Guideline Safe Use of Contrast Media Part 4 Children

This part comprises modules specifically for children on:

- **Risk stratification in the Prevention of Post Contrast Acute Kidney Injury (PC-AKI)**
- **Hydration Strategies in the Prevention of PC-AKI**
- **Profylactic Measures for Hypersensitivity Reactions**
- **Treatment of Acute hypersensitivity reactions**
- **Monitoring of Thyroid Function after Administration of Iodine-based Contrast Media**

INITIATED BY
Radiological Society of The Netherlands (NVvR)

IN ASSOCIATION WITH
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Colophon
GUIDELINE SAFE USE OF CONTRAST MEDIA - PART 4 - CHILDREN

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Overall Introduction

Reason for making this guideline
The Radiological Society of the Netherlands (Nederlandse Vereniging voor Radiologie/NVvR) deemed a set of new guidelines on the Safe Use of Contrast Media (CM) highly necessary and relevant. In radiology, contrast media, such as Iodine-based Contrast Media (ICM) and Gadolinium Based Contrast Agents (GBCA), are extensively used. The overall goal of this set of guidelines was to increase safety and awareness around contrast media. Practical recommendations are given in each chapter.

The four parts of the Safe Use of Contrast Media guidelines cover the following topics regarding CM safety:

Safe Use of Contrast Media - Part 1 (finalized in 2017):
- Prevention of post-contrast acute kidney injury (PC-AKI*) from iodine-based contrast media
- Iodine-based contrast media use in patients with type-2 diabetes taking metformin
- Iodine-based contrast media use in patients on chronic dialysis

Safe Use of Contrast Media - Part 2 (finalized in 2019):
- Prophylaxis and management of hypersensitivity reactions to contrast media
- Safe use of gadolinium-based contrast agents, in terms of prevention of post-contrast acute kidney injury (PC-AKI) and Nephrogenic systemic fibrosis (NSF)
- Contrast media injections with power injectors through (peripherally inserted) central venous lines and implantable ports
- Contrast media extravasation

Safe Use of Contrast Media - Part 3 (finalized in 2022):
- Prevention of iodine-induced hyperthyroidism
- Safe use of contrast media use during pregnancy and lactation
- Safe use of contrast media use in patients with rare diseases:
  - Patients with Multiple Myeloma (M. Kahler)
  - Patients with Pheochromocytoma and Paraganglioma
  - Patients with Myasthenia Gravis
  - Patients with Mastocytosis
- Safe time intervals between contrast-enhanced studies
- Prevention of recurrent hypersensitivity reactions to contrast media (update of part 2), including the Weber and Lalli effects
- Analytical Interference of contrast media with clinical laboratory tests
- Gadolinium deposition in the body after gadolinium-based contrast agents (both update of part 2 and a new module about strategies for GBCA dose reduction)

Safe Use of Contrast Media - Part 4 Children (finalized in 2024):
- Risk stratification in the Prevention of Post Contrast Acute Kidney Injury (PC-AKI)
- Hydration Strategies in the Prevention of PC-AKI
- Profylactic Measures for Hypersensitivity Reactions
- Treatment of Acute hypersensitivity reactions
- Monitoring of Thyroid Function after Administration of Iodine-based Contrast Media

*Note: Post-contrast acute kidney injury is synonymous with contrast-associated acute kidney injury

Aim of the current guideline
The aim of the Safe Use of Contrast Media guidelines is to critically review the recent evidence and try to formulate new practical guidelines for all hospital physicians to provide the safe use of contrast media in diagnostic and interventional studies in children (younger than 18 years) and adults (18 years and older). The ultimate goal of this guideline is to increase the quality of care, by providing efficient and expedient healthcare to children that may benefit from this healthcare and simultaneously guard patients from ineffective care. Furthermore, such a guideline should ideally be able to save money and reduce day-hospital waiting lists.

Focus of the guideline
The Safe Use of Contrast Media guidelines focus on all child (younger than 18 years) and adult (18 years and older) patients that receive CM during radiologic or cardiologic studies or interventions. The patient population for which these guidelines are developed are patients who receive intravascular, oral or intracavitary (intra-articular, intra-vesical, intra-cholangiographic) contrast media both in the clinical setting, as well as for outpatients. The guidelines do not cover radiopharmaceuticals used in nuclear medicine.

Users of this guideline
This guideline is intended for all hospital physicians that request or perform diagnostic or interventional radiologic or cardiologic studies for their patients in which CM are involved.

For children and their caretakers
The modules for children under the age of 18 are specifically designed for a relatively vulnerable patient group. Besides the child who sometimes has to undergo additional blood collections and procedures, the parents/caretakers also need to be informed about and consent to the necessary measures.

Patients and parents/caretakers want to make decisions based on the available evidence and best clinical practice. This emphasizes the importance of comprehensive and understandable information and the management of patient and parent/caretaker anxiety that can arise when using this guideline.

Keeping patient and parents/caretakers informed in a calm atmosphere, will eventually reduce stress and anxiety.

Terminology and definitions
The terminology and definitions of specific topics will be discussed in each of the specific topics/modules of this guideline. Abbreviations used in this guideline can be found below.

Guideline Disclaimers
General
The aim of clinical guidelines is to help clinicians to make informed decisions for their patients. However, adherence to a guideline does not guarantee a successful outcome. Ultimately, healthcare professionals must make their own treatment decisions about care on a case-by-case basis, after consultation with their patients, using their clinical judgement, knowledge and expertise. A guideline cannot replace a physician's judgment in diagnosing and treatment of particular patients.

Guidelines may not be complete or accurate. The guideline development group and members of their boards, officers and employees disclaim all liability for the accuracy or completeness of a guideline, and disclaim all warranties, express or implied to their incorrect use.

Guidelines users are always urged to seek out newer information that might impact the diagnostic and treatment recommendations contained within a guideline.

Individualisation

In specific high-risk patient groups clinicians may have to regress from these general guidelines and decide on individualisation to best fit the needs of their patients.

Life-threatening situations or conditions

In acute life-threatening situations or conditions clinicians may have to regress from these general guidelines and decide on individualisation to best fit the needs of their patients in these situations or conditions.

Documentation

The guideline development group recommends documenting the specific contrast medium name and dose which were administered to the patient (in the imaging report and/or with the stored images).

Summary of recommendations*

**Dutch version below*

Module 1 Risk stratification in the Prevention of PC-AKI

Clinical question

How to identify children at risk for post-contrast acute kidney injury (PC-AKI)?

Recommendations

Do not routinely determine kidney function in healthy children who do not belong to a high risk population.

Determine renal function (eGFR using the modified Schwartz formula) prior to an imaging study with intravascular iodine contrast agents:

in children with known renal disease or renal impairment
AND
In children that belong to the following (assumed) high risk groups:
- Previous kidney disease,
- History of acute kidney injury (AKI),
- Congenital abnormalities of the kidneys and urinary tract (CAKUT),
- History of Prematurity < 32 weeks,
- Trisomy 21,
- Use of nephrotoxic and renal perfusion altering medication (including ACEi, ARB (angiotensin receptor blocker), NSAIDs),
- Hypovolemia / impaired circulation (e.g. sepsis/shock),
- Diabetes.

Be vigilant to renal function problems and determine renal function (eGFR) in this population with increased risk. In a stable clinical situation, an eGFR measurement of up to 3 months for intervention support is useful.

Follow up after imaging
Calculate eGFR using the modified Schwarz formula within 2 to 7 days after intravascular iodine-containing CM administration in any patient with known eGFR < 60.

If PC-AKI is diagnosed (according to Kidney Disease Improving Global Outcomes criteria), follow the patient until normalization of serum creatinine to baseline and consult a paediatric nephrologist.

Modified Schwartz formula: height (cm) x 36.5 / serum creatinine (micromol/L)

Module 2 Hydration Strategies in the Prevention of PC-AKI

Clinical question

Which hydration strategy should be used in children undergoing intravascular administration of iodine-based contrast media and who are at increased risk for developing contrast-associated acute kidney injury (PC-AKI)?

Recommendations

Apply the following risk-reducing options in all children > 1 month old undergoing intravascular iodinated CM administration:
- Discontinue NSAIDs,
- Discontinue ACEi, ARBs and diuretics after consultation with the admitting physician.
- Discontinue, when possible, all nephrotoxic medication, such as aminoglycosides, after consultation with the admitting physician
- Aim for a euvolemic status, especially in children with evidence of compromised circulation (sepsis/shock).

Depending on eGFR (if eGFR is not known, apply advice for eGFR >60ml/min/1.73m2):
- eGFR >60 ml/min/1.73m2 (including all children without eGFR):
    - o Advise to drink sufficiently on the day of the imaging study and the day before the day of the imaging study.
- eGFR 30-60 ml/min/1.73m2:
    - o Administer 10 ml/kg/hour NaCl 0.9% IV in 1 hour prior to the imaging study (in addition to the standard fluid management or fluid intake of the type).
    - o Consider low-threshold consultation with a paediatric nephrologist.
    - o Determine serum creatinine after 24 hours and 48-72 hours.
- eGFR <30 ml/min/1.73m2:
    - o Consider an imaging study without contrast or another radiological modality, such as MRI without contrast or ultrasound.
    - o Administer 10 ml/kg/hour NaCl 0.9% IV in 1 hour prior to the imaging study.
    - Followed by:
        - NaHCO3 1.4%, 3 ml/kg/hour IV in 1 hour prior to CM administration,
        - or,
        - (*alternative option*) NaHCO3 1.4%, 3ml/kg/hour IV (max 250 ml in total) for 1 hour prior to CM administration and 1ml/kg/hour IV (max 500 ml in total) during 6 hours after CM administration.
    - o Consult with a paediatric nephrologist.
    - o Determine serum creatinine after 24 hours and after 48-72 hours.

In all neonates (infant < 1 month) and babies born prematurely with a corrected gestational age < 44 weeks the above-mentioned interventions should be CONSIDERED by the admitting physician (neonatologist).

Module 3 Prophylaxis of hypersensitivity reactions

Clinical question

What prophylactic measures should be taken in children (<18 years) with an increased risk of hypersensitivity reactions after administration of iodinated contrast agents?

Recommendations

Consider an alternative imaging modality in all patients with a (documented) history of hypersensitivity reaction to a contrast agent. If this is not possible, consider performing the imaging study without contrast agent, if the reduction in diagnostic quality is acceptable.

• If the previous hypersensitivity reaction was mild*:
Carry out the radiological imaging study as usual given the low risk of developing a more serious reaction.
If in doubt about the severity of the previous hypersensitivity reaction: consider referring the patient to a specialist in drug hypersensitivity for skin testing with different contrast media (allergologist).

• If the previous hypersensitivity reaction was moderate to severe**:
Refer patient to an allergy specialist in drug hypersensitivity for skin testing with different contrast media (allergologist). If possible, postpone imaging until skin test results are known. Apply the advice of the drug hypersensitivity specialist regarding choosing an alternative contrast agent.

• If an acute imaging study is necessary:
Choose an alternative contrast agent (based on low cross-reactivity) or an alternative imaging modality as described previously. If the suspected contrast agent from a previous reaction is not known or no alternative can be given, it is recommended to first give 10% of the contrast agent dose. Observe the patient with an intravenous access for ≥ 30 min before administering the remaining 90%. Be vigilant to respond to a possible new hypersensitivity reaction (see acute hypersensitivity reaction treatment module). The chance of an allergic reaction is very small and the chance of a severe reaction is even more decreased with this protocol.

*mild reactions: only skin symptoms (erythema, some urticaria, mild angioedema, itching), rhinitis and/or conjunctivitis, sneezing, tickle in the throat.

**moderate to severe reactions: generalized urticaria, respiratory complaints with stridor (expiratory and/or inspiratory), hoarseness, swelling of the tongue and/or pharynx, recurrent vomiting, hypotension, loss of consciousness, shock.

NB the above shows the importance of good documentation of symptoms of the reaction.
Document the specific contrast medium name and dose which were administered to the patient in the imaging report and/or with the stored images.

Module 4 Treatment of acute hypersensitivity reaction

Clinical question

What is the optimal treatment for acute hypersensitivity reactions to contrast media?

Recommendations

Acute allergic reactions differ in severity, the recommendations are formulated depending on the severity of the situation.

In case of anaphylactic reaction:
- Give adrenaline intramuscularly. Pay attention to the correct dosage:
    - o >25 kg body weight 300 micrograms adrenaline (adrenalin auto-injectors available, such as Epipen® or Jext®),
    - o 7.5-25 kg body weight 150 micrograms adrenaline (adrenalin auto-injectors available, such as Epipen Junior ® or Jext®),
    - o < 7.5 kg body weight, 10 mcg/kg, (equals 0.1 ml/kg from 1mg/10ml adrenaline vial (1:10,000).
    - o When body weight is unknown: ≥ 6 years 300 micrograms adrenaline (adrenalin auto-injectors available, such as Epipen® or Jext®), < 6 years 150 micrograms (adrenalin auto-injectors available, such as Epipen Junior® or Jext®).
- Give 15 liter/minute of oxygen through a non-rebreathing mask.
- Alert the (paediatric) resuscitation team (name varies per hospital).
- When symptoms don't decrease or progress a second dose adrenalin can be necessary. A second injection can be given 5-15 minutes after the first dose.

In non-anaphylactic acute hypersensitivity reactions:
- Consult with a paediatrician about further treatment and/or policy.

See flowchart.

Module 5 Monitoring of Thyroid Function after Administration of Iodine-based Contrast Media

Clinical question

Should thyroid function be monitored in children after administration of an iodine-containing contrast agent?

Recommendations

Monitor thyroid function (TSH measurement) 2 weeks after the administration of *intravascular or enteral* iodinated contrast, in all premature infants (gestational age < 37 weeks) under the age of 3 months.

Monitor thyroid function (TSH measurement) 2 weeks after the administration of *intravascular* iodinated contrast in term born children (gestational age ≥ 37 weeks) under the age of 3 months in case of risk factors such as small for gestational age (birthweight < -2 SDS for gestational age) critical illness, renal impairment, cardiac disease and in case of prolonged/frequent exposure to iodinated contrast such as coronary CT angiography and renal dialysis.

Consider monitoring thyroid function (TSH measurement) 2 weeks after the administration of *intravascular* iodinated contrast in children between age 3 months and 3 years in case of risk factors such as critical illness, renal impairment, cardiac disease and in case of prolonged/frequent exposure to iodinated contrast such as coronary CT angiography and renal dialysis.

Interpretation of TSH:

- TSH mU/l $\leq$ 5: no further action, except in very premature infants with a gestational age of < 32 weeks at the time of blood withdrawal. In these children a repeat TSH measurement after 1 week is recommended.
- TSH > 5 and $\leq$ 10 mU/l: repeat TSH and free T4 measurement after 1 week
- TSH > 10 and $\leq$ 20 mU/l: measure free T4. Low free T4 concentration indicates hypothyroidism with indication to treat. Consult pediatric endocrinologist.*
- TSH > 20 mU/l: measure free T4 and consult pediatric endocrinologist to start treatment.*

*Correct interpretation of free T4 is complicated by transient hypothyroxinemia of prematurity, non-thyroidal illness and lack of age-specific reference intervals. It is advised to consult a pediatric endocrinologist before starting treatment.

Samenvatting van aanbevelingen (Nederlands)

Module 1 Risico stratificatie in de preventie van PC-AKI

Uitgangsvraag

Hoe dienen kinderen die verhoogd risico lopen op post-contrast acuut nierletsel (PC-AKI) te worden geïdentificeerd?

Aanbevelingen

Bepaal niet routinematig de nierfunctie bij gezonde kinderen die niet tot een risicopopulatie behoren.

Bepaal de nierfunctie (eGFR met behulp van de gemodificeerde Schwartz formule) voor onderzoek met intravasculaire jodium contrastmiddelen:

Bij kinderen met bekende nierziekte of nierfunctie stoornis.
EN
Bij kinderen die tot een veronderstelde hoog risico groep voor PC-AKI behoren:

- Doorgemaakte nierziekte,
- Voorgeschiedenis van AKI,
- Congenital anomalies of the kidney and urinary tract (CAKUT),
- Voorgeschiedenis van Prematuriteit < 32 weken,
- Trisomie 21,
- Gebruik van nefrotoxische en renale perfusie beïnvloedende medicatie (ACEi, ARB (angiotensine receptor blokker), NSAIDs),
- Hypovolemie / bedreigde circulatie (bijvoorbeeld sepsis/ shock),
- Diabetes mellitus.

Wees in deze verhoogd risico populatie alert op nierfunctieproblemen en bepaal de nierfunctie (eGFR). Bij een stabiele kliniek is een bepaling tot 3 maanden voor het beeldvormend onderzoek geldig.

Afspraken na beeldvorming
Bereken de eGFR met behulp van de modified Schwarz formule: lengte (cm) x 36.5 / serum kreatinine (micromol/L) binnen 2 tot 7 dagen na intravasculaire jodiumhoudende CM-toediening bij elke patiënt met eGFR < 60 voor het onderzoek.

Indien er PC-AKI wordt gediagnostiseerd (volgens Kidney Disease Improving Global Outcomes criteria), vervolg de patiënt tot normalisatie van serum creatinine naar baseline en consulteer een kindernefroloog.

Gemodificeerde Schwartz formule: lengte (cm) x 36.5 / serum creatinine (micromol/L)

Module 2 Hydratatiestrategieën bij de preventie van PC-AKI

Uitgangsvraag

Welke hydratiestrategie dient te worden toegepast bij kinderen die intravasculair jodiumhoudend contrastmiddel toediening ondergaan en een hoog risico op contrast-geassocieerde acute nierschade (PC-AKI) hebben?

Aanbevelingen

Pas de volgende risico reducerende optie toe voor alle kinderen > 1 maand oud die intravasculaire jodiumhoudend CM-toediening ondergaan:

- Staak NSAID's voorafgaand aan een jodiumhoudend contrasttoediening.
- Staak ACEi, ARBs en diuretica, na overleg met de hoofdbehandelaar.
- Bespreek met de hoofdbehandelaar de mogelijkheid om nefrotoxische medicatie, zoals aminoglycosiden, te staken voorafgaand aan het onderzoek.
- Streef naar een euvolemische status bij elk kind, ongeacht de eGFR, in het bijzonder bij kinderen met tekenen van een gecompromitteerde circulatie (sepsis/shock).

Afhankelijk van eGFR (als eGFR niet bekend is, pas advies bij eGFR >60ml/min/1.73m^2 toe):

- eGFR >60 ml/min/1.73m^2 (inclusief alle kinderen zonder eGFR):
  - Adviseer om op de dag voor en de dag van het onderzoek adequaat te drinken
- eGFR 30-60 ml/min/1.73m^2:
  - Dien 2 uur voorafgaand aan het onderzoek 10 ml/kg/uur NaCl 0.9% IV in 1 uur toe (naast het standaard vochtbeleid of vochtinname van het kind).
  - Overleg laagdrempelig met een kinderarts-nefroloog.
  - Bepaal serum kreatinine na 24 uur en 48-72 uur.
- eGFR <30 ml/min/1.73m^2:
  - Overweeg onderzoek zonder contrast of andere onderzoeksmodaliteit.
  - Dien 2 uur voorafgaande aan het onderzoek 10 ml/kg/uur NaCl 0.9% IV in 1 uur toe. Gevolgd door:
    $NaHCO_3$ 1.4%, 3 ml/kg/uur IV gedurende 1 uur vooraf aan CM-toediening, of *(alternatieve optie)* $NaHCO_3$ 1.4%, 3ml/kg/uur IV (max 250 mL in totaal) gedurende 1 uur vooraf aan CM-toediening en 1ml/kg/uur IV (max 500mL in totaal) gedurende 6 uur na CM-toediening.
  - Overleg met een kinderarts-nefroloog.
  - Bepaal serum kreatinine na 24 uur en na 48-72 uur.

OVERWEEG bij alle neonaten (baby < 1 maand) en vroeggeboren baby's jonger dan gecorrigeerde post amenorroe duur van 44 weken bovenstaande maatregelen in overleg met de hoofdbehandelaar / kinderarts-neonatoloog.

Module 3 Profylaxe van overgevoeligheidsreacties

Uitgangsvraag

Welke profylactische maatregelen moeten worden genomen bij kinderen (<18 jaar) met een verhoogd risico op overgevoeligheidsreacties na toediening van jodiumhoudende contrastmiddelen?

Overweeg een alternatieve beeldvormingsmodaliteit bij alle patiënten met een (gedocumenteerde) geschiedenis van een overgevoeligheidsreactie voor een contrastmiddel. Indien dit niet mogelijk is, overweeg het uitvoeren van het onderzoek zonder contrastmiddel, indien de verminderde diagnostische kwaliteit acceptabel is.

- Indien de vorige overgevoeligheidsreactie mild* was:
  Voer het radiologisch onderzoek uit zoals gebruikelijk gezien het lage risico op het ontwikkelen van een meer ernstige reactie.
  Bij twijfel aan de ernst van de vorige overgevoeligheidsreactie: overweeg om de patiënt te verwijzen naar een specialist in geneesmiddelenovergevoeligheid voor huidtesten met verschillende contrastmedia (allergoloog).

- Indien de vorige overgevoeligheidsreactie matig tot ernstig** was:
  Verwijs patiënt naar een specialist in geneesmiddelenovergevoeligheid voor huidtesten met verschillende contrastmedia (allergoloog). Indien mogelijk, stel het beeldvormend onderzoek uit totdat de resultaten van de huidtesten bekend zijn. Pas het advies van de specialist in geneesmiddelenovergevoeligheid toe met betrekking tot het kiezen van een alternatief contrastmiddel.

- Indien acuut onderzoek noodzakelijk is:
  Kies voor een alternatief contrastmiddel (obv lage kruisreactiviteit) of een alternatieve beeldvormingsmodaliteit zoals eerder beschreven. Indien het verdachte contrastmiddel van een eerdere reactie niet bekend is of er geen alternatief gegeven kan worden, wordt geadviseerd eerst 10% van de contrastmiddeldosis te geven. Observeer de patiënt ≥ 30 min met een infuus alvorens de overige 90% toe te dienen. Wees alert om te reageren op een mogelijke nieuwe overgevoeligheidsreactie (zie module behandeling acute overgevoeligheidsreactie).

  *milde reacties: alleen symptomen van de huid (erytheem, enkele urticaria, mild angio-oedeem, jeuk), rhinitis en/of conjunctivitis, niezen, kriebel in de keel.

  **matig tot ernstige reacties: gegeneraliseerde urticaria, respiratoire klachten met stridor (expiratoir en/of inspiratoir), heesheid, zwelling van de tong en/of pharynx, herhaaldelijk braken, hypotensie, bewustzijnsverlies, shock.

NB bovenstaande laat het belang van een goede documentatie van symptomen van de reactie zien. Documenteer de naam en dosis van het gebruikte contrastmiddel in het radiologische verslag van het onderzoek en/of bij de beelden van het onderzoek.

Module 4 Behandeling acute contrastreactie

Uitgangsvraag

Wat is de optimale behandeling voor acute overgevoeligheidsreacties op contrastmiddelen?

Aanbevelingen

Acute allergische reacties verschillen in ernst, de aanbevelingen zijn per ernst van de situatie geformuleerd.

Bij anafylactische reactie:

- Geef adrenaline intramusculair. Let op de juiste dosering:
  - >25 kg lichaamsgewicht 300 microgram adrenaline (adrenaline auto-injectoren beschikbaar, bijvoorbeeld een Epipen® or Jext®)
  - 7.5-25 kg lichaamsgewicht 150 microgram adrenaline (adrenaline auto-injectoren beschikbaar, bijvoorbeeld een Epipen Junior® or Jext®),
  - < 7.5 kg lichaamsgewicht, 10 mcg/kg, overeenkomend met 0.1 ml/kg uit 1mg/10ml adrenaline ampull (1:10.000).
  - Indien het gewicht niet bekend is: ≥ 6 jaar 300 microgram (Epipen® or Jext®), < 6 jaar 150 microgram (Epipen Junior® or Jext®).
- Geef 15 liter/minuut zuurstof via een non-rebreathing masker.
- Alarmeer het (kinder)reanimatie team (naam varieert per ziekenhuis).
- Als de symptomen niet afnemen of verergeren, kan een tweede dosis adrenaline nodig zijn. Een tweede injectie kan 5-15 minuten na de eerste dosis gegeven worden.

Bij niet-anafylactische acute overgevoeligheidsreacties:

- Overleg met een kinderarts over verdere behandeling en/of beleid.

Zie stroomschema.

Module 5 Monitoring van de schildklierfunctie na toediening van op jodiumhoudende contrastmiddelen

Uitgangsvraag

Moet bij kinderen na toediening van een jodiumhoudend contrastmiddel de schildklierfunctie gemonitord worden?

Aanbevelingen

Controleer de schildklierfunctie (TSH-meting) 2 weken na toediening van *intravasculair of gastro-intestinaal* jodiumhoudend contrast*)* bij alle prematuur geboren kinderen (zwangerschapsduur < 37 weken) onder de leeftijd van 3 maanden.

Controleer de schildklierfunctie (TSH-meting) 2 weken na toediening van *intravasculair* jodiumhoudend contrast, bij a term geboren kinderen (zwangerschapsduur ≥ 37 weken) onder de leeftijd van 3 maanden in geval van risicofactoren zoals dysmaturiteit (geboortegewicht voor zwangerschapsduur < -2 SDS), ernstige ziekte, nierinsufficiëntie, cardiale aandoening en in geval van langdurige/veelvuldige blootstelling aan jodiumhoudend contrast zoals bij coronaire CT-angiografie en nierdialyse.

Overweeg controle van de schildklierfunctie (TSH-meting) 2 weken na toediening van *intravasculair* jodiumhoudend contrast bij kinderen tussen de leeftijd van 3 maanden en 3 jaar in geval van risicofactoren zoals ernstige ziekte, nierinsufficiëntie, cardiale aandoening en in geval van langdurige/veelvuldige blootstelling aan jodiumhoudend contrast zoals bij coronaire CT-angiografie en nierdialyse.

Interpretatie TSH-concentratie:

- TSH $\leq$ 5 mE/l: geen actie, tenzij het een zeer prematuur kind betreft met een berekende leeftijd van < 32 weken amenorroe duur ten tijde van de bloedafname. Herhaal in dat geval de TSH-meting na 1 week.
- TSH > 5 en $\leq$ 10 mE/l: herhaal TSH met vrijT4 meting na 1 week
- TSH > 10 en $\leq$ 20 mE/l: meet vrijT4. Een lage vrij T4 concentratie wijst op hypothyreoïdie en is een behandelindicatie. Overleg met kinderarts-endocrinoloog.*
- TSH > 20 mE/l: meet vrijT4 en start behandeling in overleg met kinderarts-endocrinoloog.*

*Interpretatie van vrij T4 wordt bemoeilijkt door transiënte hypothyroxinemie van prematuren, “non-thyroidal illness” en gebrek aan leeftijdsspecifieke referentie intervallen. Overleg met kinderarts-endocrinoloog wordt geadviseerd voordat met behandeling wordt gestart.

Justification of the guideline

Validity

The Radiological Society of the Netherlands (NVvR) will determine if this guideline (per module) is still valid and applicable around 2029. If necessary, the scientific societies will form a new guideline group to revise the guideline. The validity of a guideline can be shorter than 5 years, if new scientific or healthcare structure developments arise, asking for a revision of the guideline. The Radiological Society of the Netherlands is the owner of this guideline and therefore primarily responsible for the actuality of the guideline. Other scientific societies that have participated in the guideline development share the responsibility to inform the primarily responsible scientific society about relevant developments in their field.

Initiative

- Radiological Society of the Netherlands (NVvR)

In association with

- The Dutch Society of Paediatrics (NVK)
- The Dutch Society of Surgery (NVvH)
- The Dutch Society of Anaesthesiology (NVA)
- Kind & Ziekenhuis

General Information

The Kennisinstituut van de Federatie Medisch Specialisten assisted the guideline development group. The guideline was financed by Stichting Kwaliteitsgelden Medisch Specialisten (SKMS) which is a quality fund for medical specialists in The Netherlands.

Guideline development group (GDG)

A multidisciplinary guideline development group (GDG) was formed for the development of the guideline in 2022. The GDG consisted of representatives from all relevant medical specialization fields which were using intravascular contrast administration in their field.

All GDG members have been officially delegated for participation in the GDG by their scientific societies. The GDG has developed a guideline in the period from June 2022 until July 2024. The GDG is responsible for the complete text of this guideline.

Conflicts of interest

The GDG members have provided written statements about (financially supported) relations with commercial companies, organisations or institutions that were related to the subject matter of the guideline. Furthermore, inquiries have been made regarding personal financial interests, interests due to personal relationships, interests related to reputation management, interest is related to externally financed research and interests related to knowledge valorisation. The statements on conflict of interest can be requested from the administrative office of Kennisinstituut van de Federatie Medisch Specialisten (secretariaat@kennisinstituut.nl) and were summarised below.

Last name	*Function*	*Other positions*	*Personal financial interests*	*Personal relations*	*Reputation management*	*Externally financed research*	*Knowledge valorisation*	*Other interests*	*Signed*	*Actions*
De Graaf	Radiologist, Erasmus Medical Centre Rotterdam,	Board member of the Technology section, Netherlands. Far. for Radiology (unpaid) Board member Ned. Comm. Radiation dosimetry (NCS) (unpaid)	None	None	None	None	None	None	July 14th, 2022	No restrictions.
Geenen RWF	Radiologist, Noordwest ziekenhuisgroep /medisch specialisten Noordwest	Member of contrast media safety committee, European Society of Urogenital Radiology (no payment)	None	None	None	None	None	None	September 2nd, 2022	No restrictions
Emons	Pediatrician-allergologist, Erasmus MC-Sophia, paid	Editorial board NTvAAKI, unpaid NVvAKI communications committee, unpaid	None	None	None	Epitope study, cutaneous immunotherapy for peanut, DBV BAT cow's milk study, NWO	None	None	July 7th, 2022	No restrictions, research has no link with hypersensitivity reactions after administration of contrast

Last name	*Function*	*Other positions*	*Personal financial interests*	*Personal relations*	*Reputation management*	*Externally financed research*	*Knowledge valorisation*	*Other interests*	*Signed*	*Actions*
						Itulizax study, tree pollen immunotherapy, ALK				agents in children.
Jöbsis	Pediatrician, pediatric nephrologist	None	None	None	None	None	None	None	July 2nd, 2022	No restrictions
Sloots	Pediatric surgeon Erasmus MC Sophia Children's Hospital	None	None	None	None	None	None	None	August, 15th, 2022	No restrictions
Liebrand	Anaesthesiologist Sophia Children's Hospital/Erasmus MC Pediatrician St. Antonius Hospital, Kleve	Notarzt Kreis Kleve	None	None	None	None	None	None	December, 20th, 2022	No restrictions
Zwaveling-Soonawala	Pediatrician-endocrinologist, Emma Children's Hospital, Amsterdam UMC	None	None	None	None	None	None	None	June, 13th, 2023	No restrictions
Advisory group										
Molen AJ, van der	Radiologist LUMC	Member of contrast media safety committee, European Society of Urogenital Radiology (no	None	None	None	None	None	Received speaker fees from Guerbet, 2019-2022	June, 5th, 2023	No restrictions (given the role as a sounding board group member, no active contribution to texts and the

Last name	*Function*	*Other positions*	*Personal financial interests*	*Personal relations*	*Reputation management*	*Externally financed research*	*Knowledge valorisation*	*Other interests*	*Signed*	*Actions*
		payment). Member, Gadolinium Research and Education Committee, European Society of Magnetic Resonance in Medicine, and Biology (no payment).								mandate for decisions rests with the guideline development group, no further restrictions have been formulated for the ancillary activities at the gadopiclenol expert group)
Riedijk	Pediatrician Amsterdam UMC - Emma Children's Hospital	Board member SICK: unpaid. PICE board member: unpaid.	None	None	None	None	None	None	December, 6th, 2022	No restrictions
Doganer	Junior project manager/policy officer at the Child and Hospital Foundation	None	None	None	None	None	None	None	July, 25th, 2023	No restrictions

Input of patient's perspective
The guideline does not address a specific child patient group, but a diverse set of diagnoses. Therefore, it was decided to invite a broad spectrum of patient organisations for the stakeholder consultation, and invite the patient organisation Kind & Ziekenhuis (translated as Child and Hospital Foundation) in the Advisory group. The stakeholder consultation was performed at the beginning of the process for feedbacking on the framework of subjects and clinical questions addressed in the guideline, and during the commentary phase to provide feedback on the concept guideline. The list of organisations which were invited for the stakeholder consultation can be requested from the Kennisinstituut van de Federatie Medisch Specialisten (secretariaat@kennisinstituut.nl). In addition, patient information on safe use of contrast media in children was developed for Thuisarts.nl, a platform to inform patients about health and disease.

Implementation
During different phases of the guideline development, implementation and practical enforceability of the guideline were considered. The factors that could facilitate or hinder the introduction of the guideline in clinical practice have been explicitly considered. The implementation plan can be found in the 'Appendices to modules'. Furthermore, quality indicators were developed to enhance the implementation of the guideline. The indicators can also be found in the 'Appendices to modules'.

Methodology
AGREE
This guideline has been developed conforming to the requirements of the report of Guidelines for Medical Specialists 2.0 by the advisory committee of the Quality Counsel (www.kwaliteitskoepel.nl). This report is based on the AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II) (www.agreetrust.org), a broadly accepted instrument in the international community and based on the national quality standards for guidelines: "Guidelines for guidelines" (www.zorginstituutnederland.nl).

Identification of subject matter
During the initial phase of the guideline development, the GDG identified the relevant subject matter for the guideline. The framework is consisted of both new matters, which were not yet addressed in Part 1, 2 and 3 of the guideline, and an update of matters that were subject to modification (for example in case of new published literature). Furthermore, a stakeholder consultation was performed, whre input on the framework was requested.

Clinical questions and outcomes
The outcome of the stakeholder consultation was discussed with the GDG, after which definitive clinical questions were formulated. Subsequently, the GDG formulated relevant outcome measures (both beneficial and harmful effects). The GDG rated the outcome measures as critical, important and of limited importance (GRADE method). Furthermore, where applicable, the GDG defined relevant clinical differences.

Search and select
For clinical questions, specific search strategies were formulated, and scientific articles published in several electronic databases were searched. First, the studies that potentially had the highest quality of research were reviewed. The GDG selected literature in pairs (independently of each other) based on the title and abstract. A second selection was performed by the methodological advisor based on full text. The databases used, selection

criteria and number of included articles can be found in the modules, the search strategy can be found in the appendix.

Quality assessment of individual studies
Individual studies were systematically assessed, based on methodological quality criteria that were determined prior to the search. For systematic reviews, a combination of the AMSTAR checklist and PRISMA checklist was used. For RCTs the Cochrane risk of bias tool and suggestions by the CLARITY Group at McMaster University were used, and for cohort studies/observational studies the risk of bias tool by the CLARITY Group at McMaster University was used. The risk of bias tables can be found in the separate document "Appendices to modules".

Summary of literature
The relevant research findings of all selected articles were shown in evidence tables. The evidence tables can be found in the separate document "Appendices to modules". The most important findings in literature were described in literature summaries. When there were enough similarities between studies, the study data were pooled.

Grading quality of evidence and strength of recommendations
The strength of the conclusions of the included studies was determined using the GRADE-method. GRADE stands for Grading Recommendations Assessment, Development and Evaluation (see http://www.gradeworkinggroup.org) (Atkins, 2004). GRADE defines four levels for the quality of scientific evidence: high, moderate, low, or very low. These levels provide information about the certainty level of the literature conclusions (http://www.guidelinedevelopment.org/handbook).

The evidence was summarized in the literature analysis, followed by one or more conclusions, drawn from the body of evidence. The level of evidence for the conclusions can be found above the conclusions. Aspects such as expertise of GDG members, local expertise, patient preferences, costs, availability of facilities and organisation of healthcare are important to consider when formulating a recommendation. These aspects are discussed in the paragraph "Justifications". The recommendations provide an answer to the clinical question or help to increase awareness and were based on the available scientific evidence and the most relevant "Justifications".

Appendices
Internal (meant for use by scientific society or its members) quality indicators were developed during the conception of the guideline and can be found in the separate document "Appendices to modules". In most cases, indicators were not applicable. For most questions, additional scientific research on the subject is warranted. Therefore, the GDG formulated knowledge gaps to aid in future research, which can be found in the separate document "Appendices to modules".

Commentary and authorisation phase
The concept guideline was subjected to commentaries by the involved scientific societies. The list of parties that participated in the commentary phase can be requested from the Kennisinstituut van de Federatie Medisch Specialisten (secretariaat@kennisinstituut.nl). The commentaries were collected and discussed with the GDG. The feedback was used to improve the guideline; afterwards the guideline was made definitive by the GDG. The final version of the guideline was offered to the involved scientific societies for authorization and was authorized.

Literature

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Module 1: Risk Stratification in the Prevention of PC-AKI

Clinical question

How to identify children at risk for post-contrast acute kidney injury (PC-AKI)?

Introduction

Intravascular iodine-based contrast media could lead to PC-AKI in certain cases, especially when renal function is already impaired. At the moment there is no routine screening for impaired renal function in children exposed to intravenous contrast media as part of diagnostic or therapeutic imaging (for instance by measurement of serum creatinine or determination of Glomerular Filtration Rate or eGFR).
There are certain risk factors that may indicate renal dysfunction that worsens after administration of intravenous contrast media. These risk factors include children with Down syndrome (trisomy 21), diabetes mellitus, prematurity or congenital anomalies of the kidney and urinary tract (CAKUT) as well as the use of renovascular or nephrotoxic medication.
It is unclear whether screening for impaired renal function is necessary in children at increased risk of renal dysfunction.

Search and select

A systematic review of the literature was performed to answer the following question:
Do prematurity, trisomy 21, diabetes, CAKUT, renovascular medication, or nephrotoxic medication increase the risk of developing PC-AKI in children receiving intravenous contrast media?

P(atients):	Children (<18 years) receiving intravascular iodine-based contrast media.
I(ntervention):	Risk factors: prematurity, trisomy 21, diabetes, congenital anomalies of the kidney and urinary tract (CAKUT), renovascular medication, nephrotoxic medication.
C(ontrol):	Absence of these risk factors.
O(utcome):	Post-contrast acute kidney injury (PC-AKI), complications of PC-AKI (hospitalization, start of dialysis).

<u>Relevant outcome measures</u>
The guideline development group considered PC-AKI and complications of PC-AKI as critical outcome measures for decision making.

A priori, the guideline development group did not define the outcome measures listed above but used the definitions used in the studies. The guideline development group defined PC-AKI as described in the chapter PC-AKI: Definities, terminologie en klinisch verloop in the guideline Safe Use of Contrast Media, part 1 (NVVR, 2017). If authors used other definitions such as CA-AKI (contrast associated) or CI-AKI (contrast induced). We used their terminology for the description of the study, but for the purposes of the guideline standardized to PC-AKI.

The guideline development group defined the following as a minimal clinically (patient) important difference:

- Post-contrast acute kidney injury (PC-AKI): relative risk <0.91 or >1.10.

- Complications of PC-AKI (hospitalization, start of dialysis): relative risk <0.91 or >1.10.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 1990 until 27-03-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 210 hits.

Studies were selected based on the following criteria:

- Systematic review, randomized controlled trial or observational research comparing risk factors to absence of risk factors for the risk of PC-AKI in children receiving intravascular iodine-based contrast.
- Children (<18 years) who underwent radiological examination using intravascular iodine-based contrast media (including radiological examination during percutaneous angiography).
- Potential risk factors related either to patient characteristics and/or treatment characteristics and/or iodine-based contrast medium characteristics were studied in how they influenced the risk of PC-AKI.
- Risk factors were corrected for confounders in multivariable models.
- At least one of the outcome measures was described: PC-AKI, complications of PC-AKI (hospitalization, start of dialysis, mortality).

Eight studies were initially selected based on title and abstract screening. After reading the full text, 7 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 1 study was included.

Results
One study by Cantais (2016) was included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies
Cantais (2016) published a retrospective chart review study of contrast-induced acute kidney injury (CI-AKI) incidence, risk factors and impact in paediatric patients (<16 years). CI-AKI is a specific term used to describe a sudden deterioration in kidney function that is caused by the administration of an iodine-based contrast medium; therefore, it is a subgroup of PC-AKI (see the chapter PC-AKI: Definities, terminologie en klinisch verloop in the guideline Veilig gebruik van contrastmiddelen (NVVR, 2017)). The authors defined AKI, in accordance with the KDIGO classification system, as a serum creatinine (SCr) increase of ≥26.4 micromol/L within 48 h or of ≥150 % from baseline presumed to have occurred within the prior 7 days or as oliguria (urine output of <0.5 ml/kg/h for ≥6 h). Baseline renal function was based on the baseline Cr and estimated glomerular filtration rate at the time of contrast media injection; any degree of AKI within 48 h was considered contrast-associated nephropathy. 346 paediatric patients received an iodine-based contrast media injection as part of a CT scan between January 2005 and September 2014. 233 patients had renal function assessment before and following contrast media injection and were included in the analysis. Median patient age was 5.9 years with an CI-AKI incidence of 10.3% (95%CI: 6.4 to 14.2%). There were few patients with comorbidities that could be potential risk factors, including thirteen patients with prematurity, eight with pre-existing chronic kidney disease, two with a history of glomerular disease without renal dysfunction and no patient with diabetes. The authors did report extracting information about trisomy 21 or congenital anomalies of the kidney

and urinary tract (CAKUT) from the charts. Vasopressor medication was used in 14 of 233 patients (6%). Nephrotoxic medication use (non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, starches or iodine-based contrast media within 72h) was more common, occurring in 83 of 233 patients (36%). To identify risk factors for CI-AKI conditional forward logistic regression analyses were performed. The model included clinically relevant variables and variables yielding a P value of ≤0.20 in a bivariate analysis, the latter being maintained in the final model. Authors tested for co-linearity and interactions as well as assessing goodness of fit of the logistic regression with the Hosmer-Lemeshow test.

Results

PC-AKI

In Cantais (2016), 24 of 233 included patients (10.3 %; 95%CI 6.4 to 14.2%) developed CI-AKI. Nine of these 24 (38 %) had no previous history of chronic kidney disease, concomitant use of nephrotoxic agents or hypovolemia. Conditional forward logistic regression analysis found no factors independently associated with CI-AKI (Table 1).

Table 1. Odds ratio (OR) and 95% confidence interval (95%CI) from forward conditional logistic regression analysis of factors associated with CI- AKI (Cantais 2016).

	OR	**95%CI**
Hypovolemia or shock at contrast-media infusion	1.98	0.78 to 5.05
Underlying chronic kidney disease	3.16	0.53 to 18.6
Cumulative number of nephrotoxic agents		
None	Reference group	
1	0.93	0.32 to 2.68
≥2	3.63	0.86 to 15.40

Complications of PC-AKI

No studies describing complications of PC-AKI were included in the analysis of the literature.

Level of evidence of the literature

PC-AKI

The level of evidence regarding the outcome measure PC-AKI started as GRADE low due to the observational nature of the included study (Cantais, 2016), and was downgraded by one level to very low due to the small number of included patients (imprecision).

Complications of PC-AKI

The level of evidence could not be determined as no studies describing complications of PC-AKI were included in the analysis of the literature.

Conclusions

Very low GRADE	The evidence is very uncertain about the identification of risk factors for PC-AKI in children (<18 years of age) undergoing radiological examinations with intravascular iodine-based contrast media. *Source: Cantais, 2016*

- GRADE	No evidence was found regarding risk factors for complications of PC-AKI in children (<18 years of age) undergoing radiological examinations with intravascular iodine-based contrast media.

Considerations

Pros and cons of the intervention and quality of the evidence

The guideline development group conducted a systematic review of the increased risk for developing PC-AKI or complications related to PC-AKI after contrast exposure in children with prematurity, trisomy 21, diabetes mellitus, congenital anomalies of the kidney and urinary tract (CAKUT), renovascular medication or nephrotoxic medication. One article (Cantais, 2016) examined risk factors for developing PC-AKI. However, the evidence was of too low quality (very low GRADE) to draw a conclusion. No articles describing complications of PC-AKI met the inclusion criteria. Therefore, no conclusions could be drawn about the effects of these risk factors on the development of PC-AKI and complications related to PC-AKI (hospitalization, dialysis). A knowledge gap exists on this topic.

Multiple studies did not meet the inclusion criteria. Most of these studies were excluded based on wrong design, comparing contrast exposure to non-contrast exposure, where our PICO is aimed at identifying risk factors in contrast exposed groups only. These studies report low incidences of PC-AKI. McDonald (2018) published a cohort study on postcontrast acute kidney injury in pediatric patients, reporting a low rate of contrast associated AKI (3,3%) with no observed difference between contrast and noncontrast groups following propensity score analysis in a small sample with low rates of PC-AKI. Gilligan (2020) published similar results (PC-AKI 2.4%) in a cohort study in hospitalized children using propensity score analysis with no noticeable difference between exposed and non-exposed children in a small sample with low rates of PC-AKI.
Calle-Toro (2022) published a retrospective cohort study in children undergoing CT scans with or without contrast media. They reported a PC-AKI incidence of 1.4% after contrast exposure, showing a difference in risk between contrast exposed and non-contrast exposed groups only in children with an eGFR < 60 prior to imaging.

The quality of the evidence from the systematic literature search is too low to draw a conclusion, the recommendations in this national guideline are based mainly on the guideline for PC-AKI risk stratification and stratification tools in adults (NVVR, 2017) when applicable. The low reported PC-AKI incidence in children in combination with the low prevalence of kidney disease in children however requires a different approach then mentioned in the guideline for adults. Based on expert opinion we describe the main differences below.

The vast majority of children that are scheduled for IV contrast-enhanced studies have no medical history, (past) use of nephrotoxic medication, or hypovolemia. This patient group can safely be scheduled for imaging without renal function testing and/or prehydration strategies.

The minority of children that are scheduled for studies with IV contrast media with known renal disease (including Congenital Anomalies of the Kidney and Urinary Tract or CAKUT) OR a medical history associated with an elevated risk of renal disease, including prematurity and use of renovascular or nephrotoxic medication, should have renal function tests performed (eGFR calculated using serum creatinine (in micromol/L) and patients height (in cm). Also euvolemia / adequate circulation should be guaranteed prior to imaging. In case of impaired renal function, prehydration strategies should be performed. An eGFR based on a serum

creatinine sample within the last 3 months before imaging is considered valid, when the child is well appearing, in a stable condition and with no recent changes in his/her medical condition and medication. This is based on common practice in the absence of relevant articles/studies on this topic, in line with similar recommendations in, for example, the ESUR guidelines on contrast agents.

Patient (and their caretakers) values and preferences
Patients, parents/caretakers, and health care professionals like to make decisions based on the best available evidence. A similar case should get equal advice/treatment.
This guideline defines a patient group with an increased risk of PC-AKI. Patients at increased risk and their caretakers should be informed about the options available to them and together with their physician decide on risk reducing measures and alternative imaging modalities. The exact options will depend on many different factors such as type of examination and reason for performing a scan.
This guideline helps in identifying a population with an elevated risk, thereby reducing the chance of unnecessary tests and interventions.

Costs
Cases of PC-AKI are associated with additional healthcare costs both in the short and long term. Currently physicians are likely to be very careful in children and thus order additional diagnostic tests and interventions. The recommendations in this guideline can prevent unnecessary diagnostic tests and interventions, while simultaneously preventing unnecessary incidents of PC-AKI.

Acceptability, feasibility and implementation
The guideline development group does not anticipate any acceptance issues. The recommendations in the current guideline address longstanding uncertainty about the need for diagnostic testing and interventions. Therefore, it will contribute to a more unified and equal approach in children.

Recommendations
Rationale of the recommendation: weighing arguments for and against the interventions
We present a simple and uniform strategy to identify children at increased risk of developing PC-AKI. Children with known kidney disease are at risk and require renal function monitoring in the form of serum creatinine up to three months after contrast administration. We also identify an increased risk population where kidney problems may arise, and serum creatinine should be measured to determine renal function. This strategy should enable us to limit testing to a well-defined subgroup of patients, preventing unnecessary testing and costs. Since there are limited studies in children, the strategy is based mainly on evidence in adult populations as described in the guideline for PC-AKI risk stratification and stratification tools in adults (NVVR, 2017), supplemented by expert opinion to incorporate important difference in children. For instance, the lower prevalence of kidney disease led to no further action for children with no medical history, (past) use of nephrotoxic medication or hypovolemia. Based on the adult guideline we recommend testing for renal impairment prior to imaging. Based on expert opinion we limit this testing to a well-defined population at risk for renal impairment.

Bepaal niet routinematig de nierfunctie bij gezonde kinderen die niet tot een risicopopulatie behoren.

Bepaal de nierfunctie (eGFR met behulp van de gemodificeerde Schwartz formule) voorafgaand aan het onderzoek met intraveneuze jodiumhoudende contrastmiddelen:

Bij kinderen met bekende nierziekte of nierfunctie stoornis
EN
Bij kinderen die tot een veronderstelde hoog risico groep voor PC-AKI behoren:

- Doorgemaakte nierziekte,
- Voorgeschiedenis van AKI,
- Congenital anomalies of the kidney and urinary tract (CAKUT),
- Voorgeschiedenis van Prematuriteit < 32 weken,
- Trisomie 21,
- Gebruik van nefrotoxische en renale perfusie beïnvloedende medicatie (ACEi, ARB (angiotensine receptor blokker), NSAIDs),
- Hypovolemie / bedreigde circulatie (bijvoorbeeld sepsis/ shock),
- Diabetes mellitus.

Wees in deze verhoogd risico populatie alert op nierfunctieproblemen en bepaal de nierfunctie (eGFR). Bij een stabiele kliniek is een bepaling tot 3 maanden voor het beeldvormend onderzoek geldig.

Afspraken na beeldvorming
Bereken de eGFR met behulp van de modified Schwarz formule: lengte (cm) x 36.5 / serum kreatinine (micromol/L) binnen 2 tot 7 dagen na intravasculaire jodiumhoudende CM-toediening bij elke patiënt met eGFR < 60 voor het onderzoek.

Indien er PC-AKI wordt gediagnostiseerd (volgens Kidney Disease Improving Global Outcomes criteria), vervolg de patiënt tot normalisatie van serum creatinine naar baseline en consulteer een kindernefroloog.

Gemodificeerde Schwartz formule: lengte (cm) x 36.5 / serum creatinine (micromol/L)

Knowledge Gaps

- Do prematurity, trisomy 21, diabetes, CAKUT, renovascular medication or nephrotoxic medication increase the risk of developing PC-AKI in children receiving contrast?
- What level of renal impairment is associated with an increased risk of PC-AKI?
- What degree of prematurity (gestational age) should herald renal function testing for possible risk of impaired kidney function/ elevated risk of developing PC-AKI?

References

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NVvR, 2017. Richtlijn Veilig gebruik van contrastmiddelen - Module Risicostratificatie en stratificatietools. Beoordeeld: 01-11-2017. Link: https://richtlijnendatabase.nl/richtlijn/veilig_gebruik_van_contrastmiddelen/PC-AKI/risicostratificatie_en_stratificatietools.html

Module 2: Hydration Strategies in the Prevention of PC-AKI

Clinical question

Which hydration strategy should be used in children undergoing intravascular administration of iodine-based contrast media and who are at increased risk for developing post contrast acute kidney injury (PC-AKI)?

Introduction

When it comes to prevention of post contrast acute kidney injury (PC-AKI), the cornerstone is hydration (volume expansion). For adults, there are clear evidence-based guidelines on when to apply what kind of hydration. For children, there are none. The goal is to find out what the evidence is, specifically in children, to prevent PC-AKI, with emphasis on which eGFR cut-off value must be used in children for hydration in order to prevent PC-AKI and what the optimal hydration strategy in children is.

Search and select

A systematic review of the literature was performed to answer the following question:
What are the effects of hydration versus no hydration in a child receiving intravascular iodine-based contrast media on the risk of PC-AKI and PC-AKI-related complications?

P(atients):	Children (<18 years) undergoing radiological examinations with iodine-based contrast media.
I(ntervention):	Hydration with intravenous (IV) saline, hydration with intravenous bicarbonate, oral hydration, hydration, pre- and posthydration.
C(ontrol):	One of the hydration methods described above or no hydration.
O(utcome):	Post contrast acute kidney injury (PC-AKI), complications of PC-AKI (hospitalization, start of dialysis).

<u>Relevant outcome measures</u>

The guideline development group considered PC-AKI and complications of PC-AKI as critical outcome measures for decision making.

A priori, the guideline development group did not define the outcome measures listed above but used the definitions used in the studies. The guideline development group defined PC-AKI as described in the chapter “PC-AKI: Definities, terminologie en klinisch verloop” in the guideline Veilig gebruik van contrastmiddelen (NVVR, 2017). If authors used other definitions such as CA-AKI (contrast associated) or CI-AKI (contrast induced). We used their terminology for the description of the study, but for the purposes of the guideline standardized to PC-AKI.

The guideline development group defined the following as a minimal clinically (patient) important difference:

- Contrast-associated acute kidney injury (PC-AKI): relative risk <0.91 or >1.10;
- Complications of PC-AKI (hospitalization, start of dialysis): relative risk <0.91 or >1.10;

<u>Search and select (Methods)</u>

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 1990 until 04-04-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 192 hits.
Studies were selected based on the following criteria:

- Systematic review, randomized controlled trial, or observational research comparing hydration strategies for PC-AKI in children receiving intravascular iodine-based contrast media.
- Children (<18 years) who underwent radiological examinations with iodine-based contrast media.
- Hydration types: hydration with IV NaCl, hydration with IV bicarbonate, oral hydration, pre-hydration, pre- and posthydration.
- Follow-up time after hydration was at least 48 hours.
- At least one of the outcome measures was described: PC-AKI, complications of PC-AKI (hospitalization, start of dialysis, mortality).

Four studies were initially selected based on title and abstract screening. After reading the full text, all studies were excluded (see the table with reasons for exclusion under the tab Methods).

Results
No studies were included in the analysis of the literature.

Summary of literature
Description of studies
No studies were included in the analysis of the literature.

Results
No studies were included in the analysis of the literature.

Level of evidence of the literature
The level of evidence could not be determined as no studies were included in the analysis of the literature.

Conclusions

- GRADE	No evidence was found regarding hydration strategies to diminish PC-AKI in children (<18 years of age) undergoing radiological examinations with intravascular iodine-based contrast media.

- GRADE	No evidence was found regarding hydration strategies to prevent PC-AKI related complications for which hospitalization or dialysis was needed in children (<18 years of age) undergoing radiological examinations with intravascular iodine-based contrast media.

Considerations
Pros and cons of the intervention and quality of the evidence
The guideline development group conducted a systematic review of hydration strategies to reduce PC-AKI and PC-AKI related complications after iodine-based contrast media administration in children. No articles were found that met the inclusion criteria. Therefore, no conclusions could be drawn about the effects of hydration strategies on the development

of PC-AKI and complications related to PC-AKI (hospitalization, dialysis). Therefore, a knowledge gap exists on this topic in children.

As there are no comparative studies investigating the research question, the recommendations in this national guideline are primarily based on the guideline for hydration and complications in the prevention of PC-AKI in adults (NVVR, 2017) and on reviews of PC-AKI in the paediatric population. Unfortunately, hard scientific evidence in children is lacking, therefore recommendations are based on expert-opinion and on reviews of paediatric PC-AKI.

In children, a low prevalence of underlying kidney disease should be balanced with possible long-term effects of AKI in children (see risk factors for PC-AKI). Based on cost and long-term patient perspective, hydration strategies should be focused on the small group of children with diagnosed or high risk of underlying kidney disease.

Most children have a normal kidney function and no underlying renal disease. The small patient group with known kidney disease or high risk for kidney disease based on past medical history should have their kidney function tested (also see module "Risk stratification in the prevention of PC-AKI"). A cut-off value eGFR < 30 ml/min/1.73m^2 is advised for prehydration strategies in adults (NVvR, 2017).
The risk of PC-AKI in the adult population increases with each stepwise increase of chronic kidney disease stage, with reported incidence of 5% at eGFR greater than 60 ml/min/1.73m2, up to a incidence of 30% in patients with eGFR < 30 ml/min/1.73m2. Calle-Toro (2022) published a retrospective cohort study in children undergoing CT scans with or without contrast media, showing a difference in risk between contrast exposed and non-contrast exposed groups in children with an eGFR < 60 prior to imaging. Given the possible long-term effect of nephron loss in any episode of AKI, especially in children, we recommend to use a cut-off value eGFR < 60 ml/min/1.73m2 for prehydration strategies in children.

Based on the adult literature and guidelines, prehydration with IV $NaHCO_3$ 1.4% is recommended over IV Saline 0.9% because of the added benefit of higher tubular pH leading to a decreased cellular apoptosis in the setting of reactive oxygen species (ROS) formation.

Some classes of drugs can impair/reduce the perfusion pressure of the kidneys. The most commonly used classes include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics and non-steroidal inflammatory drugs (NSAIDs). Used solely, combined or in the presence of a hypovolemic state, they bring the added risk of impaired renal perfusion pressure, thereby increasing the risk of developing PC-AKI.
Their use in children is uncommon and in general limited to complicated disease. Therefore, this patient group is difficult to compare to adults, mandating a more cautious approach in its use prior to imaging with iodine-based contrast media. We recommend withholding this medication prior to imaging with iodine-based contrast media in children, after consultation with the referring physician.

Patient (and their caretakers) values and preferences
Parents and patients want to make decisions based on evidence and best clinical practice. This module provides guidance to doctors, parents, and patients to help in this decision process. The aim of this guideline is to decrease the small chance of PC-AKI in vulnerable children, although hard scientific evidence is lacking.

Costs

Only a small group of children is at increased risk of PC-AKI and the costs of hydration therapy is low. Reducing the incidence of PC-AKI in a high-risk group may help prevent future healthcare costs due to long-term consequences of PC-AKI in young children.

Acceptance, feasibility and implementation

As only a small group of children are at increased risk of PC-AKI, the acceptance, feasibility, and implementation are not expected to meet obstruction. The intervention is brief and does not require additional handling (child already has intravenous access for the procedure itself).

Recommendations

Rationale of the recommendations: arguments for and against the interventions

Although extensive literature exists on the prevention of PC-AKI in adults, no evidence is known in children. In the process of coming to a recommendation the key arguments to weigh were patient safety on one side versus practical feasibility on the other side. Particularly in ill children interventions should be highly effective and the risk of PC-AKI should outweigh the possible side effects of an intervention. Therefore, it was decided that all children with an eGFR<30 ml/min/1.73m^2 who will receive intravascular iodine-based CM, should be prehydrated with $NaHCO_3$ 1.4% at a rate of 3ml/kg/h during 1 hour before CM administration.

Pas de volgende risico reducerende optie toe voor alle kinderen > 1 maand oud die een intravasculaire jodiumhoudend CM-toediening ondergaan:

- Staak NSAID's voorafgaand aan de jodiumhoudende contrast toediening.
- Staak ACEi, ARBs en diuretica, na consultatie met de hoofdbehandelaar.
- Bespreek met de hoofdbehandelaar de mogelijkheid om nefrotoxische medicatie, zoals aminoglycosiden, te staken voorafgaand aan het onderzoek.
- Streef naar een euvolemische status bij elk kind, ongeacht de eGFR, in het bijzonder bij kinderen met tekenen van een gecompromitteerde circulatie (sepsis/shock).

Afhankelijk van eGFR (als eGFR niet bekend is, pas advies bij eGFR >60ml/min/1.73m^2 toe):

- eGFR >60 ml/min/1.73m^2 (inclusief alle kinderen zonder eGFR):
  - Adviseer om op de dag voor en de dag van het onderzoek adequaat te drinken
- eGFR 30-60 ml/min/1.73m^2:
  - Dien voorafgaand aan het onderzoek 10 ml/kg/uur NaCl 0.9% IV in 1 uur toe (naast het standaard vochtbeleid of vochtinname van het kind).
  - Overleg laagdrempelig met een kinderarts-nefroloog.
  - Bepaal serum kreatinine na 24 uur en 48-72 uur.
- eGFR <30 ml/min/1.73m^2:
  - Overweeg onderzoek zonder contrast of andere onderzoeksmodaliteit.
  - Dien voorafgaand aan het onderzoek 10 ml/kg/uur NaCl 0.9% IV in 1 uur toe.
    Gevolgd door:
    $NaHCO_3$ 1.4%, 3 ml/kg/uur IV gedurende 1 uur vooraf aan CM-toediening, of
    (alternatieve optie) $NaHCO_3$ 1.4%, 3ml/kg/uur IV (max 250 mL in totaal) gedurende 1 uur vooraf aan CM-toediening en 1ml/kg/uur IV (max 500mL in totaal) gedurende 6 uur na CM-toediening.
  - Overleg met een kinderarts-nefroloog.

- Bepaal serum kreatinine na 24 uur en na 48-72 uur.

OVERWEEG bij alle neonaten (baby < 1 maand) en vroeggeboren baby's jonger dan gecorrigeerde post amenorroe duur van 44 weken bovenstaande maatregelen in overleg met de hoofdbehandelaar / kinderarts-neonatoloog.

Knowledge Gaps

- What are the effects of hydration versus no hydration in a child receiving intravascular iodine-based contrast media on the risk of PC-AKI and PC-AKI-related complications?

P(atients): Children (<18 years) undergoing radiological examinations with iodine-based contrast media.
I(ntervention): Hydration with IV NaCl, hydration with IV bicarbonate, oral hydration, hydration, pre- and posthydration.
C(ontrol): One of the hydration methods described above or no hydration.
O(utcome): Post contrast acute kidney injury (PC-AKI), complications of PC-AKI (hospitalization, start of dialysis).

- Which eGFR cut-off should be used when identifying children who should receive hydration to prevent PC-AKI?

- Is a sodium bicarbonate hydration strategy to prevent PC-AKI in children receiving intravascular iodine-based contrast media as safe and effective as it is in adults?

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Module 3 Prophylaxis of hypersensitivity reactions

Clinical question

What prophylactic measures should be taken in children (<18 years) with an increased risk of hypersensitivity reactions after administration of iodinated contrast agents?

Introduction

The incidence of hypersensitivity reactions to Iodinated contrast administration is 0.18-0.46% in paediatric patients (Callahan, 2009; Dillman 2007). The incidence decreased after the switch to non-ionic iodine-based contrast media, which are the only ones still used in the Netherlands. Most of these reactions are mild to moderate, while severe reactions are very rare, especially in children. The most important risk factor for an allergic-like reaction is an history of an allergic reaction to contrast media. There is no consensus with respect to the prophylactic treatment in children with a higher risk of hypersensitivity reactions to contrast media. Furthermore, the current guideline "Safe use of contrast media" lacks advice regarding the treatment in pediatric patients in clinical practice.

Search and selection

A systematic review of the literature was performed to answer the following question: Which prophylactic treatments should be used in children (<18 years) undergoing radiological examinations with iodine-based contrast agents to prevent symptoms of hypersensitivity reactions compared to other or no treatments?

P(atients): Children (<18 years) undergoing radiological examinations with iodine-based contrast media.

I(ntervention): Prophylactic measure to prevent hypersensitivity reactions after contrast media administration.

C(ontrol): No prophylactic measure or a different prophylactic measure to prevent hypersensitivity reactions after contrast media administration.

O(utcome): Allergic reactions to contrast media, hypersensitivity reactions, type I/ type IV, severe allergic reaction.

Relevant outcome measures

The guideline development group considered allergic / hypersensitivity reactions to contrast as critical outcome measure for decision making.

A priori, the guideline development group did not define the outcome measures listed above but used the definitions used in the studies.

The guideline development group defined the following as a minimal clinically (patient) important difference:

- allergic / hypersensitivity reactions to contrast: relative risk ≤0.8 or ≥1.25 (dichotomous); 0.5 SD (continuous)

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 1990 until 24-02-2023. The detailed search strategy is depicted

under the tab Methods. The systematic literature search resulted in 201 hits. Studies were selected based on the following criteria:

- Systematic review, randomized controlled trial, or observational research comparing prophylactic measures to prevent hypersensitivity reactions after contrast administration to other or no prophylactic measurements.
- Including children (<18 years) undergoing radiological examinations with contrast media.
- Reports predefined outcome measure: allergic / hypersensitivity reactions to contrast.

53 studies were initially selected based on title and abstract screening. After reading the full text, all studies were excluded (see the table with reasons for exclusion under the tab Methods), and no studies were included.

Results
No studies were included in the analysis of the literature.

Summary of literature
Description of studies
No studies were included in the analysis of the literature.

Results
No studies were included in the analysis of the literature.

Level of evidence of the literature
The level of evidence could not be determined as no studies were included in the analysis of the literature.

Conclusions

- GRADE	No evidence was found regarding the effect of prophylactic measures to prevent allergic / hypersensitivity reactions to contrast in children (<18 years of age) undergoing radiological examinations.

Considerations
Pros and cons of the intervention and quality of evidence
The guideline development group conducted a systematic review of the optimal prophylactic treatment for acute and delayed hypersensitivity reactions to contrast agents. No articles were found that met the inclusion criteria. In most studies that included children and adults the average age was over 50 years and only few children were included. Therefore, no conclusions could be drawn about the effects of prophylactic treatments to prevent allergic / hypersensitivity reactions to contrast material in children. Consequently, a knowledge gap exists on this topic. A recent review however, suggests to be cautious about the use of corticosteroid premedication (Maloney, 2019).

As there are no comparative studies investigating the research question, the recommendations in this national guideline are based mainly on the guideline for prophylactic measures to prevent hypersensitivity reactions to contrast in adults (NVVR, 2022).

Literature shows that the prevalence of hypersensitivity reaction in children is very low, they experience less hypersensitivity reactions to contrast media compared to adults (Endrikat, 2022). In addition, severe reactions are very rare in children. A large retrospective study in

the US found an incidence of 0.46% hypersensitivity reactions to contrast material in 12,494 patients. Most of these were mild (47 of 57 in total) and no severe reaction (Callahan, 2009). However, severe reactions with anaphylaxis have been described in pediatric patients (Dillman, 2007). In case of a severe reaction intramuscular adrenalin administration is the main treatment (see section 4 of this guideline: Behandeling acute overgevoeligheidsreacties).

Pharmacologial prevention
For adults the evidence in the guideline regarding the effectivity for pharmacological prevention is very heterogeneous and of low quality. Prophylactic premedication mainly reduces the number of mild reactions and therefore the total number of reactions, but not the number of severe reactions. There is no evidence that this is different in children. One recent meta-analysis with five studies in patients with previous moderate to severe hypersensitivity reactions described a reduction in reactions with steroid premedication. However, there were several study limitations and only a few children were included (Hsieh, 2022). Therefore, in line with the Dutch guideline for adults, the guideline development group does not recommend premedication for children.

In line with the Dutch guideline for adults, major international guidelines do not recommend the use of premedication for non-severe nonimmediate reactions, however in case of more severe reactions they suggest performing allergologic skin testing and referral to an allergist (ACR, 2023; ESUR, 2018; Shaker 2020; Torres, 2021).

Antihistamines and corticosteroids
If premedication is required, two types of drugs are used: H1-antihistamines and corticosteroids. Often, they are used concomitantly, making their individual effect difficult to assess, particularly since there are many variations in premedication schedules. However, both have side effects that one should be aware of.

H1-antihistamines block histamine receptors on various effector cells, blocking the effect of one of the pivotal players in direct mast cell responses. However, mast cells and basophils secrete various other substances that are not blocked by these drugs. The main side effect of the older H1-antihistamines that are available for intravenous administration is drowsiness/sedation, but they also have a negative effect on blood pressure. Clemastine (Tavegyl) is one of the H1-antihistamines that is still widely used in treating allergic symptoms or as premedication and should be used with caution for reason. For the newer nonsedating antihistamines this effect is usually mild, but these are mainly available for oral administration.

Corticosteroids have various effects on the immune system, including mast cells, and therefore can block both mast cell degranulation by upregulating inhibitory signaling receptors, and inhibit cytokine production through suppression of gene transcription. (Andrade, 2004; Park, 2009) These membrane stabilizing effects require that administration is started >6h before contrast media administration. Unfortunately, this comes with a less favourable side effect profile, particularly with higher doses and repeated exposure. It has been shown that corticosteroid premedication can cause brief hyperglycaemia (Davenport, 2010), but may also be associated with longer hospital stay, increased costs, and worse clinical outcomes (Davenport, 2016).

There are two widely used premedication protocols; the Greenberger and Lasser protocol in which high doses of corticosteroids and antihistamines (diphenhydramine) are used.

(Greenberger, 1981; Greenberger, 1986; Lasser, 1994). In the Netherlands steroids and clemastine (Tavegyl®) are frequently used as premedication in elective procedures. There is no literature available to establish an optimal indication or protocol.

Pediatric medication dose:

- Prednisolone 1mg/kg with a max of 20 mg IV. 12h and 2h before the procedure.
- Clemastin IV 25-50 microgram/kg/dose with a max of 2mg. 1h before the procedure (Tmax within minutes). Note: this can give drowsiness/sedation.

In conclusion, there is a paucity of data on the benefits of premedication for hypersensitivity reactions in adults and even less in paediatric patients. Most of these reactions are self-limiting or can be treated symptomatically. In patients with a (documented) history of a hypersensitivity reaction to a contrast medium, an alternative imaging modality should be considered. The more severe the reaction, the stronger omitting a contrast medium should be considered. For mild reactions in which alternative imaging modalities are of substantially inferior quality, the risk – benefit ratio may shift. In many cases, CT with iodine-based contrast media can be replaced by ultrasound, with or without contrast agents, or MRI, with or without contrast agents. When this is not possible, consider performing the examination or imaging study without a contrast medium or with an alternative contrast medium (see next paragraph), but only if this has an acceptable degree of diagnostic quality. For this, close communication with the referring specialist is mandatory. Finally, in case of a suspected hypersensitivity, patients should be referred to a paediatric allergist.

Cross-reactivity between iodine-based contrast media (ICM):
Schrijvers (2018) found most cross-reactivity between agents with a N-(2,3 dihydroxypropyl)-carbamoyl side chain. This side chain is present in most media used in The Netherlands (Iopromide, Iohexol, Iomeprol, Ioversol and Iodixanol), but not in Iobitridol and Iopamidol. The table below shows cross-reactivity rates between pairs of ICM in skin positive patients with immediate hypersensitivity reactions. Risk of cross-reactivity is marked as very low (dark green, <10%), low (green, 10-20%), medium (orange 20-30%), high (red, 30-50%) and very high (dark red, >50%).

ICM Name	*Iobitridol*	*Iopamidol*	*Iopromide*	*Iohexol*	*Iomeprol*	*Ioversol*	*Iodixanol*
Iobitridol	X						
Iopamidol	**11.8%** [5.5-18]	X					
Iopromide	**22.1%** [22-22.2]	**25.6%** [11.1-40]	X				
Iohexol	**20.8%** [16.6-25]	**25.1%** [11.1-39]	**43.5%** [38.9-48]	X			
Iomeprol	**17.6%** [13-22.2]	**33.2%** [33-33.3]	**38.7%** [33-44.4]	**40.2%** [36-44.4]	X		
Ioversol	**20.6%** [19-22.2]	**35.6%** [22.2-49]	**37.7%** [33.3-42]	**50.0%** [38.9-61]	**53.3%** [51-55.5]	X	
Iodixanol	**19.3%** [16.6-22]	**36.6%** [22.2-51]	**45.5%** [38.9-52]	**51.7%** [44.4-59]	**45.5%** [41-50]	**51.5%** [38.9-64]	X

Table 1: Cross-reactivity rates between pairs of ICM in skin positive patients. The guideline for prophylactic measures to prevent hypersensitivity reactions to contrast in adults (NVVR, 2022).

Documentation of contrast medium

To prevent administration of a specific contrast media that previously triggered an allergic reaction, proper documentation in the electronic patient record (EPR) has become very important. In line with the recommendation in the guideline for prophylactic measures to prevent hypersensitivity reactions to contrast in adults (NVVR, 2022), the guideline development group recommends documenting the specific contrast medium name and dose which were administered to the patient in the imaging report and/or with the stored images.

Patient (and their caretakers) values and preferences

Allergic reactions can be a cause of concern for patients and their caregivers, especially if they have experienced allergic reactions in the past. It is important to inform patients that allergic reactions to contrast media are extremely rare in pediatric patients. Patients with previous allergic reactions often expect precautionary steps, but this is not always indicated. Time should be taken to discuss the reasoning for adapting the procedure (or not). There is no evidence that premedication reduces the risk of severe reactions. In case of a severe reaction, it is best to use a substitute contrast medium and when there is enough time to consult an allergist. It's important to document previous reactions with timing of onset and type of symptoms, preferably with pictures of skin reactions. This helps the allergist to classify the type of hypersensitivity reaction and subsequently to give a good advice.
In case of an underlying disease like eczema of chronic spontaneous urticaria it is advised to inform the patient that the procedure can cause an increase in symptoms and patients should use their own medication more intensively before and after the procedure.
In case of using premedication, patients should be warned regarding the side effects of corticosteroids and clemastine. Second generation antihistamines have less side effects.

Costs

Severe hypersensitivity reactions are associated with additional healthcare costs. Currently physicians are likely to be extra careful in children and thus order additional (and often unnecessary) premedication and interventions for all children who have a hypersensitivity reaction in their history. The recommendations in this guideline can prevent unnecessary use of premedication in specific subgroups (such as for non-severe nonimmediate reactions), while simultaneously preventing unnecessary incidents of hypersensitivity reactions. In addition, there is evidence that corticosteroid premedication can enhance a prolonged hospital stay (Davenport 2017)

Acceptability, feasibility and implementation

The guideline development group does not anticipate any acceptance issues. The recommendations in the current guideline address longstanding uncertainty about the need for prophylactic measures to prevent hypersensitivity reactions. Therefore, it will contribute to a more unified and equal approach in children.

Recommendations

Rationale of the recommendations: weighing arguments for and against the interventions

There is a paucity of data on the benefits of prophylactic measures including premedication for prevention of recurrent hypersensitivity reactions in paediatric patients. Hypersensitivity reactions are very rare and most of these reactions are classified as mild and self-limiting.
In patients with a (documented) history of a hypersensitivity reaction to a contrast medium,

an alternative imaging modality or a different contrast medium should be considered. In case of a more severe reaction a paediatric allergist should be consulted additionally. This recommendation contributes to a more unified and equal approach for prophylactic measures to prevent hypersensitivity reactions in children. One should be aware of unnecessary use of premedication in specific subgroups. Physicians are likely to accept the current recommendations, but it will be important to carefully inform patients and their caregivers regarding the low risk and possible side effects of premedication. Especially those patients who have experienced a mild allergic reaction in the past.
The risk of a severe allergic reaction is very rare, however staff should be trained how to treat and handle possible allergic symptoms that can occur.

Overweeg een alternatieve beeldvormingsmodaliteit bij alle patiënten met een (gedocumenteerde) geschiedenis van een overgevoeligheidsreactie voor een contrastmiddel. Indien dit niet mogelijk is, overweeg het uitvoeren van het onderzoek zonder contrastmiddel, indien de reductie van diagnostische kwaliteit acceptabel is.

- Indien de vorige overgevoeligheidsreactie mild* was:
  Voer het radiologisch onderzoek uit zoals gebruikelijk gezien het lage risico op het ontwikkelen van een meer ernstige reactie.
  Bij twijfel aan de ernst van de vorige overgevoeligheidsreactie: overweeg om de patiënt te verwijzen naar een allergoloog.

- Indien de vorige overgevoeligheidsreactie matig tot ernstig** was:
  Verwijs patiënt naar een allergoloog. Indien mogelijk, stel het beeldvormend onderzoek uit totdat de resultaten van de huidtesten bekend zijn. Pas het advies van de allergoloog toe met betrekking tot het kiezen van een alternatief contrastmiddel.

- Indien acuut onderzoek noodzakelijk is:
  Kies voor een alternatief contrastmiddel (obv lage kruisreactiviteit) of een alternatieve beeldvormingsmodaliteit zoals eerder beschreven. Indien het verdachte contrastmiddel van een eerdere reactie niet bekend is of er geen alternatief gegeven kan worden, wordt geadviseerd eerst 10% van de contrastmiddeldosis te geven. Observeer de patiënt minimaal 30 min met een infuus alvorens de overige 90% toe te dienen. Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie (zie module behandeling acute overgevoeligheidsreactie). De kans op een allergische reactie is heel klein en de kans op een eventuele ernstige allergische reactie wordt zo nog verder verkleint.
  *milde reacties: alleen symptomen van de huid (erytheem, enkele urticaria, mild angio-oedeem, jeuk), rhinitis en/of conjunctivitis, niezen, kriebel in de keel.

  **matig tot ernstige reacties: gegeneraliseerde urticaria, respiratoire klachten met stridor (expiratoir en/of inspiratoir), heesheid, zwelling van de tong en/of pharynx, herhaaldelijk braken, hypotensie, bewustzijnsverlies, shock.

NB bovenstaande laat het belang van een goede documentatie van symptomen van de reactie zien.

Document the specific contrast medium name and dose which were administered to the patient in the imaging report and/or with the stored images.

Knowledge gaps

There is a large knowledge gap about the effect of prophylactic treatment in hypersensitivity reactions to contrast media. An extensive search was performed but no papers were found that met the inclusion criteria. The few studies found included both children and adults with the average age over 50 years and only few children. In addition, comparative studies and meta-analyses were heterogeneous in medication use with several confounders and no control groups were included. Therefore, a knowledge gap exists on this topic and better studies are needed to address this topic with the following research question:
Which prophylactic measures should be used in children (<18 years) undergoing radiological examinations with contrast agents to prevent symptoms of hypersensitivity reactions compared to other or no treatments?

P(atients): Children (<18 years) undergoing radiological examinations after administration of iodine-based contrast media.

I(ntervention): Prophylactic measures to prevent hypersensitivity reactions after contrast media administration.

C(ontrol): No prophylactic measures or a different prophylactic measure to prevent hypersensitivity reactions after contrast media administration.

O(utcome): Allergic reactions to contrast media, hypersensitivity reactions, type I/ type IV, severe allergic reaction.

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Module 4 Treatment of acute hypersensitivity reaction

Clinical question

What is the optimal treatment for acute hypersensitivity reactions to contrast media?

Introduction

Anaphylaxis due to intravenous contrast media is rare in children. Currently, radiologists use a combination of adult guidelines and experience to treat acute hypersensitivity reactions to contrast media in children. However, children are a heterogeneous population in terms of age and background. Children have a different anatomy of the upper airways, making them especially vulnerable to airway constriction due to anaphylaxis. Also, since children come in different shapes and sizes, tailormade approach based on body weight and anatomical differences in comparison to adults, is required. Therefore, the current guideline describes the optimal treatment for acute hypersensitivity reactions to contrast media in children.

Search and select

A systematic review of the literature was performed to answer the following question:
What are the effects of different measures to reduce symptoms of hypersensitivity reactions in children (<18 years of age) undergoing radiological examinations with contrast media?

P(atients): Children (<18 years) with acute hypersensitivity reaction after administration of contrast media;
I(ntervention): Treatment, antihistamines, corticosteroids, epinephrine, adrenalin, dopamine, norepinephrine, noradrenalin, histamine H1 antagonists, histamine H2 antagonists, H1 antihistamines, H2 antihistamines, adrenergic beta-2 receptor agonists, glucocorticoids, management/treatment of hypersensitivity reactions/allergic reactions after contrast media, antihistamines, volume resuscitation, bronchodilators;
C(ontrol): Conservative treatment or comparison of interventions mentioned above;
O(utcome): Curation of acute allergic reactions, severity of complaints, morbidity, mortality, costs, hospitalization in an IC-unit, length of stay.

<u>Relevant outcome measures</u>

The guideline development group considered morbidity, mortality, and hospitalization in an IC-unit as critical outcome measures for decision making; and duration of acute reaction, length of stay and costs, as outcome measures for decision making.

A priori, the guideline development group did not define the outcome measures listed above but used the definitions used in the studies.

The guideline development group defined the following as a minimal clinically (patient) important difference:

- Duration of acute allergic reaction: 0.5 SD (continuous);
- Severity of complaints: 0.5 SD (continuous);
- Morbidity: relative risk <0.91 or >1.10;
- Mortality: relative risk <0.95 or >1.05;
- Hospitalization in an IC-unit: relative risk <0.80 or >1.25;
- Length of stay in hospital: 0.5 SD (continuous);

- Costs: 0.5 SD (continuous);

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 1990 until 14-03-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 147 hits. Studies were selected based on the following criteria:

- Systematic review, randomized controlled trial or observational research comparing treatment for acute hypersensitivity reactions to conservative treatment or another kind of treatment.
- Including children (<18 years) with an acute hypersensitivity reaction after administration of contrast media.
- Reporting at least one of the following outcome measures: duration of acute allergic reaction, severity of complaints, morbidity, mortality, costs, hospitalization in an IC-unit, length of stay.

26 studies were initially selected based on title and abstract screening. After reading the full text, all studies were excluded (see the table with reasons for exclusion under the tab Methods), and no studies were included.

Results
No studies were included in the analysis of the literature.

Summary of literature
Description of studies
No studies were included in the analysis of the literature.

Results
No studies were included in the analysis of the literature.

Level of evidence of the literature
The level of evidence could not be determined as no studies were included in the analysis of the literature.

Conclusions

- GRADE	No evidence was found regarding the effect of different kinds of treatment to reduce duration of acute allergic reaction in children (<18 years of age) undergoing radiological examinations with contrast agents.

- GRADE	No evidence was found regarding the effect of different kinds of treatment to reduce severity of complaints of acute allergic reaction in children (<18 years of age) undergoing radiological examinations with contrast agents.

- GRADE	No evidence was found regarding the effect of different kinds of treatment to reduce morbidity due to acute allergic reaction in children (<18 years of age) undergoing radiological examinations with contrast agents.

- GRADE	No evidence was found regarding the effect of different kinds of treatment to reduce mortality due to acute allergic reaction in children (<18 years of age) undergoing radiological examinations with contrast agents.

- GRADE	No evidence was found regarding the effect of different kinds of treatment to reduce costs due to acute allergic reaction in children (<18 years of age) undergoing radiological examinations with contrast agents.

- GRADE	No evidence was found regarding the effect of different kinds of treatment to reduce hospitalization in an IC-unit due to acute allergic reaction in children (<18 years of age) undergoing radiological examinations with contrast agents.

- GRADE	No evidence was found regarding the effect of different kinds of treatment to reduce length of stay in hospital due to acute allergic reaction, in children (<18 years of age) undergoing radiological examinations with contrast agents.

Considerations

Advantages and disadvantages of the intervention and quality of evidence

The work group conducted a systematic review of the optimal treatment for acute hypersensitivity reactions to contrast agents. No articles were found that met the inclusion criteria. Therefore, no conclusions could be drawn about the effects of treatment for acute hypersensitivity reactions on the outcome measures duration of acute allergic reaction, severity of symptoms, morbidity, mortality, costs, ICU admission, length of stay. Therefore, a knowledge gap exists on this topic.

As there are no comparative studies investigating the optimal treatment for acute hypersensitivity reactions to contrast agents in children, the recommendations in this national guideline are based mainly on expert opinion in combination with two other sources of relevant literature. The first is the Dutch National Advanced Paediatric Life Support book (Turner, 2022). This is considered the standard with regard to dealing with life threatening pediatric conditions, including anaphylaxis.
We also used the adult guideline for the treatment of acute hypersensitivity reactions to contrast media (NVvR, 2020). We adhere to the adult guidelines as much as possible, taking into account differences between adults and children in physiology and treatment options. First, we describe key differences to consider, followed by the treatment options.

Differences between adults and children

- The airways in children differ from those in adults in diameter and shape, making children especially vulnerable to airway narrowing due to anaphylaxis.
- Unlike adults, children in general have better developed mechanisms of compensation. Unfortunately, the degree of sickness can easily be underestimated.
- In children medication is based on body weight in kilograms. If this is unknown, age is used as a surrogate to estimate body weight.
- Like in adults, APLS guidelines with an ABC-type approach is used (NVvR, 2020).

Acute hypersensitivity reactions

Patients who develop an acute hypersensitivity reaction to contrast agents may have a variety of symptoms. Varying from mild symptoms, for example a rash, to severe potentially life-threatening reactions with symptoms like (airway) edema, inspiratory and expiratory stridor, hypotension, collapse and persistent vomiting. These severe reactions are also called anaphylaxis. Since the frequency of severe hypersensitivity reactions to contrast agents is quite rare, the guideline development group focuses on three simple but effective ways to stabilize the patient while waiting for a pediatric resuscitation team. Further treatment is best done by a pediatrician or pediatric anesthesiologist. The three measures to treat

anaphylaxis are described in more detail below. For non-anaphylactic acute hypersensitivity reactions to contrast agents, the guideline development group recommends consulting a pediatrician.

Three measures to treat anaphylaxis
Anaphylaxis or severe hypersensitivity reactions are potentially life-threatening and it is important to start treatment as soon as possible. Quick administration of intramuscular adrenaline will swiftly alleviate symptoms. The second most important treatment will be administration of 15 liter per minute of oxygen, via a non-rebreathing mask. It is important to have smaller masks suitable for children on hand in the CT room. However, since the effect of the adrenaline may be temporary, specialized pediatric care is required. So third, a (pediatric) resuscitation team needs to be called to assist immediately (the exact name and composition of this team differs between hospitals). The goal of treatment for anaphylaxis is to stabilize the patient, while waiting for a pediatric resuscitation team. Further recommendations regarding the treatment of children with hypersensitivity reactions are beyond the scope of this guideline. Pediatricians will follow APLS guidelines for further treatment of hypersensitivity reactions.
Unlike the treatment of anaphylaxis in adults, clemastine is no longer recommended for treatment of anaphylaxis in children. It's known to cause hypotension and drowsiness; this last side effect can further compromise airway patency.

Adrenaline administration
In the setting of anaphylaxis, adrenaline should be administered into the muscle (intramuscular injection). The recommended dose is:

- >25 kg body weight: 300 microgram adrenaline (adrenalin auto-injectors available, such as Epipen® or Jext®),
- 7.5-25 kg body weight: 150 microgram adrenaline (adrenalin auto-injectors available, such as Epipen Junior® or Jext®),
- < 7.5 kg body weight: 10 mcg/kg, (equals 0.1 ml/kg from 1mg/10ml adrenaline vial (1:10,000).
- When weight is unknown: ≥ 6 years 300 microgram (adrenalin auto-injectors available, such as Epipen® or Jext®), < 6 years 150 microgram (adrenalin auto-injectors available, such as Epipen Junior® or Jext®).
- When symptoms do not decrease or progress a second dose of adrenalin can be necessary. A second injection can be given 5-15 minutes after the first dose.

Adrenaline is available in vials, from which the solution must be aspirated into a syringe before it can be administered to the child. Another option is to use an adrenalin auto-injector, in which an adrenaline solution is already in a syringe. These devices can be spring loaded, such as the Epipen®. An adrenaline auto-injector is used to administer adrenaline intramuscularly in an acute setting. Since most healthcare providers in radiology do not use needles and syringes to administer medication on a daily basis, and since time is of the utmost essence, the guideline development group strongly advises use of an adrenalin auto-injector despite a higher cost (see cost paragraph below for more details).

<u>Patient (and their caretakers) values and preferences</u>
Acute hypersensitivity reactions to contrast media are a cause of concern for patients and their caregivers, especially if they have experienced acute hypersensitivity reactions in the past. It is important to distinguish severe reactions such as anaphylaxis from mild reactions such as rash, since treatment and response should be in proportion. In case of severe reactions, namely anaphylaxis, the focus is on swift intervention to reduce the immediate

concern (airway restriction), meanwhile ensuring the correct expertise is sent by contacting a pediatric resuscitation team for any further decisions on treatment. In case of mild acute hypersensitivity reactions, there is more time to formulate a treatment strategy and, if necessary, consult the appropriate experts.

Costs

It is important to act quickly and effectively to prevent serious complications from acute hypersensitivity reactions, and reduce associated additional healthcare costs both in the short and long term. Most of the recommendations in this guideline lead no or little additional costs. Oxygen is usually already available in CT suites and non-rebreathing masks cost around 5 euros each. Only for adrenaline administration in children weighing >10 kg does the guideline development group strongly advice a higher priced alternative, based on the ease of use and thus more time efficient administration. For example, the use of adrenalin auto-injectors such as the Epipen® (cost 38-42 euros) instead of adrenaline injection using vials (3 euros for 1mg/1ml solution) (Zorginstituut Nederland, n.d.). For children weighing less than 10 kilograms, the only option is to administer the (=weight adjusted) amount of adrenaline with a syringe.

Acceptability, feasibility and implementation

The guideline development group does not anticipate any acceptance or feasibility issues. The triad adrenaline / high flow oxygen / calling for help is a simple but effective strategy in cases of anaphylactic acute hypersensitivity reactions. High oxygen flow is already standard in the treatment of anaphylactic acute hypersensitivity reactions in adults. Ensuring smaller non-rebreathing masks suitable for children are present should not provide problems as these are already used and readily available in hospital. Similarly, the guideline development group anticipates it will be feasible to ensure the way to contact the paediatric resuscitation team is clearly signposted near the CT scanner and contact details for a paediatrician are available. Regarding adrenaline, many radiology departments are already familiar with the use of an adrenalin auto-injectors. Therefore, the introduction of an Adrenaline auto-injector (for children who weigh more than 7.5 kilograms) is expected to be acceptable and feasible. If contrast media is also given to children who weigh less than 7.5 kilograms, a 0,1mg/10 ml vial of adrenaline (with needles and syringes) also needs to be present.
In terms of implementation, given the rarity of these types of reactions it is important to provide adequate training of personnel on how to handle acute contrast reactions in children. Thus, ensuring the correct level of expertise is maintained to act when necessary.

Recommendations

Rationale of the recommendation: weighing arguments for and against the interventions

Unfortunately, there were no comparative studies investigating the optimal treatment for acute hypersensitivity reactions to contrast agents in children. Therefore, the recommendations in this national guideline are based mainly on expert opinion in combination with a current standard book on Advanced Paediatric Life Support (Turner, 2022) and the existing adult guideline for the treatment of acute hypersensitivity reactions to contrast media (NVvR, 2020).

Since the airways in children differ from those in adults in diameter and shape, this makes children especially vulnerable to airway narrowing due to anaphylaxis. To treat airway narrowing due to an anaphylactic acute hypersensitivity reaction to contrast media, adrenaline should be administered intramuscularly. In addition to this, high flow oxygen should be given by means of a non-rebreathing mask. Since anaphylaxis is a paediatric

emergency, advanced paediatric life support expertise is required immediately, to further treat the child and prevent rapid deterioration of the condition of the child.

Overall, there is consensus in our guideline development group that these three basic measures (adrenaline, oxygen, call for help) are critical in the primary treatment of life-threatening anaphylaxis. In case of mild acute hypersensitivity reactions, there is more time to formulate a treatment strategy and, if necessary, consult the appropriate experts.

The guideline development group does not anticipate any acceptance, feasibility or implementation issues.

Acute allergische reacties verschillen in ernst; de aanbevelingen zijn per ernst van de situatie geformuleerd.

Bij anafylactische reactie:

- Geef adrenaline intramusculair. Let op de juiste dosering:
  - >25 kg lichaamsgewicht 300 microgram adrenaline (adrenaline auto-injectors beschikbaar, zoals de Epipen® or Jext®),
  - 7.5-25 kg lichaamsgewicht 150 microgram adrenaline (adrenaline auto-injectors beschikbaar, zoals de Epipen Junior® or Jext®),
  - < 7.5 kg lichaamsgewicht , 10 mcg/kg, overeenkomend met 0.1 ml/kg uit 1mg/10ml adrenaline ampul (1:10.000).
  - Indien het gewicht niet bekend is: ≥ 6 jaar 300 microgram (Epipen® or Jext®), < 6 jaar 150 microgram (Epipen Junior® or Jext®).
- Geef 15 liter/minuut zuurstof via een non-rebreathing masker.
- Alarmeer het (kinder)reanimatie team (naam varieert per ziekenhuis).
- Als de symptomen niet afnemen of verergeren, kan een tweede dosis adrenaline nodig zijn. Een tweede injectie kan 5-15 minuten na de eerste dosis gegeven worden.

Bij niet-anafylactische acute overgevoeligheidsreacties:

- Overleg met een kinderarts over verdere behandeling en/of beleid.

Zie stroomschema.

Knowledge gaps

There is a large knowledge gap regarding the optimal treatment for acute hypersensitivity reactions to contrast media in children. An extensive search was performed but no papers were found that met the inclusion criteria. Therefore, a knowledge gap exists on this topic and better studies are needed to address this topic with the following research question:

What are the effects of different treatments to reduce symptoms of hypersensitivity reactions in children (<18 years of age) undergoing radiological examinations with contrast agents?

P(atients): Children (<18 years) with acute hypersensitivity reaction after administration of contrast media;

I(ntervention): Treatment, antihistamines, corticosteroids, epinephrine, adrenalin, dopamine, norepinephrine, noradrenalin, histamine H1 antagonists, histamine H2 antagonists, H1 antihistamines, H2 antihistamines, adrenergic

beta-2 receptor agonists, glucocorticoids, management/treatment of hypersensitivity reactions/allergic reactions after contrast media, antihistamines, volume resuscitation, bronchodilators;

C(ontrol): Conservative treatment or comparison of interventions mentioned above;

O(utcome): Curation of acute allergic reactions, severity of complaints, morbidity, mortality, costs, hospitalization in an IC-unit, length of stay.

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Module 5 Monitoring of Thyroid Function after Administration of Iodine-based Contrast Media

Clinical question

Should thyroid function be monitored in children after administration of an iodine-containing contrast agent?

Introduction

Iodine is essential for thyroid hormone synthesis, and excess iodine exposure may affect thyroid hormone levels. The use of iodine-based contrast media (ICM) for radiological studies leads to excess iodine exposure. In this context it is important to realize that only free iodide is available for uptake by the thyroid gland. ICM mainly contain organically bound iodine that is excreted in the urine unchanged and will not affect thyroid function. However ICM also contain small amounts of free iodide. This concentration varies between different ICM solutions and is batch-dependent with a longer shelf-life leading to a higher free iodine content (van der Molen 2004).

To prevent hyperthyroidism in the case of such excess iodine exposure the thyroid gland temporarily downregulates thyroid hormone production. This is called the Wolff-Chaikoff effect. Within a few days an escape from the Wolff-Chaikoff effect occurs and thyroid hormone production is usually restored to normal within 2 weeks. However, prolonged hypothyroidism may occur when the escape from the Wolff-Chaikoff effect fails. This has been well described in patients with pre-existing thyroid disease. In the fetal period, the thyroid gland is not mature enough to escape from the Wolff-Chaikoff effect until approximately 36 weeks of gestation. This makes the fetus and (premature) neonate particularly vulnerable to the suppressive effects of excess iodine (Lee, 2015). Various studies have shown that intravascular ICM administration reduces thyroid hormone levels in neonates and causes prolonged hypothyroidism. A systematic review including 11 studies with a total of 182 hospitalized neonates exposed to ICM reported hypothyroidism in 8.2% of term infants and 18.2% of premature infants (Ahmet, 2009).

Brain development is critically dependent on thyroid hormone in the first three years of life and therefore prolonged periods of hypothyroidism in infants and young children should be prevented (van Trotsenburg 2021).

In March 2022 the FDA issued a drug safety communication recommending thyroid function monitoring within 3 weeks of intravascular administration of iodine-based contrast media in all children up to 3 years of life. In a reaction to this recommendation the Pediatric Endocrine Society (PES) and American College of Radiology (ACR) published statements questioning this recommendation due to lack of sufficient evidence and proposed a more individualized approach, identifying patient groups who are most at-risk.

In this part of the guideline we address the question whether routine thyroid function monitoring after the use of ICM in children is necessary.

Search and select

A systematic review of the literature was performed to answer the following question:

What are the results of thyroid function monitoring after the use of iodinated contrast media in children (<18 years) undergoing radiological examinations?

P(atients): Children (<18 years) undergoing radiological examinations with iodinated contrast media (ICM);
I(ntervention): Monitoring of thyroid function after ICM administration.
C(ontrol): No monitoring of thyroid function after ICM administration.
O(utcome): Hypothyroidism, hyperthyroidism, irreversible effects of thyroid dysfunction on neurological development.

Relevant outcome measures
The guideline development group considered hypothyroidism and hyperthyroidism as critical outcome measures for decision making; and irreversible effects of thyroid dysfunction on neurodevelopment of children as an important measure for decision making.

A priori, the guideline development group did not define the outcome measures listed above but used the definitions used in the studies.

Per outcome the guideline development group defined the following differences as minimal clinically (patient) important differences:
- Hypothyroidism: RR ≤0.8 or ≥1.25 (dichotomous); 0.5 SD (continuous)
- Hyperthyroidism: RR ≤0.8 or ≥1.25 (dichotomous); 0.5 SD (continuous)
- Irreversible effects of thyroid dysfunction on neurodevelopment of child: RR ≤0.8 or ≥1.25 (dichotomous); 0.5 SD (continuous)

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2000 until 24-07-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 85 hits. Studies were selected based on the following criteria:
- Systematic review, randomized controlled trial or observational research comparing thyroid monitoring to no monitoring in children receiving intravascular iodine-containing contrast.
- Children (<18 years) who underwent radiological examination with iodine-containing contrast media (ICM);
- At least one of the outcome measures was described: hypothyroidism, hyperthyroidism.
- Full-text English language publication.

12 studies were initially selected based on title and abstract screening. After reading the full text, all studies were excluded (see the table with reasons for exclusion under the tab Methods).

Results
Since no studies fulfilled the PICO criteria it was not possible to perform a systematic analysis of the literature. Nine studies did have the correct patient population and performed thyroid function monitoring after the use of iodine-containing contrast. These studies are briefly described in Supplemental Table 1. Since these studies include variable age groups, variable iodine-containing contrast substances and variable follow-up they do not answer the search question, and no quality of evidence analysis or evidence tables were made.

Summary of literature

No studies fulfilled our PICO criteria. Therefore, no evidence tables, risk of bias assessment and quality assessment were performed for the studies mentioned in Supplemental Table 1.

Conclusions

- GRADE	No evidence was found regarding the effects of thyroid monitoring in children (<18 years of age) undergoing radiological examinations with intravascular iodine-containing contrast agents on *hypothyroidism*.

- GRADE	No evidence was found regarding the effects of thyroid monitoring in children (<18 years of age) undergoing radiological examinations with intravascular iodine-containing contrast agents on *hyperthyroidism*.

- GRADE	No evidence was found regarding the effects of thyroid monitoring in children (<18 years of age) undergoing radiological examinations with intravascular iodine-containing contrast agents on *irreversible effects of thyroid dysfunction on neurodevelopment of child*.

Considerations

Advantages and disadvantages of the intervention and quality of evidence

Thyroid hormone is essential for normal brain development in children, especially in the first three years of life. It is well known that untreated congenital hypothyroidism leads to neurodevelopmental problems and that timely treatment initiated within the first weeks of life prevents these developmental problems. Since exposure to ICM may lead to prolonged hypothyroidism the goal of thyroid function monitoring after the use of iodine-based contrast media (ICM) is the prevention of neurodevelopmental delay. However, studies designed to answer the question whether monitoring of thyroid function and the subsequent thyroid hormone supplementation in children exposed to ICM leads to better neurodevelopmental outcome are missing.

A systematic literature search based on the abovementioned did not result in any articles meeting the inclusion criteria. Nine studies were excluded because of missing control groups as defined in the PICO or having a design (and thus population) focused on a different question than the search question. However, these nine studies did report thyroid function monitoring after the use of ICM and are described in table 1.

The studies of Gilligan (2021) and Rath (2019) included a non-iodine exposed control group. Gilligan (2021) compared 114 children $\leq$ 24 months with either a single ICM enhanced CT (57 exposed cases) or an abdominal ultrasound (57 unexposed cases) and found no differences in TSH levels measured within three months after imaging. Rath (2019) performed a randomized controlled trial comparing 20 preterm infants receiving iodinated contrast to 21 preterm infants receiving only saline to ascertain peripherally inserted central catheter tip position. No differences in thyroid function were found.

Williams (2016) studied 173 preterm infants (<32 weeks) with exposure to either iodinated contrast or topical iodine during caesarian section and reported thyroid dysfunction mainly in the topical exposure group. The remaining six studies all included cardiac patients undergoing either cardiac CT, angiography, or catheterization. Age groups varied from preterm to eight years. Belloni (2018) reported only transient TSH decrease while the other studies reported hypothyroidism in varying frequencies and duration. Reported rates were highest in infants

under three months of age (Jick 2018), low-weight and premature infants (Rosenberg 2018) and in case of renal impairment and multiple iodine exposures (Thaker 2017).
Since these studies include variable age groups, different ICMs, and variable follow-up they do not sufficiently answer the search question.

In 2009 Ahmet and coworkers performed a systematic review in order to determine whether neonates exposed to iodinated contrast media are at risk of hypothyroidism (Ahmet, 2009). They included 11 studies, published between 1986-2000. These were older studies not included in our search. These 11 studies included 182 hospitalized neonates (72 term born, 110 preterm born) exposed to iodinated contrast. Six out of 72 (8.2%) exposed term infants were treated for hypothyroidism and 20 out of 110 (18.2%) exposed preterm infants. The authors concluded that hospitalized neonates exposed to ICM are at risk for abnormal thyroid function and hypothyroidism and that premature infants might be at increased risk. However the studies were however highly affected by bias calling for well-controlled studies.

In the various studies the reported prevalence of hypothyroidism after the use of ICM ranges from 1 to 15%. Overall children in the first three months of life seem most at risk of developing thyroid dysfunction after exposure to ICM. More specifically at high risk seem to be premature neonates, low-birth weight neonates and critically ill infants. Also, renal impairment, cardiac disease, and prolonged/frequent exposure to ICM such as during cardiac bypass and dialysis are risk factors.

An important unanswered question is whether infants between 3 months and 3 years are at risk of developing hypothyroidism after exposure to ICM. Also, whether this is dose dependent and what the duration of the hypothyroidism is and whether this would affect neurodevelopment if left untreated.

Most studies focus on the use of intravascular ICM in neonates, but iatrogenic hypothyroidism has also been described after enteral and lymphatic ICM exposure (Putnins, 2020; Cherella, 2018; Lombard, 2009, Ares 2008).

Since enteral ICM is regularly used in (premature) newborns with congenital intestinal diseases, this may lead to a high uptake of iodine in the blood system of this vulnerable patient group, particularly in case of prolonged stasis in children with intestinal obstruction (own observation, manuscript in preparation).
Although the causal relationship is not definitive, but with incidental cases of prolonged hypothyroidism after enteral ICM administration having been reported, we advise thyroid function monitoring in preterm infants exposed to intravascular and enteral administration of ICM (Putnins 2020; Lombard, 2009, Ares, 2008). Future studies need to investigate the effect on thyroid function of various modes of administration of ICM, with proper control groups not receiving ICM.

The use of ICM prior to or during pregnancy may also affect neonatal thyroid function. A systematic review on neonatal thyroid function after the use of maternal ICM found a tendency towards an increased risk for hypothyroidism especially in case of higher doses (van Welie 2021). Most ICM are water-soluble and readily cleared from the body. Lipid-based ICM have a delayed excretion. Lipid-based ICM are used for hysterosalpingography but does not seem to affect neonatal thyroid function (Mathews 2023; van Welie 2020).

In March 2022 the FDA issued a drug safety communication recommending thyroid function monitoring of children under three years of age within three weeks of intravascular administration of iodine-based contrast media (FDA, 2022). In a reaction to this recommendation the Pediatric Endocrine Society (PES) and American College of Radiology (ACR) published statements questioning this recommendation due to lack of sufficient evidence (PES 2022). Based on this criticism the FDA issued a revised statement in June 2023 (FDA, 2023).
In the revised statement the FDA states "…decisions about thyroid monitoring following administration to children 3 years and younger should be individualized based on each child's risk factors. These risk factors may include prematurity, very low birth weight, and underlying medical conditions affecting thyroid function."

In view of the lack of well-designed studies in this field and to prevent conflicting statements as much as possible, we decided to adopt several of the PES guideline recommendations (PES, 2022).

Screening for primary hypothyroidism consists of a single TSH measurement, included in the guideline. It is important to realize that due to immaturity of the hypothalamic-pituitary axis TSH rise in case of overt hypothyroidism may be delayed or even absent in premature infants, especially in very low birth weight infants (< 32 weeks' gestation and/or < 1500 grams). This means screening with TSH may miss hypothyroidism in these cases. In addition, premature infants have lower thyroid hormone levels than term born infants (transient hypothyroxinemia of prematurity) and critical illness reduces thyroid hormone concentrations, so-called non-thyroidal illness. These factors make it difficult to certify whether exposure to ICM is the actual cause of the hypothyroidism in hospitalized ill infants.

Patient (and their caretakers) values and preferences
Patients, parents/caretakers and health care professionals want to make decisions based on the best available evidence. A similar case should get equal advice/treatment. The recent FDA advice about monitoring thyroid functioning after iodinated contrast administration makes it necessary to formulate guidelines on whether children in the Netherlands should be monitored. This guideline defines which patients are at increased risk of hypothyroidism after exposure to ICM and provides recommendations on how to apply thyroid monitoring for these populations.

The main benefit of monitoring thyroid functioning is that physicians can identify cases of hypothyroidism that require treatment with daily levothyroxine supplementation to prevent potential brain damage. Monitoring itself involves additional TSH measurements for 2 to 3 weeks after administration of ICM. The populations specified in this guideline are most likely inpatients at neonatology and intensive care wards and are expected to be undergoing frequent blood withdrawals. Blood tests for thyroid monitoring can be combined with other necessary blood tests. The burden of daily levothyroxine supplementation and regular blood withdrawals is considered acceptable in view of the importance of preventing hypothyroxinemia induced brain damage.
In infants and young children pain prevention during blood withdrawal is practiced by the use of local agents such as EMLA or lidocaine and if necessary help of a pedagogical assistant

Costs
Most neonates and infants receiving ICM and at risk for developing prolonged hypothyroidism will most likely be inpatients at neonatology and intensive care wards and are expected to be undergoing frequent blood tests. The costs of an extra blood test are low

and may be combined with blood testing for another indication. The costs of levothyroxine supplementation are also low. These relatively low costs are considered acceptable given the importance of preventing hypothyroxinemia-induced brain damage. Since hypothyroxinemia-induced brain damage is associated with significant additional healthcare costs over a longer period, early detection and treatment of cases have the potential to reduce associated health costs.

Acceptance, feasibility and implementation

The monitoring itself requires TSH measurements for 2 to 3 weeks after exposure to ICM, which is currently not standard practice. However, only a small group of children at increased risk of hypothyroidism will require thyroid function monitoring. Early detection of thyroid dysfunction and prevention of hypothyroxinemia-induced brain damage by implementing relatively cheap and easy to administer drugs has clear health benefits. Furthermore, the population at-risk identified in this guideline are often inpatients at neonatology and intensive care wards with frequent blood tests. Thus, for most cases monitoring does not require additional handling. Therefore, the guideline development group does not expect obstructions in terms of acceptance, feasibility and implementation.

The guideline development group advice is to include a reference to this guideline in the radiology report when ICM is used in a child younger than 3 years (since all risk groups defined in this guideline are younger than 3 years).

Recommendations

Rationale of the recommendation: weighing arguments for and against the interventions

Given the importance of thyroid hormone for normal brain development it is necessary to prevent prolonged periods of hypothyroidism in children especially in the first 3 years of life. To prevent hyperthyroidism in the case of excess iodine exposure the thyroidal Wolff-Chaikoff effect temporarily downregulates thyroid hormone production. After a few weeks an escape from the Wolff-Chaikoff effect occurs and thyroid hormone production is restored. However, prolonged hypothyroidism may occur when the escape from the Wolff-Chaikoff effect fails. Preterm born infants are particularly vulnerable to the suppressive effects of excess iodine due to immaturity of the thyroid gland and inability to escape from the Wolff-Chaikoff effect.

Overall, there is consensus in the field based on earlier studies that children in the first 3 months of life are most at-risk of developing thyroid dysfunction after exposure to ICM in particular:premature neonates, low-birth weight neonates and critically ill infants. Also, renal impairment, cardiac disease, and prolonged/frequent exposure to ICM such as during cardiac bypass and dialysis pose as risk factors.

It remains unclear whether infants between 3 months and 3 years are at risk of developing prolonged hypothyroidism after exposure to ICM and whether this would affect neurodevelopment if left untreated.

Given the long-lasting and debilitating effect of hypothyroxinemia-induced brain damage and the relatively low-cost easy-to-implement treatment, the recommendation is to also consider thyroid function measurement in children with the specified risk factor aged 3 months to 3 years.

Controleer schildklierfunctie (TSH-meting) 2 weken na toediening van *intravasculair of gastro-intestinaal* jodiumhoudend contrast*,* bij alle prematuur geboren kinderen (zwangerschapsduur < 37 weken) onder de leeftijd van 3 maanden.

Controleer schildklierfunctie (TSH-meting) 2 weken na toediening van *intravasculair* jodiumhoudend contrast, bij a term geboren kinderen (zwangerschapsduur ≥ 37 weken) onder de leeftijd van 3 maanden in geval van risicofactoren zoals dysmaturiteit (geboortegewicht voor zwangerschapsduur < -2 SDS), ernstige ziekte, nierinsufficiëntie, cardiale aandoening en in geval van langdurige/veelvuldige blootstelling aan jodiumhoudend contrast zoals bij coronaire CT angiografie en nierdialyse.

Overweeg controle van schildklierfunctie (TSH-meting) 2 weken na toediening van *intravasculair* jodiumhoudend contrast bij kinderen tussen de leeftijd van 3 maanden en 3 jaar in geval van risicofactoren zoals ernstige ziekte, nierinsufficiëntie, cardiale aandoening en in geval van langdurige/veelvuldige blootstelling aan jodiumhoudend contrast zoals bij coronaire CT angiografie en nierdialyse.

Interpretatie TSH-concentratie:

- TSH $\leq$ 5 mE/l: geen actie, , tenzij het een zeer prematuur kind betreft met een berekende leeftijd van < 32 weken amenorroe duur ten tijde van de bloedafname. Herhaal in dat geval de TSH-meting na 1 week.
- TSH > 5 en $\leq$ 10 mE/l: herhaal TSH met vrijT4 meting na 1 week
- TSH > 10 en $\leq$ 20 mE/l: meet vrijT4. Een lage vrij T4 concentratie wijst op hypothyreoïdie en is een behandelindicatie. Overleg met kinderarts-endocrinoloog.*
- TSH > 20 mE/l: meet vrijT4 en start behandeling in overleg met kinderarts-endocrinoloog.*

*Interpretatie van vrij T4 wordt bemoeilijkt door transiënte hypothyroxinemie van prematuren, “non-thyroidal illness” en gebrek aan leeftijdsspecifieke referentie intervallen. Overleg met kinderarts-endocrinoloog wordt geadviseerd voordat met behandeling wordt gestart.

Knowledge Gap

The goal of thyroid function monitoring after the use of iodinated contrast and subsequent thyroid hormone supplementation is the prevention of neurodevelopmental delay.
However, studies designed to answer the question whether monitoring of thyroid function after the use of ICM in children leads to better neurodevelopmental outcome are missing.
Therefore, studies that answer the following question are necessary:
What are the results of thyroid function monitoring after the use of iodinated contrast media in children (<18 years) undergoing radiological examinations?

P(atients): Children (<18 years) undergoing radiological examinations with iodinated contrast media (ICM);
I(ntervention): Monitoring of thyroid function after ICM administration.
C(ontrol): No monitoring of thyroid function after ICM administration.
O(utcome): Hypothyroidism, hyperthyroidism, irreversible effects of thyroid dysfunction on neurodevelopment of child.

The following other important questions remain unanswered:

- Whether infants between 3 months and 3 years are at risk of developing hypothyroidism after exposure to ICM. Including whether this is dose dependent, what the duration of the hypothyroidism is and whether this would affect neurodevelopment if left untreated.
- The various administration routes of ICM (e.g., intra-arterial, intravenous, gastrointestinal, genitourinary) have not been sufficiently studied.

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