Thrombocytopenia. *Newborn Services Clinical Guideline - Auckland District Health Board.* http://www.adhb.govt.nz/newborn/Guidelines/Blood/Platelets/NeonatalThrombocytopenia.htm. Published 2016. Accessed July 15, 2016.

Health.vic. Thrombocytopenia in neonates. *Victoria State Government.* https://www2.health.vic.gov.au:443/hospitals?and?health?services/patient?care/perinatal? reproductive/neonatal?ehandbook/conditions/thrombocytopenia. Published 2015. Accessed July 18, 2016.

The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network. Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.

All

Hematology/Thrombocytopenia and Platelet Dysfunction

Item 32

Consider platelets transfusion in neonates with a platelet of count 50-99x10^9/L only if bleeding is present.

The recommended volume of platelets to be transfused is 10-20 mL/kg. Transfuse over 30 minutes and monitor platelet count one hour post transfusion.
In neonates receiving platelet transfusion, the administered platelet type should be:
- Human platelet antigen (HPA) compatible platelets for neonates with neonatal allo-immune thrombocytopenia (NAIT), except in emergency situations in order to avoid delays to platelet transfusion; in that case, consider IV immunoglobulin (IVIG) (1-2 g/kg) in combination with the unmatched platelets.
- Blood group-compatible, cytomegalovirus (CMV) negative for all other infants.
- Irradiation of platelets is not routinely required but consider for babies with definite or suspected immunodeficiency or those who have undergone intrauterine transfusions.

Start

Grade of recommendations: Institutional Guidelines

Roberts I, Murray N. Neonatal thrombocytopenia: causes and management. *Arch Dis Child - Fetal Neonatal Ed.* 2003;88(5):359F-364. doi:10.1136/fn.88.5.F359.

Clinical Practice Committee. Neonatal Thrombocytopenia. *Newborn Services Clinical Guideline - Auckland District Health Board.* http://www.adhb.govt.nz/newborn/Guidelines/Blood/Platelets/NeonatalThrombocytopenia.htm. Published 2016. Accessed July 15, 2016.

The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network. Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.

All — Hematology/Thrombocytopenia and Platelet Dysfunction

Item 33

Do not transfuse neonates with mild thrombocytopenia (platelet count 100-150x10^9/L) even if bleeding.

Grade of recommendations: Review

Roberts I, Murray N. Neonatal thrombocytopenia: causes and management. *Arch Dis Child - Fetal Neonatal Ed.* 2003;88(5):359F-364. doi:10.1136/fn.88.5.F359.

Stop

Clinical Practice Committee. Neonatal Thrombocytopenia. *Newborn Services Clinical Guideline - Auckland District Health Board.* http://www.adhb.govt.nz/newborn/Guidelines/Blood/Platelets/NeonatalThrombocytopenia.htm. Published 2016. Accessed July 15, 2016.

The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network. Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.

All — Hematology/Thrombocytopenia and Platelet Dysfunction

Item 34

Start / Stop	**Start intravenous immunoglobulin (IVIG) only in case of severe thrombocytopenia (platelet count of <50x109/L) or if bleeding persists despite compatible platelets transfusion or in combination with unmatched platelets transfusion in neonates with neonatal allo-immune thrombocytopenia (NAIT).** Recommended dose of IVIG is 1 g/kg, which can be repeated 24h after if thrombocytopenia persists. **Grade of recommendations: Institutional Guidelines** **The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network.** Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016. **Peterson J, McFarland J, Curtis BR, Aster R.** Neonatal alloimmune thrombocytopenia: pathogenesis, diagnosis and management. *Br J Haematol.* 2013;161(1):3-14. doi:10.1111/bjh.12235. **Neonatal Formulary.** Immunoglobulin. *Neonatal Formulary.* http://www.neonatalformulary.com/pdfs/commentary/IMMUNOGLOBULIN-(commentary).pdf. Published 2014. Accessed July 19, 2016.
All	Hematology/Thrombocytopenia and Platelet Dysfunction

Item 35

Start	**Start intravenous immunoglobulin (IVIG) as first line treatment in neonates with neonatal auto-immune thrombocytopenia and born to mothers who have idiopathic thrombocytopenic purpura (ITP), when platelet count is of <30x109/L or clinical bleeding is present.** Recommended dose of IVIG is 1g/kg. Platelets transfusions are less likely to be effective and should be used as an adjuvant treatment for those who exhibit severe bleeding. **Grade of recommendations: Institutional Guidelines** **The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network.** Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016. **Wong W, Glader B.** Approach to the newborn who has thrombocytopenia. Neoreviews. 2004;5(10). doi:10.1542/neo.5-10-e444.
All	Hematology/Thrombocytopenia and Platelet Dysfunction

Vasospasms and Thromboembolism

Item 36

	Start unfractionned heparin or low molecular weight heparin in neonates with a first event venous thromboembolism for at least 5 days.
Start	Unfractionned heparin: 75 units/kg IV over 10 minutes, followed by 28 units/kg per hour continuous infusion. Four hours after initiating therapy, measure aPTT, then adjust dose to achieve an aPTT that corresponds to an anti-factor Xa level of 0.35 to 0.7 (this is usually equivalent to an aPTT of 60 to 85 seconds). Treatment should be limited to 10 to 14 days. Some experts recommend switching to low molecular weight heparin after 3 to 5 days. For renal vein thrombosis requiring treatment, 6 weeks to 3 months of heparin/low molecular weight heparin therapy is recommended. Low molecular weight heparin: Eg: Enoxaparine: Term infants: initial, 1.7 mg/kg per dose subcutaneous every 12 hours. Preterm infants: initial, 2 mg/kg per dose subcutaneous every 12 hours. Adjust dosage to maintain anti-factor Xa level between 0.5 and 1.0 unit/mL. It will usually take several days to attain levels in the target range. Dosage requirements to maintain target anti-factor Xa levels in preterm infants are quite variable, ranging from 0.8 to 3 mg/kg every 12 hours.
	Grade of recommendations: National Guidelines
	Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest.* 2012;141(2 SUPPL.):e737S–e801S. doi:10.1378/chest.11-2308. **Neofax.** Heparin. *Micromedex.* http://neofax.micromedexsolutions.com/. Published 2016. Accessed July 21, 2016. **Neofax.** Enoxaparin. *Micromedex.* http://neofax.micromedexsolutions.com/. Published 2016. Accessed July 21, 2016.
All	Hematology/Vasospasms and Thromboembolism

Item 37

	Start alteplase or urokinase only in case of major vessel occlusion causing critical compromise of organs or limbs in infants with venous thromboembolism.
Start / stop	If thrombolysis is required, tissue plasminogen activator (tPA) (alteplase) or urokinase can be used, and plasminogen (fresh frozen plasma [FFP]) administration is suggested prior to start therapy. Alteplase recommended doses for dissolution of intravascular thrombi: 200 mcg/kg per hour (0.2 mg/kg per hour). Duration of therapy is 6 to 48 hours. If administering directly into the thrombus, dose may be increased after 6 hours to a maximum of 500 mcg/kg per hour. If localized bleeding occurs, stop infusion for 1 hour and restart using 100 mcg/kg per hour. Discontinue heparin several hours prior to initiation of therapy. Use urokinase as follows: try a dose of 5000 unit/kg an hour, and consider increasing the dose two- or even four-fold if blood flow does not improve within 8 hours.
	Grade of recommendations: National Guidelines **Monagle P, Chan AKC, Goldenberg NA, et al.** Antithrombotic therapy in neonates and children: Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest.* 2012;141(2 SUPPL.):e737S–e801S. doi:10.1378/chest.11-2308.
All	Hematology/Vasospasms and Thromboembolism

4. PNEUMOLOGY

Definition	**Oxygen saturation targets** **The lowest oxygen saturation level recommended to commence oxygen therapy:** <u><36 weeks GA:</u> commence oxygen when saturations fall below 90% in ambiant air <u>≥36 weeks GA:</u> commence oxygen when saturations fall below 93% in ambiant air **Target oxygen saturations and alarm limits for babies needing supplemental oxygen:** <u><36 weeks GA:</u> 90-94% <u>≥36 weeks GA:</u> 93-97% (except infants with Persistent Pulmonary Hypertention of the Newborn: ≥95%). **Austin N, Newborn Clinical Network.** Practice recommendation for Oxygen saturation targets for newborns cared for in neonatal units, New Zealand. *The Paeditric Society New Zealand & The National Child & Youth Clinical Network.* 2015.. 2015.

Pneumothorax

Definition	**Primary pneumothorax:** pneumothorax without any obvious lung diseases. **Spontaneous pneumothorax (SP)** is a form of primary pneumothorax in neonates. It usually occurs in the absence of inciting risk factors at birth. **Shaireen H, Rabi Y, Metcalfe A, et al.** Impact of oxygen concentration on time to resolution of spontaneous pneumothorax in term infants: a population based cohort study. *BMC Pediatr.* 2014;14(1):1-8. doi:10.1186/1471-2431-14-208.

Item 38

Stop	**Do not use routine supplemental oxygen use in infants with spontaneous pneumothorax.** In infants with pneumothorax and respiratory distress, oxygen supplementation should be provided as needed to maintain adequate saturation. The rate of recovery for spontaneous pneumothoraces is not improved with oxygen supplementation or nitrogen washout (60 to 100% inspired O2 concentration) which expose infants to the risks of hyperoxia. **Grade of recommendations: Cohort Study** **Shaireen H, Rabi Y, Metcalfe A, et al.** Impact of oxygen concentration on time to resolution of spontaneous pneumothorax in term infants: a population based cohort study. *BMC Pediatr.* 2014;14(1):1-8. doi:10.1186/1471-2431-14-208. **Austin N, Newborn Clinical Network.** Practice recommendation for Oxygen saturation targets for newborns cared for in neonatal units, New Zealand. *The Paeditric Society New Zealand & The National Child & Youth Clinical Network.* 2015.. 2015.
≥37w GA	Pneumology/Pneumothorax Oxygen, nitrogen

Apnea of Prematurity

Definition	**Clinically significant apnea of prematurity** Apnea is a cessation of breathing for 20 seconds or longer or a shorter pause accompanied by bradycardia (<100 beats per minute), cyanosis, or pallor. **Eichenwald EC, American Academy of Pediatrics Committee on Fetus and Newborn.** Apnea of prematurity. *Pediatrics.* 2016;137(1):1-7.

Item 39

Start	**Start caffeine citrate in patients with apnea of prematurity (loading dose 20 mg/kg; maintenance dose 5mg/kg/day). Dose may be increased to 10 mg/kg/day if apnea persists.** Caffeine citrate is a safe and effective treatment of apnea of prematurity and improves neurodevelopmental outcomes at 2 years of age. When caffeine is not available, use theophylline treatment at a 5-6 mg/kg loading dose and 2-6 mg/kg/day maintenance dose, divided every 8-12h. 2mg of caffeine citrate contains 1 mg of caffeine. **Grade of recommendations: Randomized Controlled Trial** **Eichenwald EC, American Academy of Pediatrics Committee on Fetus and Newborn.** Apnea of prematurity. *Pediatrics.* 2016;137(1):1-7. **Schmidt B, Roberts RS, Davis P, et al.** Caffeine Therapy for Apnea of Prematurity. *The New England Journal of Medicine.* 2006;354(20):2112–2121. **Schmidt B, Roberts RS, Davis P, et al.** Long-Term Effects of Caffeine Therapy for Apnea of Prematurity. *New England Journal of Medicine.* 2007;357(19):1893–1902. https://doi.org/10.1056/NEJMoa073679 **Schmidt B, Anderson PJ, Doyle LW, et al.** Survival Without Disability to Age 5 Years for Apnea of Prematurity. *Jama.* 2012;307(3):275–282. https://doi.org/10.1001/jama.2011.2024 **Henderson-Smart David J, Steer Peter A.** Caffeine versus theophylline for apnea in preterm infants. *Cochrane Database Syst Rev.* 2010;(1). doi:10.1002/14651858.CD000273.pub2.
<37w GA	Pneumology/Apnea

Item 40

Stop	**Reassess the need for caffeine citrate treatment.** Timely discontinuation of methylxanthines is advised to avoid unnecessary delays in discharge. A clinically significant apnea event–free period before discharge of 7 days is recommended after methylxanthine discontinuation, although a longer period may be suitable for infants born at less than 26 weeks' gestation. **Grade of recommendations: National Guidelines** **Eichenwald EC, American Academy of Pediatrics Committee on Fetus and Newborn.** Apnea of prematurity. *Pediatrics.* 2016;137(1):1-7. **Doyle J, Davidson D, Katz S, et al.** Apnea of prematurity and caffeine pharmacokinetics: potential impact on hospital discharge. *J Perinat.* 2016;36:141-144. doi:10.1038/jp.2015.167.
<37w GA	Pneumology/Apnea Caffeine citrate

Item 41

	Reassess the indication of anti-gastroesophageal reflux therapy in neonates with apnea.
Stop	Evidence suggests that gastroesophageal reflux (GER) is not associated with apnea of prematurity, and treatment of presumed or proven GER solely for the reduction in apnea events is not supported by currently available evidence.
	Grade of recommendations: National Guidelines
	Eichenwald EC, American Academy of Pediatrics Committee on Fetus and Newborn. Apnea of prematurity. *Pediatrics.* 2016;137(1):1-7.
<37w GA	Pneumology/Apnea Esomeprazole, Omeprazole

Bronchopulmonary Dysplasia (BPD)

Definition

Bronchopulmonary Dysplasia (BPD)

Gestational Age	< 32 wk	≥ 32 wk
Time point of assessment	36 wk PMA or discharge to home, whichever comes first	> 28d but < 56d postnatal age or discharge to home, whichever comes first
	Treatment with oxygen > 21% for at least 28 d plus	
Mild BPD	Breathing room air at 36 wk PMA or discharge, whichever comes first	Breathing room air by 56d postnatal age or discharge, whichever comes first
Moderate BPD	Need for 30% oxygen at 36 wk PMA or discharge, whichever comes first	Need for 30% oxygen at 56 d postnatal age or discharge, whichever comes first
Severe BPD	Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 wk PMA or discharge, whichever comes first	Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56d postnatal age or discharge, whichever comes first

Definition of abbreviations: BPD = bronchopulmonary dysplasia; NCPAP = nasal continuous positive airway pressure; PMA = postmenstrual age; PPV = positive-pressure ventilation

BPD usually develops in neonates being treated with oxygen and positive pressure ventilation for respiratory failure, most commonly respiratory distress syndrome. Persistence of clinical features of respiratory disease (tachypnea, retractions, rales) are considered common to the broad description of BPD and have not been included in the diagnostic criteria describing the severity of BPD. Infants treated with oxygen > 21% and/or positive pressure for nonrespiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung disease and exhibit clinical features of respiratory distress. A day of treatment with oxygen > 21% means that the infant received oxygne > 21% for more than 12 h on that day. Treatment with oxygen > 21% and/or positive pressure at 36 wk PMA, or at 56 d postnatal age or discharge, should not reflect an “acute” event, but should rather reflect the infant’s usual daily therapy for several days preceding and following 36 wk PMA, 56 d postnatal age, or discharge.

Jobe A, Bancalari E. Bronchopulmonary Dysplasia. *Am J Respir Crit Care Med.* 2001;163(7):1723-1729. doi:10.1164/ajrccm.163.7.2011060.

Item 42

	Do not use dexamethasone in the prevention or the treatment of bronchopulmonary dysplasia.
Stop	Administering high-dose dexamethasone to prevent or treat chronic lung disease (CLD) is not recommended. The routine use of low-dose dexamethasone for all infants who require assisted ventilation after seven days of age to prevent or treat CLD is not recommended.
	Grade of recommendations: National Guidelines
	Jefferies A, Canadian Paediatric Society. Treat of prevent chronic lung disease in preterm infants. *Paediatr Child Health.* 2012;17(10):573.
<37w GA	Pneumology/BPD AND Pneumology/Prevention of BPD OR Prevention/Prevention of BPD Dexamethasone

Item 43

	Do not use loop diuretics for prevention of BPD in preterm neonates.
Stop	Current evidence does not support the use of loop diuretics for prevention of BPD.
	Grade of recommendations: Review
	Tropea K, Christou H. Current pharmacologic approaches for prevention and treatment of bronchopulmonary dysplasia. *Int J Pediatr.* 2012;2012:598606. doi:10.1155/2012/598606.
All	Pneumology/Prevention of BPD OR Prevention/Prevention of BPD Furosemide, torasemide

Item 44

	Do not use thiazid diuretics for prevention of BPD in preterm neonates. Use them judiciously for treatment of BPD in preterm neonates.
Stop	No clear evidence is present for use of thiazide diuretics for the prevention or management of BPD. In patient with BPD, thiazide and spironolactone were shown to decreased oxygen requirement and improved lung function in the treatment group compared to placebo but failed to show any improvement in the survival rate, duration of oxygen requirement, or length of hospital stay.
	Grade of recommendations: Review
	Tropea K, Christou H. Current pharmacologic approaches for prevention and treatment of bronchopulmonary dysplasia. *Int J Pediatr.* 2012;2012:598606. doi:10.1155/2012/598606.
<37w GA	Pneumology/BPD AND Pneumology/Prevention of BPD OR Prevention/Prevention of BPD Hydrochlorthiazid, chlorthalidone, spironolactone

Respiratory Distress Syndrome (= Hyaline Membrane Disease)

Definition	**Respiratory Distress Syndrome (RDS)** PaO_2 <50 mmHg (<6.6 kPa) in room air, central cyanosis in room air or need for supplemental oxygen to maintain PaO_2 >50 mmHg (>6.6 kPa), as well as the classical chest X-ray appearances. **Sweet DG, Carnielli V, Greisen G, et al.** European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants-2013 update. *Neonatology.* 2013;103(4):353-368.

Item 45

Start	**Start surfactant therapy in infants born <26 weeks of gestational age who need FiO2 >0.30.** In infants born <26 weeks of gestational age who need FiO2 >0.30, porcine-derived surfactant poractant alpha therapy is recommended at a dose of 200 mg/kg. In infants with signs of persistant RDS and respiratory support, give 100 mg/kg 6-12 hours after the first dose and 12 hours after the second dose. Maximum dose is 400 mg/kg. Administering more than three doses of surfactant has not shown to have a benefit. **Grade of recommendations: International Guidelines** **Sakonidou S, Dhaliwal J.** The management of neonatal respiratory distress syndrome in preterm infants (European Consensus Guidelines—2013 update). *Arch Dis Child - Educ Pract Ed.* 2015;100(5):257-259. doi:10.1136/archdischild-2014-306642. **Davis DJ, Barrington KJ, Canadian Paediatric Society.** Recommendations for neonatal surfactant therapy. *Paediatr Child Health (Oxford)*. 2015;10(2):109-116.
<26w GA	Pneumology/RDS

Item 46

Start	**Start surfactant therapy in infants born ≥26 weeks of gestational age who need FiO2 >0.40.** In infants born ≥26 weeks of gestational age who need FiO2 >0.40, porcine-derived surfactant poractant alpha therapy is recommended at a dose of 200mg/kg. In infant with signs of persistant RDS and respiratory support, give 100 mg/kg 6-12 hours after the first dose and 12 hours after the 2nd dose. Maximum dose is 400 mg/kg. Administering more than three doses of surfactant has not shown to have a benefit. **Grade of recommendations: International Guidelines** **Sakonidou S, Dhaliwal J.** The management of neonatal respiratory distress syndrome in preterm infants (European Consensus Guidelines—2013 update). *Arch Dis Child - Educ Pract Ed.* 2015;100(5):257-259. doi:10.1136/archdischild-2014-306642. **Davis DJ, Barrington KJ, Canadian Paediatric Society.** Recommendations for neonatal surfactant therapy. *Paediatr Child Health (Oxford)*. 2015;10(2):109-116.
≥26w GA	Pneumology/RDS

Meconium Aspiration Syndrome

Definition	**Meconium Aspiration Syndrome (MAS)** Presence of respiratory distress and chest X-ray changes, not explained by other pathology, where there has been meconium stained amniotic fluid prior to delivery. **Stenson BJ, Smith CL.** Management of meconium aspiration syndrome. *Paediatr Child Heal (United Kingdom).* 2012;22(12):532-535. doi:10.1016/j.paed.2012.08.015.

Item 47

Start	**Consider inhaled nitric oxide (iNO) in neonates with hypoxic respiratory failure due to MAS.** For hypoxic respiratory failure due to MAS, infants responded well to combined iNO and high frequency ventilation treatment in comparison to either iNO or high frequency ventilation. **Grade of recommendations: Review** **Swarnam K, Soraisham AS, Sivanandan S.** Advances in the Management of Meconium Aspiration Syndrome. *Int J Pediatr.* 2012;2012:1-7. doi:10.1155/2012/359571.
All	Pneumology/MAS

Item 48

Stop	**Reassess the indication for antibiotics in patients with MAS alone.** Prophylactic use of antibiotics in meconium aspiration syndrome is not recommended unless there is an identified risk of infection. **Grade of recommendations: Review** **Swarnam K, Soraisham AS, Sivanandan S.** Advances in the Management of Meconium Aspiration Syndrome. *Int J Pediatr.* 2012;2012:1-7. doi:10.1155/2012/359571.
All	Pneumology/MAS Antibiotics

Item 49

	Administer a bolus instillation of surfactant in intubated infants with MAS requiring more than 50% oxygen.
	In infants with MAS, surfactant administration may reduce the severity of respiratory illness and decrease the number of infants with progressive respiratory failure requiring support with extracorporeal membrane oxygenation (ECMO) (A). At the time of review, more trials are needed to evaluate the place of diluted surfactant as lavage therapy in MAS, and no recommendation can be made (FRN).
Start	**Grade of recommendations: A** **Davis DJ, Barrington KJ, Canadian Paediatric Society.** Recommendations for neonatal surfactant therapy. *Paediatr Child Health (Oxford)*. 2015;10(2):109-116. **El Shahed A, Dargaville PA, Ohlsson A, Soll R.** Surfactant for meconium aspiration syndrome in term and late preterm infants. *Cochrane Database Syst Rev.* 2014;(12). doi:10.1002/14651858.CD002054.pub3. **Hahn S, Choi HJ, Soll R, Dargaville PA.** Lung lavage for meconium aspiration syndrome in newborn infants. *Cochrane Database Syst Rev.* 2013;(4):CD003486. doi:10.1002/14651858.CD003486.pub2.
All	Pneumology/MAS

Persistent Pulmonary Hypertension of the Newborn (PPHN)

Definition	**Persistent Pulmonary Hypertension of the Newborn (PPHN)** Elevated pulmonary vascular resistance and right-left shunt through the ductus arteriosus and/or foramen ovale, and absence of congenital heart abnormalities, demonstrated by echocardiography. **Severe PPHN** PPHN with a oxygenation index ≥25. **Cabral JEB, Belik J.** Persistent pulmonary hypertension of the newborn: Recent advances in pathophysiology and treatment. *J Pediatr (Rio J).* 2013;89(3):226-242. doi:10.1016/j.jped.2012.11.009. **Adams JM, Stark AR.** Persistent pulmonary hypertension of the newborn. *UpToDate.com.* http://www.uptodate.com/contents/persistent-pulmonary-hypertension-of-the-newborn. Published 2013. Accessed April 1, 2016.

Item 50

Start	**Start inhaled nitric oxide (iNO) in neonates who have severe PPHN.** Inhaled nitric oxide (iNO) is indicated to reduce the need for extracorporeal membrane oxygenation (ECMO) support in term and near-term infants with severe PPHN. Currently, **the initial recommended concentration of iNO is 20 ppm.** Using higher concentrations is not anymore effective, and is associated with a higher incidence of methemoglobinemia and formation of nitrogen dioxide (D). Once oxygenation improves, iNO can usually be weaned relatively rapidly to 5 ppm, and discontinued within 5 days. It should be weaned gradually in steps to the lowest dose possible for a period before discontinuation (D). **Grade of recommendations: A** **American Heart Association, American Thoracic Society, Abman SH, et al.** Pediatric pulmonary hypertension. *Circulation.* 2015;132:2037-2099. doi:10.1161/CIR.0000000000000329. **Cabral JEB, Belik J.** Persistent pulmonary hypertension of the newborn: Recent advances in pathophysiology and treatment. *J Pediatr (Rio J).* 2013;89(3):226-242. doi:10.1016/j.jped.2012.11.009.
All	Pneumology/PPHN

Item 51

Stop	**Do not use sildenafil as initial therapy for PPHN.** Sildenafil is not recommended as initial therapy for PPHN when inhaled nitric oxyde is available. Sildenafil can be used as adjunctive therapy for infants with PPHN who are refractory to iNO or to attenuate rebound pulmonary hypertension after iNO withdrawal or to shorten the time to extubation. **Grade of recommendations: FRN** **Shah PS, Ohlsson A.** Sildenafil for pulmonary hypertension in neonates. *Cochrane database Syst Rev.* 2011;(8). doi:10.1002/14651858.CD005494.pub3. **American Heart Association, American Thoracic Society, Abman SH, et al.** Pediatric pulmonary hypertension. *Circulation.* 2015;132:2037-2099. doi:10.1161/CIR.0000000000000329.
All	Pneumology/PPHN

Definition

Definition of acute kidney injury (AKI)

Stage	Serum Creatinine (SCr)
0	No change in SCr or rise <0.3 mg/dL
1	1.5–1.9 times reference SCr (lowest previous SCr value) OR ≥0.3 mg/dl (≥26.5 µmol/l) increase within 48h
2	2.0–2.9 times reference SCr
3	3.0 times reference SCr OR Increase in serum creatinine to ≥4.0 mg/dL (≥353.6 µmol/L) OR SCr ≥2.5 mg/dL OR Initiation of dialysis

Selewski DT, Charlton JR, Jetton JG, et al. Neonatal Acute Kidney Injury. *Pediatrics.* 2015;136(2):e463. doi:10.1542/peds.2014-3819.

Item 52

Stop

Do not use nephrotoxic drugs in neonates if possible, especially in preterm infants.

Nephron mass is lower in preterm infants since nephrogenesis is active until 36 weeks of gestational age and interruption of gestation results in a loss of total nephron number. Moreover, preterm infants are more vulnerable to acute kidney injury (AKI) with the potential loss of nephrons after birth. Nonsteroidal anti-inflammatory drugs (NSAIDs), including indomethacin and ibuprofen, paracetamol, aspirin, aminoglycosides (gentamicin, amikacin, tobramycin) and glycopeptide antibiotics (vancomycin, teicoplanin), betalactams (penicillins, cephalosporins), amphotericin B, antiviral agents (aciclovir), diuretics, proton pump inhibitors, and phenytoin can be nephrotoxic and cause AKI in neonates. This list is not exhaustive. When nephrotoxic agents must be started, monitor cystatin-C and/or serum creatinine before and after the initiation of treatment.

Grade of recommendations: Review

Rodieux F, Wilbaux M, van den Anker JN, Pfister M. Effect of Kidney Function on Drug Kinetics and Dosing in Neonates, Infants, and Children. *Clin Pharmacokinet.* 2015;54(12):1183-1204. doi:10.1007/s40262-015-0298-7.

Abitbol CL, Seeherunvong W, Galarza MG, et al. Neonatal kidney size and function in preterm infants: What is a true estimate of glomerular filtration rate? *J Pediatr.* 2014;164(5):1026-1031.e2. doi:10.1016/j.jpeds.2014.01.044.

Naughton CA. Drug-induced nephrotoxicity. *Am Fam Physician.* 2008;78(6):743-750. doi:10.1016/S0025-7125(05)70541-1.

All — Nephrology/Acute Kidney Injury (AKI) OR Prevention/Acute Kidney Injury (AKI)

Item 53

	Stop all nephrotoxic drugs when possible in neonates with AKI (stage 1-3).
Stop	Nonsteroidal anti-inflammatory drugs (NSAIDs), including indomethacin and ibuprofen, paracetamol, aspirin, aminoglycosides (gentamicin, amikacin, tobramycin) and glycopeptide antibiotics (vancomycin, teicoplanin), amphotericin B, antiviral agents (aciclovir), diuretics, and phenytoin can be nephrotoxic and cause AKI in neonates. This list is not exhaustive.
	Grade of recommendations: D **Rodieux F, Wilbaux M, van den Anker JN, Pfister M.** Effect of Kidney Function on Drug Kinetics and Dosing in Neonates, Infants, and Children. *Clin Pharmacokinet.* 2015;54(12):1183-1204. doi:10.1007/s40262-015-0298-7.
All	Nephrology/Acute Kidney Injury (AKI) Nephrotoxics

Item 54

	Consider dosage adjustement for drugs highly excreted by renal elimination in neonates with AKI (stage 1-3). When needed, refer to a specialist.
Other	
	Grade of recommendations: - -
All	Nephrology/Acute Kidney Injury (AKI)

6. GASTROENTEROLOGY
Direct hyperbilirubinemia (Conjugated Hyperbilirubinemia)

Definition	**Direct hyperbilirubinemia** Direct bilirubinemia >17 µmol/L if total bilirubin is <85.5 µmol/L, or a value of direct bilirubin that represents >20% of the total bilirubin if total bilirubin is >85.5 µmol/L. **Moyer V, Freese DK, Whitington PF, et al.** Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2004;39(2):115-128. doi:10.1097/00005176-200408000-00001.

Item 55

	Decrease or stop intravenous soybean-based lipid emulsion in neonates with marked progressive cholestasis associated with parenteral nutrition.
	Consider switching soybean-based lipid emulsion to fish oil-based lipid emulsions or emulsions with reduced omega-6 fatty acids and increased omega-3 fatty acids. Exemples of these type of lipid emulsions are Omegaven® (fish-oil), SMOFlipid® (soy-oil, medium-chain triglycerides, olive-oil, omega-3 fatty acids) and Lipoplus® (soy-oil, medium-chain triglycerides, omega-3 fatty acids).
Others	**Grade of recommendations: International Guidelines** **Dani C, Pratesi S, Raimondi F, Romagnoli C.** Italian guidelines for the management and treatment of neonatal cholestasis. *Ital J Pediatr.* 2015;41(69):1-12. doi:10.1186/s13052-015-0178-7. **Lauriti G, Zani A, Aufieri R, et al.** Incidence, Prevention, and Treatment of Parenteral Nutrition–Associated Cholestasis and Intestinal Failure– Associated Liver Disease in Infants and Children: A Systematic Review. *J Parenter Enter Nutr.* 2014;38(1):70-85. doi:10.1177/0148607113496280. **Koletzko B, Goulet O, Hunt J, et al.** Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr.* 2005;41(Suppl 2):S1-S4. doi:10.1097/01.mpg.0000181841.07090.f4.
All	Gastroenterology/Direct hyperbilirubinemia Total Parenteral Nutrition (TPN), lipid emulsion

Item 56

	Administer adequate protein intake of 2 to 3 g/kg/day to neonates with direct hyperbilirubinemia.
Start	
	Grade of recommendations: Review **Feldman AG, Sokol RJ.** Neonatal Cholestasis. Neoreviews - *Am Acad Pediatr.* 2013;14(2). doi:10.1542/neo.14-2-e63.
All	Gastroenterology/Direct hyperbilirubinemia

Item 57

Start fat-soluble vitamins (ADEK) in neonates with cholestasis.

Prescribe fat-soluble vitamins during cholestasis and for 3 months following resolution of jaundice; doses will require daily monitoring. Follow your institution guidelines for dosage.
- Vitamin A: monitor serum vitamin A
- Vitamin D: Monitor bone biochemistry
- Vitamin E: monitor serum vitamin E
- Vitamin K: monitor PT and APTT

Start

Grade of recommendations: National Guidelines

The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network. Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.

Dani C, Pratesi S, Raimondi F, Romagnoli C. Italian guidelines for the management and treatment of neonatal cholestasis. *Ital J Pediatr.* 2015;41(69):1-12. doi:10.1186/s13052-015-0178-7.

All | Gastroenterology/Direct hyperbilirubinemia

Item 58

Consider ursodeoxycholic acid (UDCA) in neonate with direct hyperbilirubinemia.

Consider ursodeoxycholic acid (UDCA) treatment at the dosage of 20–30 mg/kg/day in divided doses until jaundice resolve. Ursodeoxycholic acid (UDCA) has been found to have beneficial effects on many forms of cholestasis, and is generally used as first-line therapy for pruritus due to cholestasis, parenteral nutrition-induced cholestasis, biliary atresia after surgical treatment, and α1-antitrypsin deficiency (C).

Start

Grade of recommendations: National Guidelines

Dani C, Pratesi S, Raimondi F, Romagnoli C. Italian guidelines for the management and treatment of neonatal cholestasis. *Ital J Pediatr.* 2015;41(69):1-12. doi:10.1186/s13052-015-0178-7.

The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network. Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.

All | Gastroenterology/Direct hyperbilirubinemia

Indirect hyperbilirubinemia (Unconjugated Hyperbilirubinemia)

Item 59

	Administer intravenous immunoglobulin (IVIG) to neonates with a positive direct Coombs test and severe hyperbilirubinemia, or to those progressing to severe hyperbilirubinemia despite initial treatment.
Start	IVIG should be administered, if not so already, in infants with isoimmunisation. Dose: 1 g/kg
	Grade of recommendations: National Guidelines **Barrington KJ, Sankaran K, Canadian Paediatric Society Fetus and Newborn.** Guidelines for detection , management and prevention of hyperbilirubinemia in term and late preterm. *Paediatr Child Heal.* 2007;12(Suppl B):1B-12B.
All	Gastroenterology/Indirect hyperbilirubinemia

Definition

Necrotizing Enterocolitis

Review of Bell's Stages	Clinical Findings	Radiographic Findings	Gastrointestinal Findings	Bell's stages
Stage I	Apnea and bradycardia, temperature instability	Normal gas pattern or mild ileus	Gastric residuals, occult blood in stool, mild abdominal distention	**Suspect**
Stage II A	Apnea and bradycardia, temperature instability	Ileus gas pattern with one or more dilated loops and focal pneumatosis	Grossly bloody stools, prominent abdominal distention, absent bowel sounds	**Proven**
Stage II B	Thrombocytopenia and mild metabolic acidosis	Widespread pneumatosis, ascites, portal-venous gas	Abdominal wall edema with palpable loops and tenderness	
Stage III A	Mixed acidosis, oliguria, hypotension, coagulopathy	Prominent bowel loops, worsening ascites, no free air	Worsening wall edema, erythema and induration	**Advanced**
Stage III B	Shock, deterioration in laboratory values and vital signs	Pneumo-peritoneum	Perforated bowel	

Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am.* 1986;33(1):179-201.

Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg*. 1978;187(1):1-7.

Item 60

	Start probiotics in preterm neonates at high risk of developing NEC.
Start	In patient at high risk of developing NEC (preterm < 32 weeks GA or <1500g), initiate a probiotic treatment, with a preparation combining Lactobacillus and Bifidobacterium species. Initiate at the time of the first feed until 36 weeks of gestational age or discharge. Use only probiotic drugs fulfilling pharmaceutical regulations.
	Grade of recommendations: Systematic Review / Meta-analysis
	AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane database Syst Rev.* 2014;(4). doi:10.1002/14651858.CD005496.pub4.
	ProPrems Study Group, Jacobs SE, Tobin JM, et al. Probiotic effects on late-onset sepsis in very preterm infants: a randomized controlled trial. *Pediatrics.* 2013;132(6):1055-1062. doi:10.1542/peds.2013-1339.
	Deshpande GC, Rao SC, Keil AD, Patole SK. Evidence-based guidelines for use of probiotics in preterm neonates. *BMC Med.* 2011;9(1):92. doi:10.1186/1741-7015-9-92.
<32w GA and/or <1500g	Prevention/Prevention of NEC OR Gastroenterology/Necrotizing enterocolitis (NEC)

Item 61

	Stop all enteral medications in neonates suspected to have NEC.
Stop	When an infant is suspected to have NEC (stage I), all enteral medications should be discontinued. Enteral route can be used again if investigation exclude NEC. In stage II-III NEC, enteral route must not be used for 7-14 days to allow gastrointestinal rest.
	Grade of recommendations: Review
	Sharma R, Hudak M. A clinical perspective of necrotizing enterocolitis: past, present, and future. *Clin Perinatol.* 2013;40(1):27-51. doi:10.1016/j.clp.2012.12.012.
All	Gastroenterology/Necrotizing enterocolitis (NEC) All oral treatments

Item 62

	Do not use enteral antibiotics for the prevention of NEC.
Stop	Evidence suggests that enteral antibiotics reduce the incidence of NEC in low birth weight infants. However, concerns about adverse outcomes persist, particularly related to the development of resistant bacterial infection.
	Grade of recommendations: Systematic Review / Meta-analysis
	Bury RG, Tudehope D. Enteral antibiotics for preventing necrotizing enterocolitis in low birthweight or preterm infants. *Cochrane Database Syst Rev.* 2001;(1). doi:10.1002/14651858.CD000405.
<32w GA and/or <1500g	Prevention/Prevention of NEC OR Gastroenterology/Necrotizing enterocolitis (NEC) Antibiotics, immunoglobulin

Item 63

	Start broad spectrum antibiotic promptly after blood cultures have been drawn in neonates with any stage of NEC.
	After blood cultures have been drawn, prompt initiation of treatment with IV gentamicin and amoxicillin. If evolving to Bell's stage II-IV NEC, antibiotic treatment should be continued for 7 to 14 days. Follow your institution guideline for dosage.
Start	**Grade of recommendations: Textbook**
	Sharma R, Hudak M. A clinical perspective of necrotizing enterocolitis: past, present, and future. *Clin Perinatol.* 2013;40(1):27-51. doi:10.1016/j.clp.2012.12.012.
	Schanler R, Abrams SA, Kim MS. Management of necrotizing enterocolitis in newborns. *UpToDate.com.* http://www.uptodate.com/contents/management-of-necrotizing-enterocolitis-in-newborns. Published 2015. Accessed April 25, 2016.
	Lin PW, Stoll BJ. Necrotising enterocolitis. *Lancet.* 2006;368:1271-1283. doi:10.1016/S0140-6736(06)69525-1.
All	Gastroenterology/Necrotizing enterocolitis (NEC)

Gastrointestinal Bleeding from the Upper Tract

Item 64

	Check that a Vitamin K prophylaxis was administered postdelivery in neonates with upper gastro-intestinal bleeding, to guide diagnostic.
Other	All neonates who have hematemesis should be screened for coagulopathy due to: - failure to administer prophylaxis postdelivery - maternal thrombocytopenic purpura - hemophilia - von Willebrand disease
	Grade of recommendations: Review
	Boyle JT. Gastrointestinal bleeding in infants and children. *Pediatr Rev.* 2008;29(2):39-52. doi:10.1542/pir.29-2-39.
All	Gastroenterology/Gastrointestinal Bleeding from the Upper Tract

Gastroesophageal Reflux

Definition	**Gastroesophageal Reflux (GER)** Gastroesophageal reflux is physiologic in the neonate. Only rarely does reflux become a "disease" (GERD). **Gastresophageal Reflux Disease (GERD)** Cause overt oesophagitis or is associated with other symptoms. This should be assessed by clinical judgment. **Health.vic.** Gastro-oesophageal reflux (GOR) in neonates. *Victoria State Government.* https://www2.health.vic.gov.au/hospitals-and-health-services/patient-care/perinatal-reproductive/neonatal-ehandbook/conditions/gastro-oesophageal-reflux. Published 2016. Accessed June 24, 2016. **Neonatal Formulary.** Omeprazole Web Commentary. *Neonatal Formulary.* http://www.neonatalformulary.com/pdfs/commentary/OMEPRAZOLE-(commentary).pdf. Published 2014. Accessed June 24, 2016.

Item 65

	Consider proton pump inhibitors or H2-blockers only in neonates with severe cases of acid gastroesophageal reflux disease (GERD), when non-pharmacological measures (including milk thickeners) have failed.
Start / stop	Do not offer acid-suppressing drugs, such as proton-pump inhibitors or H2-receptor antagonists, to treat overt regurgitation in infants with isolated symptoms. In severe cases of GERD, omeprazole should be administered orally at an initial dose of 0.7 mg/kg once a day. It can be raised to a maximum dose of 1.4 mg/kg once a day after 7-14 days if this does not inhibit gastric acid production. IV use: Give 0.5 mg/kg once a day over 5 min. Recommended dose of ranitidine is 1.5 mg/kg 3x/day for term infants and 0.5 mg/kg 3x/day for preterm infants. Treatment should be reassessed regularly.
	Grade of recommendations: National Guidelines **National Institute For Health and Care Excellence.** Managing gastro-oesophageal reflux and reflux disease in infants. *NICE Pathways.* https://pathways.nice.org.uk/pathways/dyspepsia-and-gastro-oesophageal-reflux-disease. Published 2016. Accessed June 24, 2016. **Neonatal Formulary.** Omeprazole Web Commentary. *Neonatal Formulary.* http://www.neonatalformulary.com/pdfs/commentary/OMEPRAZOLE-(commentary).pdf. Published 2014. Accessed June 24, 2016. **Czinn SJ, Blanchard S.** Gastroesophageal reflux disease in neonates and infants : when and how to treat. *Paediatr Drugs.* 2013;15:19-27. doi:10.1007/s40272-012-0004-2.
All	Gastroenterology/Gastroesophargeal reflux Proton pump inhibitors, H2-receptor antagonists

Item 66

Stop	**Do not use metoclopramide, domperidone or erythromycin to treat gastroesophageal reflux or gastroesophageal reflux disease.** Pro-kinetics such as metoclopramide and domperidone are not recommended for the treatment of GER due to lack of evidence and concerns regarding adverse effects. Erythromycin has limited benefit, may facilitate bacterial resistance and should not be routinely prescribed. **Grade of recommendations: National Guidelines** **Chakraborty M, Damodaran K, Barr S.** Guidelines for the management of gastro-oesophageal reflux disease (GORD) in neonates. *UHW Cardiff NICU.* http://www.cardiffnicu.com/Portal/Nutrition/GORD.pdf. Published 2013. Accessed June 24, 2016. **National Institute For Health and Care Excellence.** Managing gastro-oesophageal reflux and reflux disease in infants. *NICE Pathways.* https://pathways.nice.org.uk/pathways/dyspepsia-and-gastro-oesophageal-reflux-disease. Published 2016. Accessed June 24, 2016. **The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network.** Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.
All	Gastroenterology/Gastroesophargeal reflux Metoclopramide, domperidone, erythromycin

7. NEUROLOGY
Seizures

Definition	**A seizure** is defined clinically as a paroxysmal alteration in neurologic function. This definition includes: 1. Epileptic seizures: phenomena associated with corresponding EEG seizure activity e.g. clonic seizures 2. Non-epileptic seizures: clinical seizures without corresponding EEG correlate e.g. subtle and generalized tonic seizures 3. EEG seizures: abnormal EEG activity with no clinical correlation. **WHO Collaborating Center For Training and Research in Newborn Care.** Management of neonatal seizures. *Newbornwhocc.org.* http://www.newbornwhocc.org/2014_pdf/Neonatal seizures 2014.pdf. Published 2014. Accessed May 11, 2016.

Item 67

	Start phenobarbital as the first line agent in neonates with either EEG diagnosed or clinically apparent seizures when prolonged or frequent.
Start	Phenobarbital should be used as the first line agent (at a loading dose of 20 mg/kg IV over 10-15 min and a maintenance dose of 2.5-5 mg/kg IV, IM or oral, once daily beginning 12-24h after loading dose) in neonates with either EEG diagnosed or clinically apparent seizures when prolonged (greater than 3 minutes), frequent (greater than 3 per hour). Phenobarbital is recommended as first-line treatment given its inclusion in the only RCT of first-line treatment of neonatal seizure, the fact that it is the most studied anti-epileptic medication in animals, and its historical precedence as the first-line antiepileptic drug for neonates. Use phenobarbital with caution since there is extremely limited evidence on its effect on long-term neonatal neurodevelopment.
	Grade of recommendations: International Guidelines **WHO Collaborating Center For Training and Research in Newborn Care.** Management of neonatal seizures. *Newbornwhocc.org.* http://www.newbornwhocc.org/2014_pdf/Neonatal seizures 2014.pdf. Published 2014. Accessed May 11, 2016. **Slaughter LA, Patel AD, Slaughter J.** Pharmacological Treatment of Neonatal Seizures: A Systematic Review. *J Child Neurol.* 2013;28(3):351-364. doi:10.1177/0883073812470734.
All	Neurology/Seizures

Item 68

	Consider phenytoin or a benzodiazepine or lidocaine in neonates with persistant seizures, despite adequate phenobarbital treatment.
Start	In neonates who continue to have seizures despite administation of the maximal tolerated dose of phenobarbital, either phenytoin or a benzodiazepine or lidocaine may be used as the second-line agent for the control of seizures. **The use of phenytoin or lidocaine requires cardiac monitoring facilities.**
	Grade of recommendations: International Guidelines
	WHO Collaborating Center For Training and Research in Newborn Care. Management of neonatal seizures. *Newbornwhocc.org.* http://www.newbornwhocc.org/2014_pdf/Neonatal seizures 2014.pdf. Published 2014. Accessed May 11, 2016.
All	Neurology/Seizures
	Phenobarbital

Item 69

	Stop antiepileptic drugs if seizure-free for >72 hours in neonates with normal neurological examination and/or normal electroencephalography.
Stop	In neonates in whom seizure control is achieved with a single antiepileptic drug, the drug can be discontinued abruptly without any tapering of doses. In neonates requiring more than one antiepileptic drugs for seizure control, the drugs may be stopped one by one, with phenobarbital being the last drug to be withdrawn.
	Grade of recommendations: International Guidelines
	WHO Collaborating Center For Training and Research in Newborn Care. Management of neonatal seizures. *Newbornwhocc.org.* http://www.newbornwhocc.org/2014_pdf/Neonatal seizures 2014.pdf. Published 2014. Accessed May 11, 2016.
All	Neurology/Seizures
	Phenobarbital, phenytoin, lidocaine, benzodiazepines

Item 70

	Consider pyridoxine only in neonates with recurrent seizures with no obvious cause.
Start	If there are recurrent seizures with no obvious cause consider pyridoxine dependency. A therapeutic trial of **pyridoxine IV 50 -100 mg** may be helpful (this may be considered during EEG).
	Grade of recommendations: International Guidelines
	WHO Collaborating Center For Training and Research in Newborn Care. Management of neonatal seizures. *Newbornwhocc.org.* http://www.newbornwhocc.org/2014_pdf/Neonatal seizures 2014.pdf. Published 2014. Accessed May 11, 2016.
All	Neurology/Seizures
	Pyridoxine

8. PAIN, SEDATION & NEONATAL ABSTINENCE SYNDROME

Pain, Analgesia & Sedation

Item 71

Stop	**Start pain management in neonates with non-pharmacological techniques (incl. Sucrose) if aproppriate.** If moderate-severe pain is evident (including post-surgery, severe illness, major injury, congenital malformations or palliative care), progress to pharmacological agents. **Grade of recommendations: Institutional Guidelines** **The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network.** Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.
All	Pain, sedation & neonatal abstinence syndrome/Pain, Analgesia & Sedation Analgesics

Item 72

Start / stop	**Start paracetamol in neonates who are still in pain despite adequate non-pharmacological interventions.** Recommended doses are 10–15 mg/kg orally or 20–25 mg/kg rectally administered every 6–8 hours. Recommendations for intravenous paracetamol, are a loading dose of 20 mg/kg, followed by 10 mg/kg every 6–8 hours. Maximum doses should not exceed 40 mg/kg/day for infants at 26–32 weeks PMA and 60 mg/kg/day for infants at 32–42 weeks PMA. Hepatotoxicity occurs very rarely, if ever, following routine administration of paracetamol in neonates. Priority to the oral route. **Grade of recommendations: International Guidelines** **Barrington K, Batton D, Finley G, Wallman C, Canadian Paediatric Society.** Prevention and Management of Pain in the Neonate : An Update. *Paediatr Child Heal.* 2007;12(2):137-138. doi:10.1542/peds.2006-2277. **Ballantyne JC, Cousins MJ, Giamberardino MA, et al.** Acute Pain Management in Newborn Infants. *Pain Clin Updat.* 2011;19(6):1-6.
All	Pain, sedation & neonatal abstinence syndrome/Pain, Analgesia & Sedation Paracetamol, opioids

Item 73

	Do not use nonsteroidal antiinflamatory agents (NSAID) as analgesics.
	NSAIDs are not recommended for neonatal analgesia, as safer and more effective agents are available. Treatment should be switched to other pharmacologic classes.
Stop	**Grade of recommendations: International Guidelines**
	Ballantyne JC, Cousins MJ, Giamberardino MA, et al. Acute Pain Management in Newborn Infants. *Pain Clin Updat.* 2011;19(6):1-6.
	Batton DG, Barrington KJ, Wallman C, American Academy of Pediatrics, Canadian Paediatric Society. Prevention and Management of Procedural Pain in the Neonate: An Update. *Pediatrics.* 2006;118(5):2231-2241. doi:10.1542/peds.2006-2277.
All	Pain, sedation & neonatal abstinence syndrome/Pain, Analgesia & Sedation
	NSAID

Item 74

Start / stop	**Start morphine as first line treatment for pain relief in neonates who are still in pain despite adequate non-pharmacological techniques and paracetamol treatment.** Morphine is recommended as the first-line strong opioid for the treatment of persistant moderate to severe pain in children with medical illnesses. There is insufficient evidence to recommend any alternative opioid in preference to morphine as the opioid of first choice. Intermittent dose 50-100 µg/kg IV every 4-8 hours, Infusion dose 10-30 µg/kg/h (for opioid naive patients). Start at the lower dose and titrate carefully to effect using small incremental doses. When opioids are administered for greater than 4 days, physical dependence and tolerance may develop. This means that higher opioid doses are required in order to maintain patient confort and that treatment should be weaned over a period of days at the rate of 10% of the prescribed dose per day, based on the clinical assessment of the neonate. Caution should be taken when treating newborns with opioids, especially preterm neonates, as they are more sensitive to opioids and are at risk for respiratory depression, apnea, hypotension and urinary retention. **Grade of recommendations: International Guidelines** **World Health Organization.** WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses. Geneva, Switzerland: *World Health Organization*; 2012. **Anand KJ, International Evidence-Based Group for Neonatal.** Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med.* 2001;155(2):173-180. **Lexicomp.** Morphine : Pediatric drug information. *UpToDate.com.* http://www.uptodate.com/contents/morphine-pediatric-drug-information?source=search_result&search=morphine&selectedTitle=2~150#F11443893. Published 2016. Accessed June 22, 2016. **Australian and New Zealand Neonatal Network.** Assessment and Management of Neonatal Pain. *Best Pract Clin Guidel Assess.* 2007;(September):1-14. http://www.acnn.org.au/acnn-resources/clinical-guidelines/newborn-pain-practice-guideline-2007.pdf.
All	Pain, sedation & neonatal abstinence syndrome/Pain, Analgesia & Sedation Paracetamol, opioids

Item 75

	Start opioids as first line treatment for postoperative analgesia, and use them as long as pain assessment scales deem necessary.
	Morphine dosage: intermittent dose 50-100 µg/kg IV every 4-8 hours, Infusion dose 10-30 µg/kg/h (for opioid naive patients). Clinical titration using small incremental doses (5–20 µg/kg) may be required When opioid are administered for greater than 4 days, physical dependence and tolerance may develop. This means that higher opioid doses are required in order to maintain patient confort and that treatment should be weaned over a period of days at the rate of 10% of the prescribed dose per day, based on the clinical assessment of the neonate. Caution should be taken when treating newborns with opioids, especially preterm neonates, as they are more sensitive to opioids and are at risk for respiratory depression, apnea, hypotension and urinary retention.
Start	**Grade of recommendations: International Guidelines**
	Barrington K, Batton D, Finley G, Wallman C, Canadian Paediatric Society. Prevention and Management of Pain in the Neonate : An Update. *Paediatr Child Heal.* 2007;12(2):137-138. doi:10.1542/peds.2006-2277.
	Anand KJ, International Evidence-Based Group for Neonatal. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med.* 2001;155(2):173-180.
	Lexicomp. Morphine : Pediatric drug information. *UpToDate.com.* http://www.uptodate.com/contents/morphine-pediatric-drug-information?source=search_result&search=morphine&selectedTitle=2~150#F11443893. Published 2016. Accessed June 22, 2016.
	Australian and New Zealand Neonatal Network. Assessment and Management of Neonatal Pain. *Best Pract Clin Guidel Assess.* 2007;(September):1-14. http://www.acnn.org.au/acnn-resources/clinical-guidelines/newborn-pain-practice-guideline-2007.pdf.
All	Pain, analgesia & neonatal abstinence syndrome/Pain & analgesia

Item 76

Stop	**Reassess the indication of morphine or fentanyl in chronically ventilated preterm neonates without pain.** In the absence of pain, discomfort or difficulties for improving gas exchange, use of continuous infusions of morphine or fentanyl in chronically ventilated preterm neonates is not recommended. There is insufficient evidence to recommend routine use of opioids in mechanically ventilated newborns. Opioids should be used selectively, when indicated by clinical judgment and evaluation of pain indicators. If sedation is required, morphine is safer than midazolam. Newborns, especially preterm neonates, are more sensitive to opioids and are at risk for respiratory depression, apnea, hypotension, and urinary retention **Grade of recommendations: National Guidelines** **Barrington K, Batton D, Finley G, Wallman C, Canadian Paediatric Society.** Prevention and Management of Pain in the Neonate : An Update. *Paediatr Child Heal.* 2007;12(2):137-138. doi:10.1542/peds.2006-2277. **Ballantyne JC, Cousins MJ, Giamberardino MA, et al.** Acute Pain Management in Newborn Infants. *Pain Clin Updat.* 2011;19(6):1-6. **Bellù R, de Waal K, Zanini R.** Opioids for neonates receiving mechanical ventilation: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2010;95:F241-51. doi:10.1136/adc.2008.150318.
<37w GA	Pain, sedation & neonatal abstinence syndrome/Pain, Analgesia & Sedation Morphine, fentanyl, opioids

Item 77

Stop	**Do not use ketamine treatment for routine management of pain.** In spite of its theoretical advantages, ketamine is a potent anesthetic that has received minimal study in neonates. As such, it should only be used for surgery or highly invasive procedures. **Grade of recommendations: FRN** **Ballantyne JC, Cousins MJ, Giamberardino MA, et al.** Acute Pain Management in Newborn Infants. *Pain Clin Updat.* 2011;19(6):1-6. **Witt N, Coynor S, Edwards C, Bradshaw H.** A Guide to Pain Assessment and Management in the Neonate. *Curr Emerg Hosp Med Rep.* 2016;4:1-10. doi:10.1007/s40138-016-0089-y.
All	Pain, sedation & neonatal abstinence syndrome/Pain, Analgesia & Sedation Ketamine

Neonatal Abstinence Syndrome (NAS)

Item 78

	Consider non-pharmacological interventions for the initial management of all infants suspected of having or at risk of developing NAS. This may mitigate the need for medication.
Stop	Infants at risk for NAS should be monitored diligently during the initial days after birth. At present, the modified Finnegan scores remains the most common tool that is used. Start modified Finnegan scoring within 24h of birth and monitor score every 3-4h. Treatment is indicated when the average of three scores is ≥8 or when the average of two scores is ≥12.
	Grade of recommendations: National Guidelines
	Kocherlakota P, American Academy of Pediatrics. Neonatal Abstinence Syndrome. *Pediatrics.* 2014;134(2):e547-61. doi:10.1542/peds.2013-3524.
	Wiles JR, Isemann B, Ward LP, et al. Current management of neonatal abstinence syndrome secondary to intrauterine opioid exposure. *J Pediatr.* 2014;165(3):440-446. doi:10.1016/j.jpeds.2014.05.010.
All	Pain, analgesia & neonatal abstinence syndrome/NAS
	Opioids

Item 79

	Start morphine as the first line pharmacological treatment for NAS when opioids are used by the mother and supportive measures failed.
Start	Morphine is indicated when the average of three Modified Finnegan Scores is ≥8 on the scoring tool or when the average of two scores is ≥12. Recommended doses for oral morphine are variable. Try 50 µg/kg every 3–4 h, then 10% or 50 µg increments to a maximum dose of 1300 µg/kg/day. Phenobarbital should be considered at this point.
	Grade of recommendations: National Guidelines
	Kocherlakota P, American Academy of Pediatrics. Neonatal Abstinence Syndrome. *Pediatrics.* 2014;134(2):e547-61. doi:10.1542/peds.2013-3524.
	Canadian Society of Pharmacology and Therapeutics, Dow K, Ordean A, et al. Neonatal Abstinence Syndrome: Clinical Practice Guidelines For Ontario. *J Popul Ther Clin Pharmacol.* 2012;19(3):e488-e506.
All	Pain, analgesia & neonatal abstinence syndrome/NAS

Item 80

Stop	**Start weaning of morphine as soon as Modified Finnegan scores are <8 for 24 to 48 hours in neonates with NAS.**
	Initiate weaning of morphine when Modified Finnegan scores are <8 for 24 to 48 hours by a 10% decrease of the total daily dose with each wean occurring no more frequently than every 48 to 72 hours. Morphine can be discontinued when scores are stable for 48 to 72 hours on a dose of 0.05 to 0.1 mg/kg/day.
	Grade of recommendations: Institutional Guidelines
	Provincial Council for Maternal and Child Health. Neonatal Abstinence Syndrome (NAS). *Perinatal Quality Collaborative of North Carolina.* http://www.pqcnc.org/documents/nas/nasresources/NASGuidelines.pdf. Published 2012. Accessed June 21, 2016.
All	Pain, analgesia & neonatal abstinence syndrome/NAS Morphine

Item 81

Stop	**Do not use morphine in neonates with NAS when the drugs used by the mother are non-opioids.**
	If needed, use phenobarbital (see phenobarbital recommendations).
	Grade of recommendations: -
	-
All	Pain, analgesia & neonatal abstinence syndrome/NAS Morphine, opioids

09. INFECTIOLOGY
Meningitis

Item 82

Start

Start empirical antibiotic treatment with high dose amoxicilline and gentamicin in neonates with diagnosed or strongly suspected meningitis.

Follow your institution guidelines for dosage.

Grade of recommendations: Textbook

Département de l'enfant et de l'adolescent - HUG. Cahier de l'interne. *Hôpitaux Univ Genève.* 2015;(Décembre).

Edwards MS, Baker CJ. Bacterial meningitis in the neonate: Treatment and outcome. *UpToDate.com.* http://www.uptodate.com/contents/bacterial-meningitis-in-the-neonate-treatment-and-outcome#H26. Published 2016. Accessed May 30, 2016.

All

Infectiology/Meningitis

Item 83

Other

Check results of cerebro-spinal fluid (CSF) culture as soon as they are available in order to reassess the need for treatment or the choice of antibiotics in neonates with suspected meningitis treated with empirical antibiotics.

If low clinical suspicion of meningitis, stop antibiotics after 48 hr if:
- CSF glucose >2/3 simultaneous blood glucose and
- CSF protein <1 g/L, culture results are negative and baby remains well.

Grade of recommendations: Institutional Guidelines

Polin RA, Committee on Fetus and Newborn, American Academy of Pediatrics. Management of Neonates With Suspected or Proven Early-Onset Bacterial Sepsis. *Pediatrics.* 2012;129(5):1006-1015. doi:10.1542/peds.2012-0541.

The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network. Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.

All

Infectiology/Meningitis

Antibiotics

Item 84

Stop	**Do not use corticosteroids for the treatment of neonates with suspected or confirmed bacterial meningitis. Reassess the corticosteroid indication.** At present, there is insufficient data to make a recommendation on the use of adjunctive corticosteroids in neonates with bacterial meningitis. Very low-quality data from two randomised controlled trials suggest that some reduction in death and hearing loss may result from use of adjunctive steroids alongside standard antibiotic therapy for treatment of patients with neonatal meningitis. Benefits are not yet seen with regards to a reduction in neurological consequences. **Grade of recommendations: FRN**
All	Infectiology/Meningitis Corticosteroids

Ogunlesi TA, Odigwe CC, Oladapo OT. Adjuvant corticosteroids for reducing death in neonatal bacterial meningitis. *Cochrane database Syst Rev.* 2015;11(11):CD010435. doi:10.1002/14651858.CD010435.pub2.

National Collaborating Centre for Women's and Children's Health. Bacterial meningitis and meningococcal septicaemia. *NICE Clin Guidel* 102. 2010;(September):271. doi:10.1136/bmj.c3209.

Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *ClinInfectDis.* 2004;39(9):1267-1284. doi:10.1086/425368.

Sepsis

Definition

Sepsis: According to the onset of age, neonatal sepsis is divided into early-onset sepsis (EOS) and late-onset sepsis (LOS). EOS reflects transplacental or, more frequently, ascending infections from the maternal genital tract, whereas LOS is associated with the postnatal nosocomial or community environment, with the peak incidence reported to be between the 10th and 22nd day of life. The onset of LOS is most frequently defined at 72 h after birth, a cut-off time point considered to adequately differentiate LOS from EOS in terms of the spectrum of causative pathogens

Early-Onset Sepsis (EOS): Onset of sepsis symptoms during the first 72 hours of life.
Risk factors of EOS:
- Maternal group B Streptococcus colonisation;
- Signs of chorioamnionitis (maternal fever >38 °C plus at least two of the following symptoms: maternal leucocytosis (>15 G/l), foetal tachycardia (>160/min), uterine tenderness, foul-smelling amniotic fluid);
- Prolonged rupture of membranes (>18 hours before delivery),
- Preterm birth <37 weeks,
- Previous neonate with an invasive group B streptococcus infection;
- Suspected infection in a sibling in the case of a multiple pregnancy.

Late-Onset Sepsis: Onset of sepsis symptoms at 72 hours of life or later.
Risk factors of LOS:
- Risk of infection is inversely related to gestational age and birth weight and directly related to severity of illness at birth, reflecting need for invasive interventions e.g. prolonged ventilation, central venous access and parenteral nutrition.
- Delayed introduction of enteral feeds is associated with higher infection rates
- Increased risk of sepsis after gut surgery especially if enteral feeds slow to establish e.g. post-gastroschisis or necrotising enterocolitis (NEC) with stoma

Symptoms of sepsis:
-Tachypnoea, respiratory distress, apnoea;
-Tachycardia/bradycardia, poor peripheral perfusion (i.e. capillary refill time >3 seconds), mottling;
-Temperature instability (hyperthermia >38.0 °C or hypothermia <36.0 °C);
-Lethargy, irritability, altered muscular tone or floppiness;
-Vomiting, poor feeding.

Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. *Arch Dis Child Fetal Neonatal Ed.* 2015;100(3):F257-63. doi:10.1136/archdischild-2014-306213.

Stocker M, Berger C, McDougall J, Giannoni E, Swiss Society of Neonatology, Paediatric Infectious Disease Group of Switzerland. Recommendations for term and late preterm infants at risk for perinatal bacterial infection. *Swiss Med Wkly.* 2013;143(September):1-5. doi:10.4414/smw.2013.13873.

The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network. Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.

Item 85

	Do not use empirical antibiotic therapy for asymptomatic neonates with a single risk factor of infection (incl. mother with suspected chorioamnionitis or unexplained premature delivery).
	Only close observation for the first 48 hours is advised.
Stop	**Grade of recommendations: National Guidelines** **Stocker M, Berger C, McDougall J, Giannoni E, Swiss Society of Neonatology, Paediatric Infectious Disease Group of Switzerland.** Recommendations for term and late preterm infants at risk for perinatal bacterial infection. *Swiss Med Wkly.* 2013;143(September):1-5. doi:10.4414/smw.2013.13873. **National Institute For Health and Care Excellence.** Neonatal infection : antibiotics for prevention and treatment. *NICE Clin Guidel* 149. nice.org.uk/guidance/cg149. Published 2012. Accessed May 26, 2016.
All	Infectiology/Sepsis Antibiotics

Item 86

	Start empirical antibiotic treatment after blood cultures have been drawn in all newborn infants with suggestive signs of neonatal infection.
	Use amoxicillin and gentamicin at doses recommended by your institution. There is a need for therapeutic drug monitoring for aminoglycoside therapy (aiming for a residual gentamicine blood concentration of 0.5-2 mg/L before 3rd dose).
Start	**Grade of recommendations: National Guidelines** **Stocker M, Berger C, McDougall J, Giannoni E, Swiss Society of Neonatology, Paediatric Infectious Disease Group of Switzerland.** Recommendations for term and late preterm infants at risk for perinatal bacterial infection. *Swiss Med Wkly.* 2013;143(September):1-5. doi:10.4414/smw.2013.13873. **Barrington KJ, Canadian Paediatric Society, Fetus and Newborn Commitee.** Management of the infant at increased risk for sepsis. *Paediatr Child Health.* 2007;12(10):893-905.
All	Infectiology/Sepsis

Item 87

Stop	**Reassess the need for antibiotics after 48 hours in neonates treated empirically with antibiotics for suspected sepsis.** This is important since clinical and laboratory signs of neonatal infection are nonspecific and symptomatic neonates are treated empirically. In most cases, based on the clinical course, negative culture results and laboratory parameters, a decision can be made to stop safely antibiotic therapy after this time (C-reactive protein (CRP) and procalcitonin (PCT) have a high negative predictive value and can be used to stop empirically started antibiotic therapy early). Frequently, prolonged antibiotic therapy (>5 days) causes an increased mortality and a higher incidence of necrotising enterocolitis in preterm infants. This emphasises the need to stop empirical treatment in the absence of proven infection as early as possible and at the latest after 48–72 hours. **Grade of recommendations: National Guidelines** **Stocker M, Berger C, McDougall J, Giannoni E, Swiss Society of Neonatology, Paediatric Infectious Disease Group of Switzerland.** Recommendations for term and late preterm infants at risk for perinatal bacterial infection. *Swiss Med Wkly.* 2013;143(September):1-5. doi:10.4414/smw.2013.13873. **National Institute For Health and Care Excellence.** Antibiotics for neonatal infection. *NICE quality standard* 75. guidance.nice.org.uk/qs75. Published 2014. Accessed May 26, 2016. **Brady MT, Polin RA.** Prevention and Management of Infants With Suspected or Proven Neonatal Sepsis. *Pediatrics.* 2013;132(1):166-168. doi:10.1542/peds.2013-1310.
All	Infectiology/Sepsis

Item 88

Stop	**Do not use cephalosporins as first-line treatment in infant with suspected neonatal infection, because of the high risk of developing resistance. Use is restricted to special cases** **Grade of recommendations: National Guidelines** **Stocker M, Berger C, McDougall J, Giannoni E, Swiss Society of Neonatology, Paediatric Infectious Disease Group of Switzerland.** Recommendations for term and late preterm infants at risk for perinatal bacterial infection. *Swiss Med Wkly.* 2013;143(September):1-5. doi:10.4414/smw.2013.13873.
All	Infectiology/Sepsis Cephalosporins

Item 89

Stop	**Do not use intravenous immunoglobulin in the treatment of suspected or proven neonatal sepsis.** Therapy with intravenous immunoglobulin had no effect on the outcomes of suspected or proven neonatal sepsis and should be discontinued. **Grade of recommendations: Randomized Controlled Trial** **The INIS Collaborative Group.** Treatment of Neonatal Sepsis with Intravenous Immune Globulin. *N Engl J Med.* 2011;365(13):1201-1211. doi:10.1056/NEJMoa1100441.
All	Infectiology/Sepsis Intravenous immunoglobulin (IVIG)

Item 90

Stop	**Do not use Vancomycin as prophylaxis against sepsis in preterm neonates.** Vancomycin prophylaxis should not be undertaken in preterm infants with additional risk factors for infection such as a birth weight less than 1500 grams, use of central venous catheters, and administration of intravenous hyperalimentation. **Grade of recommendations: FRN** **Ap C, Finer N, Kj B, Craft AP, Finer N, Barrington KJ.** Vancomycin for prophylaxis against sepsis in preterm neonates. *Cochrane Database Syst Rev.* 2000;(1). doi:10.1002/14651858.CD001971.
<37w GA	Infectiology/Sepsis OR Prevention/Sepsis Vancomycin

Hepatitis

Item 91

Administer an initial dose of hepatitis-B vaccine within 12 hours of birth in infants born to HBsAg-positive mothers, including infants weighing <2000g. Administer Hepatitis-B immune globulins (HBIG) 200 IU concurrently but at a different anatomic site.

The later HBIG is administered after exposure, the less it is effective. The interval of effectiveness is unlikely to exceed 7 days. For infants who weigh less than 2000g at birth, the initial vaccine dose should not be counted in the required 3-dose schedule. Give low-birth-weight and premature babies full neonatal dose of hepatitis B vaccine. Monitor infants born <28 weeks of gestational age for 72h after HBIG.

Start

Grade of recommendations: National Guidelines

Groupe de travail "Prévention de la transmission mère-enfant de l'hépatite B"; Commission fédérale pour les vaccinations; Office de la santé publique., Anderau R, Bachmann G, et al. Recommandations pour la prévention de la transmission mère-enfant de l'hépatite B. *Paediatrica.* 2007;18(2):20-26.

Committee on Infectious Diseases, American Academy of Pediatrics. Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.

Brook G, Soriano V, Bergin C. European guideline for the management of hepatitis B and C virus infections, 2010. *Int J STD AIDS.* 2010;21:669-678. doi:10.1258/ijsa.2010.010234.

Frieden TR, Jaffe HW, Cono J, Richards CL, Iademarco MF. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Reports.* 2015;64(RR-3):1-140. doi:10.1097/00008480-200308000-00006.

All — Infectiology/Hepatitis

Item 92

Do not use <u>early</u> hepatitis-B vaccine in infants born to mothers whose HBsAg and HBeAg status is negative but with positive anti-HBs status (prior infection or at risk of infection).

Stop

They should receive three hepatitis-B vaccine doses at 2, 3 and 4 months of life along with other recommended vaccines (DTPa-IPV-Hib).

Grade of recommendations: Institutional Guidelines

Département de l'enfant et de l'adolescent - HUG. Cahier de l'interne. *Hôpitaux Univ Genève.* 2015;(Décembre).

All — Infectiology/Hepatitis

Human Immunodeficiency Virus (HIV)

Item 93

Start HIV prophylaxis with zidovudine as close to birth as possible for at least 4 weeks or consider tritherapy in neonates born to HIV-infected mothers who did not follow proper antenatal treatment or whose viremia are detectable.

Follow your institution guidelines for doses.

Start

Grade of recommendations: National Guidelines

Commission fédérale pour la santé sexuelle (CFSS) en matière de prévention contre la transmission du VIH de la mère à l'enfant. Maladies transmissibles : Recommandations de la Commission fédérale pour la santé sexuelle (CFSS) en matière de prévention contre la transmission du VIH de la mère à l'enfant. *Office Féréral de la Santé Publique (OFSP)*, Suisse. 2016;4:80-81.

AIDSinfo. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. *U.S. Department of Health and Human Services (HHS).* https://aidsinfo.nih.gov/contentfiles/lvguidelines/peri_recommendations.pdf. Published 2015. Accessed June 6, 2016.

Département de l'enfant et de l'adolescent - HUG. Cahier de l'interne. *Hôpitaux Univ Genève.* 2015;(Décembre).

All

Infectiology/HIV

Item 94

Start tritherapy immediately in the neonate aged <72 hr if the mother is diagnosed postpartum with HIV infection.

Follow your institution guidelines for the choice of molecule and doses.

Start

Grade of recommendations: Institutional Guidelines

The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network. Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.

All

Infectiology/HIV

Respiratory Syncytial Virus (RSV)

Item 95

Start / Stop	**Start respiratory syncytial virus prophylaxis with palivizumab in neonates with severe bronchopulmonary dysplasia (BPD).** Use palivizumab 15 mg/kg/dose IM once a month during RSV season (~october till february). In those with moderate BPD, consider palivizumab prophylaxis. Palivizumab is not indicated for neonates with mild BPD. **Grade of recommendations: National Guidelines** **Aebi C, Barazzone C, Hammer J, Kind C, Nadal D, Pfister RE.** Consensus concernant la prévention des infections par le virus respiratoire syncitial (VRS) avec l 'anticorps humanisé nonoclonal palivizumab (Synagis). *Paediatrica.* 2004;15(6):17-19.
All	Infectiology/RSV AND Pneumology/BPD Palivizumab

Item 96

Start / stop	**Start respiratory syncytial virus prophylaxis with palivizumab in neonates with haemodynamically significant congenital heart disease AND other associated risk factors.** Use palivizumab 15 mg/kg/dose once every month during RSV season (~october till february). It is not advised to administer such prophylaxis in infants solely with haemodynamically significant congenital heart disease. Associated risk factors: cyanotic heart disease, severe pulmonary hypertension and overt heart failure. **Grade of recommendations: National Guidelines** **Aebi C, Barazzone C, Hammer J, Kind C, Nadal D, Pfister RE.** Consensus concernant la prévention des infections par le virus respiratoire syncitial (VRS) avec l 'anticorps humanisé nonoclonal palivizumab (Synagis). *Paediatrica.* 2004;15(6):17-19.
All	Infectiology/RSV AND Cardiology/congenital heart failure Palivizumab

Item 97

Stop	**Dot not use respiratory syncytial virus prophylaxis with palivizumab routinely in preterm neonates.** This statement was made considering: - The modest efficacy of palivizumab; - That in Switzerland the outcomes of hospitalization due to RSV infection in former preterm neonates without additionnal risk factors did not differ substantially from those of term neonates; - The high cost of palivizumab. **Grade of recommendations: National Guidelines** **Aebi C, Barazzone C, Hammer J, Kind C, Nadal D, Pfister RE.** Consensus concernant la prévention des infections par le virus respiratoire syncitial (VRS) avec l 'anticorps humanisé nonoclonal palivizumab (Synagis). *Paediatrica.* 2004;15(6):17-19.
All	Infectiology/RSV AND Prevention/RSV Palivizumab

Item 98

Stop	**Do not use palivizumab for the treatment of respiratory syncytial virus (RSV) infection. Stop the treatment, even if it was given before the infection.** **Grade of recommendations: National Guidelines** **Aebi C, Barazzone C, Hammer J, Kind C, Nadal D, Pfister RE.** Consensus concernant la prévention des infections par le virus respiratoire syncitial (VRS) avec l 'anticorps humanisé nonoclonal palivizumab (Synagis). *Paediatrica.* 2004;15(6):17-19. **American Academy of Pediatrics.** Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics.* 2014;134(2):415-420. doi:10.1542/peds.2014-1665. **Robinson JL, Le Saux N, Canadian Paediatric Society.** Preventing hospitalizations for respiratory syncytial virus infection. *Paediatr Child Health.* 2015;20(6):321-333.
All	Infectiology/RSV Palivizumab

Toxoplasmosis

Definition	**Confirmed Case:** > Clinical illness in a child with laboratory evidence of Toxoplasma gondii infection born to a mother with documented seroconversion during pregnancy (post-conceptually) OR > Laboratory confirmation of infection in the neonate with or without clinical illness: - Detection of IgA and/or IgM antibodies to T. gondii from a single peripheral blood specimen from the neonate OR - Demonstration of rising T. gondii IgG titres in sequential sera from the neonate OR - Detection of T. gondii nucleic acid (e.g., PCR) in amniotic fluid, placental tissue, fetal or neonatal tissue, blood or CSF OR - Isolation of T. gondii from blood or body fluid of the neonate by mouse inoculation OR - Microscopic demonstration of T. gondii in an appropriate neonatal clinical specimen. **Clinical illness:** Fetal infection early in pregnancy may manifest as fetal death, chorioretinitis, brain damage with intracerebral calcifications, hydrocephaly, microcephaly, fever, jaundice, rash, hepatosplenomegaly or convulsions. Fetal infection later in pregnancy results in mild or subclinical disease with delayed manifestations (recurrent or chronic chorioretinitis, developmental delay, hearing loss or blindness). **Probable Case:** > Clinical illness in a child with laboratory evidence of T. gondii infection born to a seropositive mother OR > Clinical illness in a neonate born to a female with reactivated toxoplasma infection (rare). **Alberta Health and Wellness.** Public Health Notifiable Disease Management Guidelines: Congenital Toxoplasmosis. *Government of Alberta.* http://www.ncbi.nlm.nih.gov/pubmed/23761154. Published 2011.

Item 99

	Administer a combination of pyrimethamine-sulfadiazine-folinic acid during the first year of life to neonates in whom a diagnosis of congenital toxoplasmosis is confirmed or probable.
	Follow your institution guideline for dosage.
Start	**Grade of recommendations: Textbook** **Guerina NG, Lee J, Lynfield R.** Congenital toxoplasmosis: Treatment, outcome, and prevention. *UpToDate.com.* http://www.uptodate.com/contents/congenital-toxoplasmosis-treatment-outcome-and-prevention. Published 2015. Accessed June 9, 2016. **Rudin C, Boubaker K, Raeber PA, et al.** Toxoplasmosis during pregnancy and infancy a new approach for Switzerland Swiss Working Group on congenital Toxoplasmosis. *Swiss Med Wkly.* 2008;138(49-50 SUPPL. 168):1-8. **Département de l'enfant et de l'adolescent - HUG.** Cahier de l'interne. *Hôpitaux Univ Genève.* 2015;(Décembre).
All	Infectiology/Toxoplasmosis

Item 100

	Do not use spiramycin in neonates. Stop treatment and screen for potential QT interval prolongation.
Stop	Spiramycin is no longer used in suspected toxoplasmosis. It was indicated in the past while waiting for a conclusive diagnosis, but no benefit has ever been demonstrated and it can cause cardiac toxicity (QT prolongation).
	Grade of recommendations: Review **Tomasoni LR, Meroni V, Bonfanti C, et al.** Multidisciplinary approach to congenital Toxoplasma infection: An Italian nationwide survey. *New Microbiol.* 2014;37(3):347-354.
All	Infectiology/Toxoplasmosis Spiramycin

Cytomegalovirus (CMV)

Definition	**Life-threatening disease:** **-** Viral sepsis-like syndrome - Pneumonitis - Myocarditis - Severe hepatitis - Enterocolitis - Severe and refractory thrombocytopenia - Sight-threatening retinitis - Severe neurologic disease - Underlying primary immune disorder (eg, severe combined immunodeficiency [SCID]) regardless of degree of symptoms **Severe focal disease** is defined as severe hepatitis, severe bone marrow suppression, colitis or pneumonia. **Demmler-Harrison GJ.** Congenital cytomegalovirus infection: Management and outcome. *UpToDate.com.* http://www.uptodate.com/contents/congenital-cytomegalovirus-infection-management-and-outcome. Published 2015. Accessed June 13, 2016. **D'Oronzio U, Arlettaz MR, Hagmann C, Swiss Society of Neonatology.** Congenital cytomegalovirus infection. *Swiss Soc Neonatol.* 2015;(May):1-22.

Item 101

Start / Stop	**Start antiviral treatment <u>as soon as virologic testing is confirmed</u> and within the first 30 days of life in symptomatic cytomegalovirus (CMV) infected newborns with central nervous system involvement or if life-threatening.** Treatment can be considered in symptomatic newborns with severe focal disease. IV ganciclovir and oral valganciclovir can be used, depending on the severity of the disease. Follow your institution guideline for dosage. Monitor full blood count, liver function tests, creatinine, urea and electrolytes. Suspend treatment if absolute neutrophil count < 500⁄µL or platelet count < 25 000⁄µL. Asymptomatically infected or mild/moderate symptomatic neonates should not be treated with antiviral agents. **Grade of recommendations: National Guidelines** **D'Oronzio U, Arlettaz MR, Hagmann C, Swiss Society of Neonatology.** Congenital cytomegalovirus infection. *Swiss Soc Neonatol.* 2015;(May):1-22. **Swanson EC, Schleiss MR.** Congenital Cytomegalovirus Infection : New Prospects for Prevention and Therapy. *Pediatr Clin North Am.* 2013;60(2):1-17. doi:10.1016/j.pcl.2012.12.008. **Buonsenso D, Serranti D, Gargiullo L, et al.** Congenital cytomegalovirus infection: Current strategies and future perspectives. *Eur Rev Med Pharmacol Sci.* 2012;16(7):919-935. **Committee on Infectious Diseases, American Academy of Pediatrics.** Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.

All	Infectiology/CMV

Item 102

	Stop antiviral treatment in neonates with asymptomatic cytomegalovirus infection
	Antiviral therapy is not recommended routinely in neonates and young infants because of possible toxicities, including neutropenia in a significant proportion of recipients.
Stop	**Grade of recommendations: International Guidelines** **Committee on Infectious Diseases, American Academy of Pediatrics.** Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012. **Buonsenso D, Serranti D, Gargiullo L, et al.** Congenital cytomegalovirus infection: Current strategies and future perspectives. *Eur Rev Med Pharmacol Sci.* 2012;16(7):919-935. **Coll O, Benoist G, Ville Y, et al.** Guidelines on CMV congenital infection. *J Perinat Med.* 2009;37(5):433-445. doi:10.1515/JPM.2009.127.
All	Infectiology/CMV Antiviral agents

Herpes Simplex Virus (HSV)

Definition	**Clinical suspicion of neonatal herpes infection:** Since most neonatal herpes infections occur where the mother has no history of genital herpes, an HSV infection must be suspected immediately if the neonate exhibits suspicious symptoms (B). The possibility of neonatal herpes infection must be especially considered in case of: – characteristic skin or mucosal lesions – conjunctivitis, particularly if there is injection of the conjunctiva, bulbi, or keratitis – seizures and/or lethargy without any other explanation – fever or other systemic symptoms without any other explanation. **Swiss Herpes Management Forum.** Swiss recommendations for the management of genital herpes and herpes simplex virus infection in neonate. *Swiss Med Wkly.* 2004;134:205-2014.

Item 103

Start aciclovir IV in neonates with Herpes Simplex Virus (HSV) disease, regardless of maternal history or pending laboratory confirmation or exclusion of HSV.

Localised HSV infections (skin, eyes and mouth) are treated for 14 days with parenteral aciclovir and CNS forms or disseminated infection for 21 day (C). Follow your institution guideline for dosage. For infants with CNS disease, CSF should be sampled near the end of a 21-day course of therapy. If the PCR remains positive, treatment should be extended with weekly CSF sampling and aciclovir stopped when a negative result is obtained (D). After acute HSV treatment, suppressive therapy with oral aciclovir should be given for six months to infants with CNS disease (D). Do not treat acute HSV infection with oral aciclovir because this leads to non-therapeutic drug levels (D).

Start

Grade of recommendations: National Guidelines

Swiss Herpes Management Forum. Swiss recommendations for the management of genital herpes and herpes simplex virus infection in neonate. *Swiss Med Wkly.* 2004;134:205-2014.

Frieden TR, Jaffe HW, Cono J, et al. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Reports.* 2015;64(RR-3):1-140. doi:10.1097/00008480-200308000-00006.

Allen UD, Robinson JL, Canadian Paediatric Society. Prevention and management of neonatal herpes simplex virus infections. *Paediatr Child Heal.* 2014;19(4):201-206.

Committee on Infectious Diseases, American Academy of Pediatrics. Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.

All

Infectiology/HSV

Item 104

Start a topical antiviral treatment in combination with aciclovir IV in neonates with Herpes Simplex Virus (HSV) disease with ocular involvment.

An ophtalmological consultation should be advised.

Start

Grade of recommendations: National Guidelines

Swiss Herpes Management Forum. Swiss recommendations for the management of genital herpes and herpes simplex virus infection in neonate. *Swiss Med Wkly.* 2004;134:205-2014.

Allen UD, Robinson JL, Canadian Paediatric Society. Prevention and management of neonatal herpes simplex virus infections. *Paediatr Child Heal.* 2014;19(4):201-206.

Committee on Infectious Diseases, American Academy of Pediatrics. Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.

All

Infectiology/HSV

Varicella-Zoster Virus (VZV)

Item 105

Start Varicella-Zoster Immune Globulin (VZIG) 125IU IM as soon as exposure is known and within a 72 hour period, independent of maternal history of varicella, in neonates born at <28 weeks of gestational age or who weighed <1000g at birth who have been significantly exposed to Varicella-Zoster Virus (VZV).

Start

Grade of recommendations: National Guidelines

Swiss Herpes Management Forum, Meylan P, Kempf W, et al. Recommandations suisses pour la prise en charge des infections dues au virus de la varicelle-zoster. *Forum Med Suisse.* 2007;7:895-905.

Centers for Disease Control and Prevention. Updated Recommendations for Use of VariZIG — United States, 2013. *Morbidity and Mortality Weeekly Report (MMWR).* https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6228a4.htm. Published 2013. Accessed June 29, 2016.

Cobelli-Kett J. Perinatal varicella. *Pediatr Rev.* 2013;34(1). doi:10.1542/pir.34-1-49.

<28w GA or <1000g BW

Infectiology/VZV

Item 106

Start Varicella-Zoster Immune Globulin (VZIG) 125IU IM in neonates ≥28w GA or ≥1000g BW who have been significantly exposed postnatally to Varicella-Zoster Virus (VZV), only if born to mother who has no or unkown history of varicella.

VZIG must be administered as soon as exposure is known and within a 72 hour period.

Start / stop

Grade of recommendations: National Guidelines

Swiss Herpes Management Forum, Meylan P, Kempf W, et al. Recommandations suisses pour la prise en charge des infections dues au virus de la varicelle-zoster. *Forum Med Suisse.* 2007;7:895-905.

Centers for Disease Control and Prevention. Updated Recommendations for Use of VariZIG — United States, 2013. *Morbidity and Mortality Weeekly Report (MMWR).* https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6228a4.htm. Published 2013. Accessed June 29, 2016.

Cobelli-Kett J. Perinatal varicella. *Pediatr Rev.* 2013;34(1). doi:10.1542/pir.34-1-49.

≥28w GA or ≥1000g BW

Infectiology/VZV

Item 107

Start Varicella-Zoster Immune Globulin (VZIG) 125IU IM as soon as possible, after birth or with onset of maternal illness, in term or late preterm neonates whose mother had varicella disease 5 days prior to or 2 days after delivery.

Start

Grade of recommendations: Institutional Guidelines

Wilson L, Bowers L. Chicken Pox (Varicella Zoster Virus) VZ Immunoglobulin (VZIG) Information. *Newborn Services Clinical Guideline - Auckland District Health Board.* http://www.adhb.govt.nz/newborn/Guidelines/Infection/Varicella/VZIGInformation.htm. Published 2009. Accessed June 29, 2016.

The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network. Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.

Cobelli-Kett J. Perinatal varicella. *Pediatr Rev.* 2013;34(1). doi:10.1542/pir.34-1-49.

All

Infectiology/VZV

Item 108

Start aciclovir IV in neonates who develop systemic symptoms or severe cutaneous Varicella-Zoster disease, or who are at high risk of infection.

Infants at high risk of infection are those who did not receive Varicella-Zoster immunoglobulin (VZIG) as indicated, and/or are immunocompromised, and/or are <28 weeks' GA at birth. Do not give oral aciclovir as absorption is unpredictable in neonates.

Start

Grade of recommendations: National Guidelines

Swiss Herpes Management Forum, Meylan P, Kempf W, et al. Recommandations suisses pour la prise en charge des infections dues au virus de la varicelle-zoster. *Forum Med Suisse.* 2007;7:895-905.

Royal Berkshire, Boden J. Varicella Infection in the Neonate GL366. *NHS Found Trust.* 2009;(October).

Committee on Infectious Diseases, American Academy of Pediatrics. Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.

All

Infectiology/VZV

Item 109

Stop	**Stop Varicella-Zoster immunoglobulin (VZIG)if neonatal chickenpox has developed.** Varicella-Zoster immunoglobulin (VZIG) is of no benefit once neonatal chickenpox has developed and treatment should be discontinued. **Grade of recommendations: Institutional Guidelines** **The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network.** Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.
All	Infectiology/VZV Varicella-Zoster immunoglobulin (VZIG)

Chlamydia

Item 110

Stop	**Do not use prophylactic antibiotic treatment in neonates at high risk of chlamydial infection (born to mothers who have untreated chlamydia).** Neonates born to mothers who have untreated chlamydia are at high risk of infection; however, prophylactic antibiotic treatment is not indicated, as the efficacy of such treatment is unknown. Infants should be monitored to ensure appropriate treatment if symptoms develop. **Grade of recommendations: National Guidelines** **Frieden TR, Jaffe HW, Cono J, et al.** Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Reports.* 2015;64(RR-3):1-140. doi:10.1097/00008480-200308000-00006.
All	Infectiology/Chlamydia OR Prevention/Chlamydia Antibiotics

Item 111

	Start erythromycin orally for 14 days in neonates with chlamydial conjunctivitis or with suspected or confirmed chlamydial pneumonia.
	Follow your institution guideline for dosage. Because the efficacy of erythromycin therapy is approximately 80%, a second course may be required, and a follow-up of infants is recommended. Neonates treated with erythromycin or azithromycin should be observed for signs and symptoms of hypertrophic pyloric stenosis.
Start	**Grade of recommendations: National Guidelines**
	Frieden TR, Jaffe HW, Cono J, et al. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Reports.* 2015;64(RR-3):1-140. doi:10.1097/00008480-200308000-00006. **Committee on Infectious Diseases, American Academy of Pediatrics.** Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.
All	Infectiology/Chlamydia

Item 112

	Start azithromycin as second line treatment when erythromycin is not avaliable in neonates with chlamydial conjunctivitis or with suspected or confirmed chlamydial pneumonia.
	Azithromycin suspension should be administered for 3 days. Neonates treated with erythromycin or azithromycin should be observed for signs and symptoms of hypertrophic pyloric stenosis.
Start	**Grade of recommendations: National Guidelines**
	Frieden TR, Jaffe HW, Cono J, et al. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Reports.* 2015;64(RR-3):1-140. doi:10.1097/00008480-200308000-00006. **Committee on Infectious Diseases, American Academy of Pediatrics.** Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.
All	Infectiology/Chlamydia

Item 113

Stop	**Stop topical antibiotics for the treatment of chlamydial conjunctivitis in neonates.** Topical antibiotic therapy alone is inadequate for the treatment of ophthalmia neonatorum caused by chlamydia and is unnecessary when systemic treatment is administered. **Grade of recommendations: National Guidelines** **Frieden TR, Jaffe HW, Cono J, et al.** Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Reports.* 2015;64(RR-3):1-140. doi:10.1097/00008480-200308000-00006. **Committee on Infectious Diseases, American Academy of Pediatrics.** Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.
All	Infectiology/Chlamydia Topical antibiotics

Gonorrhea

Definition	**Suspicion of Gonorrhea infection:** Gonococcal ophthalmia is strongly suspected when intracellular gram-negative diplococci are identified on Gram stain of conjunctival exudate. Frieden, T. R., Jaffe, H. W., Cono, J., Richards, C. L., & Iademarco, M. F. (2015). Sexually transmitted diseases treatment guidelines, 2015. MMWR Recommendations and Reports, 64(RR-3), 1–140. http://doi.org/10.1097/00008480-200308000-00006

Item 114

Start	**Administer 1 dose of ceftriaxone IV or IM in all neonates born to mothers who have untreated gonorrhea.** Follow your institution guideline for dosage. Treatment must be preceded by testing the infant for gonorrhea at exposed sites. Avoid giving ceftriaxone to premature infants till 41 weeks postmenstrual age, hyperbilirubinemic infants and those receiving calcium-containing intravenous fluids. When ceftriaxone must not be used, cefotaxime can be considered. **Grade of recommendations: National Guidelines** **Frieden TR, Jaffe HW, Cono J, et al.** Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Reports.* 2015;64(RR-3):1-140. doi:10.1097/00008480-200308000-00006. **Committee on Infectious Diseases, American Academy of Pediatrics.** Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.
All	Infectiology/Gonorrhea OR Prevention/Gonorrhea

Item 115

	Administer 1 dose of ceftriaxone IV or IM in neonates with suspected or confirmed gonococcal ophtalmia neonatorum or other localized gonococcal infection.
Start	Follow your institution guideline for dosage. Infant should receive eye irrigations with saline solution immediately and at frequent intervals until discharge is eliminated. Avoid giving ceftriaxone to premature infants till 41 weeks total age, hyperbilirubinemic infants and those receiving calcium-containing intravenous fluids. When ceftriaxone must not be used, cefotaxime can be considered.
	Grade of recommendations: Textbook
	Speer ME. Gonococcal infection in the newborn. *UpToDate.com.* http://www.uptodate.com/contents/gonococcal-infection-in-the-newborn#H19. Published 2015. Accessed May 31, 2016.
All	Infectiology/Gonorrhea

Item 116

	Stop topical antibiotics in neonates with suspected or confirmed gonococcal ophtalmia neonatorum.
Stop	They should receive IV antimicrobial therapy and eye irrigations with saline solution immediately and at frequent intervals until discharge is eliminated. Topical antimicrobial treatment alone is inadequate and unnecessary when recommended systemic antimicrobial treatment is given. This statement does not apply to gonococcal ophtalmia neonatorum prophylaxis, which is practiced in certain medical centers by giving topical treatment at birth to all newborn infants.
	Grade of recommendations: National Guidelines
	Committee on Infectious Diseases, American Academy of Pediatrics. Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.
All	Infectiology/Gonorrhea

Item 117

	Start ceftriaxone IV or IM in neonates with disseminated gonococcal infection.
	Follow your institution guideline for dosage. Avoid giving ceftriaxone to premature infants till 41 weeks total age, hyperbilirubinemic infants and those receiving calcium-containing intravenous fluids. When ceftriaxone must not be used, cefotaxime can be considered.
Start	**Grade of recommendations: National Guidelines**
	Frieden TR, Jaffe HW, Cono J, et al. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Reports.* 2015;64(RR-3):1-140. doi:10.1097/00008480-200308000-00006. **Committee on Infectious Diseases, American Academy of Pediatrics.** Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.
All	Infectiology/Gonorrhea

Methicillin-Resistant Staphylococcal Aureus (MRSA) Infections

Item 118

	Start vancomycin IV until bacteremia is excluded for localized Methicillin-resistant Staphylococcus aureus (MRSA) disease in preterm or very low-birthweight neonates or in more-extensive forms of the disease involving multiple sites in full-term neonates.
Start	
	Grade of recommendations: National Guidelines
	Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis.* 2011;52(3). doi:10.1093/cid/ciq146.
<37w GA	Infectiology/MRSA infections

Definition	**Confirmed congenital infection:** Treponema pallidum demonstrated by darkfield examination (DFE) or polymerase chain reaction (PCR) in placenta or autopsy material, exudate from suspicious lesions or body fluids, e.g. nasal discharge. **Presumed congenital infection:** • Children with a positive treponemal test for syphilis in combination with one or several of the following: - persistent rhinitis, condylomata lata, osteitis, periostitis, osteochondritis, ascites, cutaneous and mucous membrane lesions, hepatitis, hepatosplenomegaly, glomerulonephritis, haemolytic anaemia; - radiological abnormalities of the long bones suggestive of congenital syphilis; - a positive Rapid Plasma Reagin (RPR) test / Venereal Diseases Research Laboratory (VDRL) test in the cerebrospinal fluid; - a fourfold increase or more of the T. pallidum Passive Particle Agglutination (TPPA) / T. pallidum Haemagglutination (TPHA) titre in the child's as opposed to the mother's serum (both obtained simultaneously at birth); - a fourfold increase or more of the titre of a non-treponemal test in the child's as opposed to the mother's serum (both obtained simultaneously at birth); - a fourfold increase or more of the titre of a non-treponemal test within 3 months after birth; - a positive anti-treponemal IgM EIA,19S-IgM-FTA-abs test and/or IgM- immunoblot for T. pallidum in the child's serum; - a mother, in whom syphilis was confirmed during pregnancy, but who was not adequately treated either before or during pregnancy. **Carlin E, Ziza J, Keat A, Janier M.** 2014 European Guideline on the management of sexually acquired reactive arthritis. *Int J STD AIDS.* 2014;25(13):901-912. doi:10.1177/0956462414540617.

Item 119

Start	**Administer benzylpenicillin G IV, OR procaine penicillin to neonates with confirmed or presumed congenital syphilis, or born to syphilis infected mothers who have not been treated with penicillin at least four weeks prior delivery.** Follow your institution guideline for dosage. **Grade of recommendations: National Guidelines** **Frieden TR, Jaffe HW, Cono J, et al.** Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Reports.* 2015;64(RR-3):1-140. doi:10.1097/00008480-200308000-00006. **Committee on Infectious Diseases, American Academy of Pediatrics.** Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.
All	Infectiology/Syphilis

Item 120

	Administer 1 dose of benzathine penicillin G IM in neonates with normal examination, born to syphilis infected mothers who have been adequately treated during pregnancy more than 4 weeks prior to delivery.
Start	Follow your institution guideline for dosage. If mother's nontreponemal serologic titer remained low and stable before and during pregnancy and at delivery (Venereal Disease Research Laboratory (VDRL) slide test <1:2; rapid plasma reagin (RPR) test <1:4), no treatment is required. If follow-up is uncertain, a single dose of benzathin penicillin G IM can be considered.
	Grade of recommendations: National Guidelines **Frieden TR, Jaffe HW, Cono J, et al.** Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Reports.* 2015;64(RR-3):1-140. doi:10.1097/00008480-200308000-00006. **Committee on Infectious Diseases, American Academy of Pediatrics.** Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.
All	Infectiology/Syphilis

Ureaplasma Urealyticum Infection

Item 121

	Reassess the use of macrolides or other antibiotics for the treatment of Ureaplasma urealyticum in neonates.
Stop	Despite in vitro susceptibility of Ureaplasma spp. to erythromycin and favorable pharmacokinetic activity, trials of erythromycin therapy in ureaplasma-colonized preterm infants have failed to demonstrated efficacy to prevent BPD or to eradicate respiratory tract colonization (C). The efficacy of azithromycin and related macrolide, clarithromycin, to prevent BPD has been assessed in single center studies of at-risk preterm infants, but the safety and optimal dosing regimens for these antibiotics have not been determined in appropriate pharmacokinetic and pharmacodynamic studies. It is currently unknown whether eradicating Ureaplasma spp. from the preterm respiratory tract with appropriate antibiotic therapy will prevent ureaplasma infection-mediated lung injury (FRN).
	Grade of recommendations: Review **Viscardi RM.** Ureaplasma species: Role in Neonatal Morbidities and Outcomes. *Arch Dis Child Fetal Neonatal Ed.* 2014;99(1):1-14. doi:10.1136/archdischild-2012-303351.
All	Infectiology/Ureaplasma Urealyticum Infection Macrolides

Urinary Tract Infection (UTI)

Definition	**Urinary tract infection is defined here as:** 1. Pyuria as determined with an “enhanced urinalysis” (hemocytometer counting chamber) of ≥10 WBC/μL; 2. A urine culture colony count of ≥10 000 CFU/mL for a single organism. **Vesico-ureteric reflux (VUR):** Grade I: urine refluxes into the ureter only; Grade II: urine refluxes into the ureter and up to the kidney without dilation; Grade III: urine refluxes into the ureter and kidney and causes mild dilation; Grade IV: urine refluxes into ureter and kidney and causes dilation without twisting of the ureter; Grade V: urine refluxes into ureter and kidney and causes significant dilation with twisting of the ureter. **Santoro JD, Carroll VG, Steele RW.** Diagnosis and Management of Urinary Tract Infections in Neonates and Young Infants. *Clin Pediatr (Phila).* 2012;52(2):111-114. doi:10.1177/0009922812471713. **UCSF Department of Urology.** Vesicoureteral Reflux (VUR). *Urology care foundation.* https://urology.ucsf.edu/patient-care/children/additional/vesicoureteral-reflux. Published 2016. Accessed June 30, 2016.

Item 122

Start	**Start empiric antibiotics after urine samples and cultures are collected in neonates with fever when urinary tract infection is suspected.** Follow your institution guidelines for dosage and choice of antibiotic agents. **Grade of recommendations: International Guidelines** **Bradley JS, Nelson JD.** Nelson’s Pediatric Antimicrobial Therapy. 19th Editi. *(American Academy of Pediatrics, ed.)*. San Diego: American Academy of Pediatrics; 2012. **O’Donovan DJ.** Urinary tract infections in neonates. *UpToDate.com.* http://www.uptodate.com/contents/urinary-tract-infections-in-neonates#H776291741. Published 2015. Accessed June 30, 2016. **European Association of Urology, Stein R, Dogan HS, et al.** Urinary tract infections in children: EAU/ESPU guidelines. *Eur Urol.* 2015;67:546-558. doi:10.1016/j.eururo.2014.11.007.
All	Infectiology/UTI

Item 123

	Consider antibiotic prophylaxis after an urinary tract infection (UTI) only in neonates with grade IV-V vesico-ureteric reflux.
	Antibiotic prophylaxis in order to avoid recurrent UTI is no longer routinely recommended after a UTI but may still be considered when a child is known to have a grade IV or V VUR, or a significant uro- logical anomaly. Grade IV-V are defined as urine refluxes into ureter and kidney and causes dilatation with or without twisting of the ureter.
Start / stop	**Grade of recommendations: International Guidelines**
	Canadian Paediatric Society, Robinson JL, Finlay JC, Lang ME, Bortolussi R. Prophylactic antibiotics for children with recurrent urinary tract infections. *Paediatr Child Heal.* 2015;20(1):45-47. doi:10.1093/jac/25.4.505.
	European Association of Urology, Stein R, Dogan HS, et al. Urinary tract infections in children: EAU/ESPU guidelines. *Eur Urol.* 2015;67:546-558. doi:10.1016/j.eururo.2014.11.007.
	Bradley JS, Nelson JD. Nelson's Pediatric Antimicrobial Therapy. 19th Editi. *(American Academy of Pediatrics, ed.)*. San Diego: American Academy of Pediatrics; 2012.
All	Infectiology/UTI Antibiotics

Pertussis

Definition	**Suspicion of Pertussis infection:** Pertussis should be suspected (regardless of vaccination status or wheezing) in the following patients (see 'Clinical suspicion' above): •Infants <4 months with a cough illness, usually without significant fever, who have: -Cough that is not improving (of any duration); the cough may or may not be paroxysmal (movie 1) -Rhinorrhea in which the nasal discharge remains watery -Apnea, seizures, cyanosis, vomiting, or poor weight gain -Leukocytosis with lymphocytosis (WBC count ≥20,000 cells/microL with ≥50 percent lymphocytes) -Pneumonia **Yeh S, Mink CM.** Bordetella pertussis infection in infants and children: Clinical features and diagnosis. *UpToDate.com.* http://www.uptodate.com/contents/bordetella-pertussis-infection-in-infants-and-children-clinical-features-and-diagnosis?source=see_link. Published 2016. Accessed August 30, 2016.

Item 124

Start	**Start azithromycin oral daily for 5 days in neonates with suspected or confirmed pertussis infection, or in those in close contact with confirmed and contagious cases of pertussis.** Follow your institution guideline for dosage. A person is contagious when < 21 days of cough and < 5 days effective antibiotics. Neonates on macrolide should be monitored for infantile hypertrophic pyloric stenosis (IHPS). **Grade of recommendations: National Guidelines** **The Royal Children's Hospital Melbourne.** Whooping Cough (Pertussis). The *Royal Children's Hospital Melbourne.* http://www.rch.org.au/clinicalguide/guideline_index/Whooping_Cough_Pertussis/. Published 2016. Accessed June 30, 2016. **Committee on Infectious Diseases, American Academy of Pediatrics.** Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012. **Amirthalingam G, Pertussis Guidelines Group.** HPA guidelines for the public health management of pertussis. *Heal Prot Agency.* 2012;(October):1-45. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1287142671506.

All	Infectiology/Pertussis

Tuberculosis

Item 125

Start isoniazid prophylaxis orally in neonates born to mothers with tuberculosis (TB), or those in close contact with people with smear-positive pulmonary or laryngeal TB who have not had at least 2 weeks of anti-tuberculosis treatment.

Start

Prophylaxis for babies born to mothers with active TB is 9 months, and 2-3 months in those born to mothers with inactive TB, if the infant remains asymptomatic. Infants exposed postnatally should be treated 2-3 months after last exposure, if the infant remains asymptomatic. Follow your institution guideline for dosage.

Grade of recommendations: National Guidelines

Centre for Communicable Diseases and Infection Control. Pediatric Tuberculosis. In: Public Health Agency of Canada, ed. *Canadian Tuberculosis Standards.* 7th Editio. Public Health Agency of Canada; 2007. http://www.lung.ca/cts-sct/pdf/tbstand07_e.pdf.

National Institute For Health and Care Excellence. Tuberculosis. *NICE Clin Guidel.* 2016;33. nice.org.uk/guidance/ng33.

Bradley JS, Nelson JD. Nelson's Pediatric Antimicrobial Therapy. 19th Editi. *(American Academy of Pediatrics, ed.)*. San Diego: American Academy of Pediatrics; 2012.

All — Infectiology/Tuberculosis OR Prevention/Tuberculosis

Item 126

Start anti-tuberculosis treatment in neonates with congenital tuberculosis or postnatal tuberculosis primary pulmonary disease.

Start

Follow your institution guideline for dosage.

Grade of recommendations: Textbook

Bradley JS, Nelson JD. Nelson's Pediatric Antimicrobial Therapy. 19th Editi. *(American Academy of Pediatrics, ed.)*. San Diego: American Academy of Pediatrics; 2012.

Mittal H, Das S, Faridi MMA. Management of newborn infant born to mother suffering from tuberculosis: Current recommendations & gaps in knowledge. *Indian J Med Res.* 2014;140:32-39.

All — Infectiology/Tuberculosis

10. ENDOCRINOLOGY
Metabolic Bone Disorder (MBD)

Definition	**Metabolic Bone Disorder** Decreased bone mineral content relative to the expected level of mineralization for a fetus or infant of comparable size or gestational age seen in conjunction with biochemical and/or radiographic changes. **Rustico SE, Calabria AC, Garber SJ.** Metabolic bone disease of prematurity. *J Clin Transl Endocrinol.* 2014;1:85-91. doi:10.1016/j.jcte.2014.06.004.

Definition	**Risk factors for Metabolic Bone Disorder**
	- <32 weeks' gestation or <1500 g birth-weight
	- Male gender
	- Inadequate nutrition
	  - Suboptimal intake
	  - Enteral feeds with low mineral content/bioavailability (unfortified expressed breast milk, term formula given to a preterm infant)
	- Phosphorus deficiency (primary nutritional reason)
	- Vitamin D deficiency
	- Prolonged total parenteral nutrition
	- Chronic use of drugs that increase mineral excretion (diuretics, dexamethasone, sodium bicarbonate)
	- Lack of mechanical stimulation e.g. sedation/paralysis
	- Bronchopulmonary dysplasia
	- Cholestatic jaundice
	- Short gut syndrome (malabsorption of vitamin D and Ca)
	The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network. Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.

Item 127

	Administer calcium, phosphate and vitamin D in preterm infants <32 weeks of gestational age or <1500g or infants at risk of metabolic bone disorders.
Start	When receiving enteral feed, neonates should be given a fortifier (in breastfed infants) or preterm formula with calcium (3.5-5.5 mmol/kg/day) and phosphate (2.5-4.5 mmol/kg/day). If parenteral nutrition is needed, use parenteral nutrition with optimised calcium and phosphate content (Ca 1.8 mmol/kg/day and PO4 1.4 mmol/kg/day) and vitamin D 160-400 IU/kg/day. Maximal mineral accretion rates have been reported with Ca/PO4 (mol/mol) ratio 1.3. In neonates with biochemical features found in metabolic bone disease, aim for the upper end of the recommended range of calcium and phosphate intake to prevent fractures.
	Grade of recommendations: Review
	Royal Prince Alfred Hospital Care Newborn. Metabolic bone disease. *Sydney Local Health District - New South Wales government.* http://www.slhd.nsw.gov.au/rpa/neonatal\content/pdf/guidelines/metabolicBD.pdf. Published 2016. Accessed June 24, 2016. **Rustico SE, Calabria AC, Garber SJ.** Metabolic bone disease of prematurity. *J Clin Transl Endocrinol.* 2014;1:85-91. doi:10.1016/j.jcte.2014.06.004. **Pereira-da-Silva L, Costa A, Pereira L, et al.** Early high calcium and phosphorus intake by parenteral nutrition prevents short-term bone strength decline in preterm infants. *J Pediatr Gastroenterol Nutr.* 2011;52(2):203-209. doi:10.1097/MPG.0b013e3181f8b295.
All	Prevention/Prevention of MBD OR Endocrinology/MBD

Item 128

Start	**Administer the maximal recommended doses of calcium, phosphate and vitamin D to prevent fractures in neonates with biochemical features of metabolic bone disease.** Recommended range are: When receiving enteral feed, neonate should be given fortifier (for breastfed infant) or preterm formula with calcium (3.5-5.5 mmol/kg/day) and phosphate (2.5-4.5 mmol/kg/day). Do not give Ca and PO4 at the same time because they may precipitate; so give at alternate feeds. If parenteral nutrition is needed, use parenteral nutrition with optimised calcium and phosphate content (Ca 1.8 mmol/kg/day and PO4 1.4 mmol/kg/day) and vitamin D 160-400 IU/kg/day. Maximal mineral accretion rates have been reported with Ca/PO4 (mol/mol) ratio 1.3. **Grade of recommendations: Institutional Guidelines** **Royal Prince Alfred Hospital Care Newborn.** Metabolic bone disease. *Sydney Local Health District - New South Wales government.* http://www.slhd.nsw.gov.au/rpa/neonatal\content/pdf/guidelines/metabolicBD.pdf. Published 2016. Accessed June 24, 2016. **Rustico SE, Calabria AC, Garber SJ.** Metabolic bone disease of prematurity. *J Clin Transl Endocrinol.* 2014;1:85-91. doi:10.1016/j.jcte.2014.06.004. **Pereira-da-Silva L, Costa A, Pereira L, et al.** Early high calcium and phosphorus intake by parenteral nutrition prevents short-term bone strength decline in preterm infants. *J Pediatr Gastroenterol Nutr.* 2011;52(2):203-209. doi:10.1097/MPG.0b013e3181f8b295.
All	Endocrinology/MBD

Item 129

Stop	**Stop steroids and furosemide as soon as possible in neonates at risk of metabolic bone disorder.** In the primary prevention and treatment strategy for MBD, limiting the prolonged exposure to commonly prescribed medications that further reduce mineral stores (e.g. loop diuretics and methylxanthines) or increase bone resorption (e.g. glucocorticoids) is equally important to optimizing nutrition. **Grade of recommendations: National Guidelines** **Rustico SE, Calabria AC, Garber SJ.** Metabolic bone disease of prematurity. *J Clin Transl Endocrinol.* 2014;1:85-91. doi:10.1016/j.jcte.2014.06.004. **Abrams SA, Committee on Nutrition, American Academy of Pediatrics.** Calcium and Vitamin D Requirements of Enterally Fed Preterm Infants. *Pediatrics.* 2013;131(5):e1676-83. doi:10.1542/peds.2013-0420.
All	Prevention/Prevention of MBD OR Endocrinology/MBD

Thyroid Disorders (OR Hypothyroidism)

Item 130

	Start levothyroxine (L-T4) immediately in neonates with thyroid function test (TFT) that results in either a free T4 (FT4) concentration below norms for age or a venous TSH concentration > 20 mIU/L.
Start	TFT is normaly performed when capillary TSH concentration from blood obtained on neonatal screening was elevated; therefore this recommendation assumes a high capillary TSH value. Imaging should never be allowed to delay the initiation of treatment. Recommended treatment is levothyroxine (L-T4), given at an initial oral dose of 10 –15 µg/kg/day. Infants with very low total T4 or free T4 should be treated with the highest initial dose. Any change in source of the L-T4 (brand) or in formulation (liquid vs tablets) requires retitration of the dose. If intravenous treatment is necessary the dose should be no more than 80% of the oral dose. The dose should then be adjusted according to TSH and FT4 levels.
	Grade of recommendations: International Guidelines
	Léger J, Olivieri A, Donaldson M, et al. European Society for Paediatric Endocrinology Consensus Guidelines on Screening, Diagnosis, and Management of Congenital Hypothyroidism. *J Clin Endocrinol Metab.* 2014;99(2):363–384. doi:10.1159/000358198.
	Rose SR, Brown RS, American Academy of Pediatrics, American Thyroid Association, Lawson Wilkins Pediatric Endocrine Society. Update of Newborn Screening and Therapy for Congenital Hypothyroidism. *Pediatrics.* 2006;117(6):2290-2303. doi:10.1542/peds.2006-0915.
All	Endocrinology/Congenital hypothyroidism OR Endocrinology/Thyroid disorders

Hyperglycemia

Definition	**Hyperglycemia** There is no established definition of hyperglycemia. However, start management if: - two blood sugars are ≥14 on 2 occasions measured at least 2 hr apart or - blood sugars are ≥12 on 2 occasions measured at least 2 hr apart with evidence of significant glycosuria (positive on the urine dipstick). The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, & Southern West Midlands Maternity and Newborn Network. (2015). Neonatal Guidelines 2015-17. Retrieved January 1, 2016, from https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines

Item 131

	Decrease glucose intake if necessary and decrease or stop drugs that worsen hyperglycemia, in neonates with hyperglycemia.
	If glucose delivery rate >10 mg/kg/min, decrease glucose in increments to 6–10 mg/kg/min. If on TPN, 8–10 mg/kg/min is acceptable. Medications that can worsen hyperglycemia include corticosteroids and phenytoin.
Stop	**Grade of recommendations: Textbook** **Stark AR, Simmons R.** Neonatal hyperglycemia. *UpToDate.com.* http://www.uptodate.com/contents/neonatal-hyperglycemia? Published 2015. Accessed July 5, 2016. **The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network.** Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.

All	Endocrinology/Hyperglycemia

Item 132

Start insulin only in patients with persistent hyperglycemia when other methods of glucose control have failed.

Other methods of glucose control include decrease of glucose infusion rates, stop of medications predisposing patients to hyperglycemia, and correction of underlying causes of hyperglycemia (i.e., sepsis). Starting dose of insulin is usually 0.05 units/kg/hr, then adjusted according to requirements. Do not include insulin in the total daily fluid intake - it should be titrated on top of the prescribed fluid intake. Monitor the blood glucose concentration, initially once every 2 hours, and once stable at least once every 8 hours. Aim for a blood glucose concentration between 6 and 10 mmol/L.
To prevent hypoglycaemia in neonate on insulin:
- 6-8 mmol/L and stable -> maintain insulin infusion
- 6-8 mmol/L with a moderate decrease: reduce insulin infusion rate to 50% of present rate
- <6 mmol/L or 6-8 mmol/L with a rapid decrease: stop infusion

Start / stop

Grade of recommendations: National Guidelines

The Bedside Clinical Guidelines Partnership, Staffordshire Shropshire & Black Country Newborn and Maternity Network, Southern West Midlands Maternity and Newborn Network. Neonatal Guidelines 2015-17. *NHS network.* https://www.networks.nhs.uk/nhs-networks/staffordshire-shropshire-and-black-country-newborn/neonatal-guidelines. Published 2015. Accessed January 1, 2016.

Stark AR, Simmons R. Neonatal hyperglycemia. *UpToDate.com.* http://www.uptodate.com/contents/neonatal-hyperglycemia? Published 2015. Accessed July 5, 2016.

Fallon EM, Nehra D, Potemkin AK, et al. A.S.P.E.N. Clinical Guidelines: Hyperglycemia and Hypoglycemia in the Neonate Receiving Parenteral Nutrition. *J Parenter Enter Nutr.* 2012;36(1):81-95. doi:10.1177/0148607111418980.

Alsweiler J. Hyperglycaemia Causes of Hyperglycaemia Complications of Hyperglycaemia Management of Hyperglycaemia Management of Insulin Infusion. *Newborn Services Clinical Guideline - Auckland District Health Board.* http://www.adhb.govt.nz/newborn/Guidelines/Nutrition/Hyperglycaemia.htm. Published 2013. Accessed July 4, 2016.

All

Endocrinology/Hyperglycemia

Item 133

Stop	**Do not provide high glucose infusion rates to prevent hypoglycemia in neonates receiving parenteral nutrition.** Excess glucose delivery should be avoided to maintain optimal blood glucose concentrations in neonates receiving parenteral nutrition as this may lead to hyperglycemia. **Grade of recommendations: National Guidelines** **Fallon EM, Nehra D, Potemkin AK, et al.** A.S.P.E.N. Clinical Guidelines: Hyperglycemia and Hypoglycemia in the Neonate Receiving Parenteral Nutrition. *J Parenter Enter Nutr.* 2012;36(1):81-95. doi:10.1177/0148607111418980.
All	Prevention/Prevention of hyperglycemia OR Endocrinology/Hyperglycemia Total Parenteral Nutrition (TPN)

Item 134

Stop	**Do not use early insulin therapy in neonates at risk of hyperglycemia.** The use of early insulin therapy to prevent hyperglycemia is not recommended. There has been substantial research regarding the use of early, continuous insulin infusion to prevent hyperglycemia in the neonate. While a number of small studies suggest a benefit, other larger studies have raised significant concerns regarding this practice. Specifically, a large RCT was terminated early due to increased incidence of hypoglycemia and mortality in the early continuous insulin infusion group. A recent Cochrane review also determined that there is insufficient evidence to recommend early, continuous insulin infusion. **Grade of recommendations: A** **Fallon EM, Nehra D, Potemkin AK, et al.** A.S.P.E.N. Clinical Guidelines: Hyperglycemia and Hypoglycemia in the Neonate Receiving Parenteral Nutrition. *J Parenter Enter Nutr.* 2012;36(1):81-95. doi:10.1177/0148607111418980.
All	Prevention/Prevention of hyperglycemia OR Endocrinology/Hyperglycemia OR Prevention/Prevention of hypoglycemia OR Endocrinology/Hypoglycemia Insulin

Hypoglycemia

Definition	**Symptoms of hypoglycemia in newborns include:** Irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding. **Neonates at increased risk of hypoglycemia:** 1. Symptoms of hypoglycemia 2. Large for gestational age (even without maternal diabetes) 3. Perinatal stress a. Birth asphyxia/ischemia; cesarean delivery for fetal distress b. Maternal preeclampsia/eclampsia or hypertension c. Intrauterine growth restriction (small for gestational age) d. Meconium aspiration syndrome, erythroblastosis fetalis, polycythemia, hypothermia 4. Premature or postmature delivery 5. Infant of diabetic mother 6. Family history of a genetic form of hypoglycemia 7. Congenital syndromes (eg, Beckwith-Wiedemann), abnormal physical features (eg, midline facial malformations, microphallus) **Persistent hypoglycemia** Hypoglycemia that persists or occurs for the first time beyond the first 3 days of life.

Adamkin DH. Postnatal Glucose Homeostasis in Late-Preterm and Term Infants Clinical Report—Postnatal Glucose Homeostasis in Late-Preterm and Term Infants. *Pediatrics.* 2013;127(3):575-579. doi:10.1542/peds.2010-3851.

Thornton PS, Stanley CA, De Leon DD, et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. *J Pediatr.* 2015;167(2):238-245. doi:10.1016/j.jpeds.2015.03.057.

Item
135

Start IV glucose infusion in asymptomatic neonates with serum glucose level of <2.6 mmol/L if increased enteral caloric intake is not effective.

Start with an initial glucose infusion regime of 5.5 mg/kg/min. Infants with very low glucose levels, particularly those with levels less than 1.8 mmol/L, should be managed with some expedience, confirming response to intervention in a timely fashion (a response to intravenous interventions should occur within 30 min). Breastfeeding may be continued without risk of overhydration because the volume of colostrum is small. Blood glucose levels should be checked frequently until interventions result in stable glucose levels of 2.6 mmol/L or higher. In neonates with persistent hypoglycemia, consider investigation, consultation and pharmacological intervention if target blood glucose levels are not achieved by intravenous glucose.

Start

Grade of recommendations: Institutional Guidelines

Canadian Paediatric Society Fetus and Newborn Committee, Aziz K, Dancey P. Screening guidelines for newborns at risk for low blood glucose. *Paediatr Child Heal.* 2004;(March 2004, reaffirmed in 2016):1-7.

Queensland Clinical Guidelines Queensland Health. Maternity and Neonatal Clinical Guideline Induction of labour. *Queensl Gov Dep Heal.* 2015;(April). www.health.qld.gov.au/qcg.

Weston P, Harris D, Battin M, Brown J, Hegarty J, Harding J. Oral dextrose gel for the prevention of hypoglycaemia in newborn infants. *Cochrane Database Syst Rev.* 2016;(5). doi:10.1002/14651858.CD011027.pub2.

Thornton PS, Stanley CA, De Leon DD, et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. *J Pediatr.* 2015;167(2):238-245. doi:10.1016/j.jpeds.2015.03.057.

All

Endocrinology/Hypoglycemia

Item
136

Start	**Start IV glucose infusion immediately in symptomatic neonates with glucose levels <2.6 mmol/L.** Because severe, prolonged, symptomatic hypoglycemia may result in neuronal injury, prompt intervention is necessary for infants who manifest clinical signs and symptoms. At-risk infants with glucose levels less than 1.8 mmol/L on one occasion (assuming one effective feed), or repeatedly less than 2.6 mmol/L, require intervention (C). There should be concurrent investigation and management of the underlying cause. Breastfeeding may be continued without risk of overhydration because the volume of colostrum is small. Blood glucose levels should be checked frequently until interventions result in stable glucose levels of 2.6 mmol/L or higher. In neonates with persistent hypoglycemia, consider investigation, consultation and pharmacological intervention if target blood glucose levels are not achieved by intravenous glucose.
	Grade of recommendations: National Guidelines **Canadian Paediatric Society Fetus and Newborn Committee, Aziz K, Dancey P.** Screening guidelines for newborns at risk for low blood glucose. *Paediatr Child Heal.* 2004;(March 2004, reaffirmed in 2016):1-7. **Adamkin DH, American Academy of Pediatrics Committee on Fetus and Newborn.** Postnatal Glucose Homeostasis in Late-Preterm and Term Infants Clinical Report—Postnatal Glucose Homeostasis in Late-Preterm and Term Infants. *Pediatrics.* 2013;127(3):575-579. doi:10.1542/peds.2010-3851. **Thornton PS, Stanley CA, De Leon DD, et al.** Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. *J Pediatr.* 2015;167(2):238-245. doi:10.1016/j.jpeds.2015.03.057.
All	Endocrinology/Hypoglycemia

11. PHARMACOLOGY
Drug & Breast-Feeding

Item 137

	Check the possible milk transfer of drugs taken by mothers to breastfed neonates, and monitor for potential adverse drug effects.
Other	Different references can be consulted or refere to a specialist (clinical pharmacist or pharmacologist). For exemple, several reported cases of codeine toxicity, in breastfed neonates (including death) have been published. Keep in mind that drugs given to the breastfeeding mother can also interact with the treatment of the neonate. Here are exemples of common sources of information about drugs and lactation: - **Briggs GG, Freeman RK, Yaffe SJ.** Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. 9th Editio. *(Wolters Kluwer Health/Lippincott Williams & Wilkins, ed.).* California; 2012. - **Swiss teratogen information service**: http://www.swisstis.ch/ - **Centre de référence sur les agents tératogènes** (in french): www.lecrat.org
	Grade of recommendations: -

All

Pharmacology/Drug & Breast-Feeding
All

Drug-drug Interactions

Item 138

Check changes in drug effect when initiating strong inhibitors or inducers of the cytochrome P450 and/or P-glycoprotein.

Other

Although difficult to predict, modification of plasma concentration may occur when initiating strong inhibitors or inducers of the cytochrome P450 and/or P-glycoprotein.
Exemples of strong inhibitors and inducers used in neonates are:
Inhibitors: erythromycine, fluconazole.
Inducers: phenobarbital, phenytoin, rifampicin.
Keep in mind that drugs given to the breastfeeding mother can also interact with the treatment of the neonate, if transfer to milk occurs.
Here are exemples of common sources of information about drug interactions:
- Lexicomp's Lexi-Interact: http://www.uptodate.com/crlsql/interact/frameset.jsp
- HUG pocket's card, Drug interaction, cytochrome and P-glycoprotein (validated for adult patient): http://www.hug-ge.ch/sites/interhug/files/structures/pharmacologie_et_toxicologie_cliniques/documents/interactions_medicamenteuses_et_cyp450.pdf
- Theriaque: http://www.theriaque.org/

Grade of recommendations: D

de Wildt SN, Tibboel D, Leeder JS. Drug metabolism for the paediatrician. *Arch Dis Child.* 2014;99(12):1137-1142. doi:10.1136/archdischild-2013-305212.

Tayman C, Rayyan M, Allegaert K. Neonatal pharmacology: extensive interindividual variability despite limited size. *J Pediatr Pharmacol Ther.* 2011;16(3):170-184. doi:10.5863/1551-6776-16.3.170.

Centre d'information thérapeutique et de pharmacovigilance. Interactions Medicamenteuses, Cytochromes P450 et p-Glycoproteine (pgp). *Hôpitaux Universitaires de Genève.* http://www.hug-ge.ch/sites/interhug/files/structures/pharmacologie_et_toxicologie_cliniques/documents/interactions_medicamenteuses_et_cyp450.pdf. Published 2016. Accessed September 16, 2016.

All

Pharmacology/Drug-drug Interactions

Erythromycine, fluconazole, phenobarbital, phenytoin, rifampicin.

Various

Item 139

Do not use ceftriaxone in neonates who are being, or who have recently been given any IV fluids that contain calcium (such as TPN or Ringer Lactate)

Precipitation may occur even when the two products are administered in different tubes and could be potentially lethal. Ceftriaxone can also induce kernicterus in the neonate by displacing bilirubin from plasmatic proteins, and its use should be avoided when possible.

Stop

Grade of recommendations: Manufacturer

Bradley JS, Wassel RT, Lee L, Nambiar S. Intravenous ceftriaxone and calcium in the neonate: assessing the risk for cardiopulmonary adverse events. *Pediatrics.* 2009;123(4):e609-13. doi:10.1542/peds.2008-3080.

Ainsworth SBA. Neonatal Formulary. 7th ed. *(John Wiley & Sons, ed.).* Chichester, UK; 2015.

Choonara I, Sammons H. Paediatric clinical pharmacology in the UK. *Arch Dis Child.* 2014;99(12):1143-1146. doi:10.1136/archdischild-2014-306853.

Roche Laboratories Inc. Product Information: Rocephin IV, IM injection, powder for solution. *Swissmedicinfo.ch.* Swissmedic.ch. Published 2010. Accessed July 25, 2016.

All

Pharmacology/Various

Calcium, ceftriaxone

Item 140

	Do not use trimethoprime - sulfamethoxazole in neonates.
	Trimethoprime-sulfamethoxazole is contra-indicated in neonates. Sulphonamides can induce kernicterus in the neonate by displacing bilirubin from plasmatic proteins.
Stop	**Grade of recommendations: National Guidelines**
	Committee on Infectious Diseases, American Academy of Pediatrics. Redbook: Report of the Committee on Infectious Diseases. 29th Editi. *(American Academy of Pediatrics, ed.)*. Elk Grove Village, IL: American Academy of Pediatrics; 2012.
	Choonara I, Sammons H. Paediatric clinical pharmacology in the UK. *Arch Dis Child.* 2014;99(12):1143-1146. doi:10.1136/archdischild-2014-306853.
All	Pharmacology/Various
	Trimethoprime - sulfamethoxazole, Co-trimoxazole

Item
141

Check excipients contained in prescribed drug formulations administered orally or parenterally since they can be harmful and responsible for adverse events in neonates, due to immature metabolism.

Benzyl alcohol must not be given to premature babies or neonates due to risks of serious adverse effects (gasping syndrome and deaths have been reported).
Propylenglycol must not be administrated to neonates at a dose higher than 1 mg/kg/day because it could lead to metabolic acidosis.
Excipients identified as known to be harmful to neonates should be avoided as much as possible. The sum of methyl-, ethyl- and propylparaben should not be >10mg/kg/day in oral drugs and propylparaben oral daily intake should not be >2mg/kg/day.
Other excipients known to be harmful in neonates are: polysorbate 80, sodium benzoate, benzalkonium chloride, saccharin sodium, sorbitol and ethanol. High dose and long term use should be avoided when possible.

Grade of recommendations: D

Stop

European Commission. Guidelines Medicinal products for human use Safety , environment and information. Excipients in the label and package leaflet of medicinal products for human use. *Pharm Regul Framew Mark Auth.* 2003. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf.

Lass J, Naelapää K, Shah U, et al. Hospitalised neonates in Estonia commonly receive potentially harmful excipients. *BMC Pediatr.* 2012;12:136. doi:10.1186/1471-2431-12-136.

Shehab N, Lewis CL, Streetman DD, Donn SM. Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. *Pediatr Crit Care Med.* 2009;10(2):256-259. doi:10.1097/PCC.0b013e31819a383c.

Souza A, Santos D, Fonseca S, et al. Toxic excipients in medications for neonates in Brazil. *Eur J Pediatr.* 2014;173(7):935-945. doi:10.1007/s00431-014-2272-z.

Nellis G, Metsvaht T, Varendi H, et al. Potentially harmful excipients in neonatal medicines: a pan-European observational study. *Arch Dis Child.* 2015;100(7):694-699. doi:10.1136/archdischild-2014-307793.

Committee for Human Medicinal Products (CHMP). Background review for the excipient propylene glycol. *Eur Med Agency.* 2014;44(EMA/CHMP/334655/2013):1-96.

Committee for Medicinal Products for Human Use (CHMP). Reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use. *Eur Med Agency.* 2015;44(EMA/CHMP/SWP/272921/2012):1-3. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143139.pdf.

Kozarewicz P, European Medicines Agency (EMA). Preservatives: Are they safe? *Eur Med Agency.* 2010;(May).

European Food Safety Authority (EFSA). Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a Request from the Commission related to para hydroxybenzoates (E 214-219). *EFSA J.* 2006;965(October 2000):1-7. doi:10.2903/j.efsa.2007.428.

All

Pharmacology/Various

All

Appendix 6: age/weight restrictions for NeoCheck items

TABLE A6-3 Distribution of age/weight restrictions among NeoCheck items

Age/weight restriction	Number of statements (%)
None	111 (79)
GA < 37 weeks	18 (13)
GA ≥ 37 weeks	2 (1)
GA < 34 weeks or BW < 2500 g	1 (1)
GA < 32 weeks and/or BW < 1500 g	4 (3)
GA < 28 weeks or BW < 1000 g	1 (1)
GA ≥ 28 weeks or BW ≥ 1000 g	2 (1)
GA < 26 weeks	3 (1)
GA ≥ 26 weeks	4 (1)

GA, gestational age; BW, body weight.