# Hereditaire hemochromatose (HH)

Deze richtlijn is tot stand gekomen op initiatief van Nederlandse Internisten Vereniging

# Inhoudsopgave

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### Waar gaat deze richtlijn over?

Deze richtlijn gaat over diagnostiek, behandeling en follow-up van volwassenen met hereditaire hemochromatose, dan wel verdenking op of een verhoogde kans daarop.
De richtlijn bevat nieuwe aanbevelingen voor:

- Diagnostisch vervolgonderzoek bij klinische verdenking hereditaire hemochromatose (inclusief flow-chart voor work-up bij verdenking hemochromatose/verhoogd ferritine met plaatsbepaling aanvullend genetisch onderzoek en MRI-lever-ijzer)
- Genetisch onderzoek bij familieleden van mensen met hereditaire hemochromatose
- Interpretatie van genetisch onderzoek bij mensen met ijzerstapeling
- Starten en stoppen met aderlaten, in de ontijzeringsfase en de onderhoudsfase
- De plaats van erythrocytaferese in de behandeling van hereditaire hemochromatose
- Follow-up van mensen met hereditaire hemochromatose met betrekking tot orgaanschade

Daarnaast zijn de teksten van de richtlijn uit 2007 geactualiseerd, zodat de richtlijn aanbevelingen bevat voor het gehele spectrum van diagnostiek, behandeling en follow-up bij hereditaire hemochromatose.

### Voor wie is deze richtlijn bedoeld?

De doelgroep van deze richtlijn zijn professionals die zich bezighouden met medisch specialistische zorg voor mensen met (verdenking op of verhoogde kans op) hereditaire hemochromatose. Hieronder worden in ieder geval verstaan: internisten, maag-darm-leverartsen, hematologen, radiologen, klinisch chemici en klinisch genetici. Maar, ook anderen kunnen deze richtlijn gebruiken.

### Voor patiënten

Deze richtlijn gaat over diagnose, behandeling en begeleiding van mensen met hereditaire hemochromatose. Het gaat hierbij om een erfelijke ziekte, waarbij mensen teveel ijzer in hun lichaam hebben. Om de diagnose hereditaire hemochromatose te stellen, wordt bloedonderzoek en DNA-onderzoek gedaan. Als er teveel ijzer in het lichaam blijft kunnen organen, zoals de lever, beschadigen. Bij de behandeling van hemochromatose wordt daarom het teveel aan ijzer uit het bloed gehaald. Mensen met hereditaire hemochromatose hebben niet altijd klachten, maar moeten soms wel behandeld worden om ernstige gevolgen te voorkomen. Daarom kan genetisch onderzoek van familieleden van mensen met hereditaire hemochromatose nuttig zijn.
De richtlijn geeft aanbevelingen voor al deze onderwerpen.
Betrouwbare informatie voor patiënten kan gevonden worden op: https://www.thuisarts.nl/hemochromatose en https://hemochromatose.nl/hemochromatose-in-het-kort/.

### Hoe is de richtlijn tot stand gekomen?

Het initiatief voor de ontwikkeling van deze richtlijn is genomen door de Nederlandse Internisten Vereniging. De richtlijn is ontwikkeld door een multidisciplinaire richtlijnwerkgroep. Deze werkgroep werd ondersteund door PROVA en het bureau van de Nederlandse Internisten Vereniging. Na inventarisatie van knelpunten werd een aantal nieuwe uitgangsvragen voor de richtlijn uitgewerkt. Ook is een update van de richtlijn uit 2007 doorgevoerd en geïntegreerd tot een nieuwe richtlijn.

## Verantwoording

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Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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## Afbakening en definities van Hemochromatose

*Deze module is afkomstig uit de richtlijn 2007, en beperkt herzien zonder systematisch literatuuronderzoek.*

Primaire Hemochromatose, internationaal als Hereditaire Hemochromatose (HH) aangeduid, is een ziekte die wordt gekarakteriseerd door teveel aan ijzer met name in de lever, die op termijn leidt tot orgaanschade. Hemochromatose wordt onderscheiden in primaire (hereditaire) en secundaire vormen. Er zijn diverse vormen van hereditaire hemochromatose (tabellen 1 en 2). In de bevolking van Noord-Europese afkomst is HH grotendeels veroorzaakt door homozygotie voor de C282Y mutatie in het HFE-gen.(3, 4) Een andere veel voorkomende mutatie is de H63D-mutatie, al is de pathofysiologische betekenis hiervan veel minder duidelijk. Volgens de huidige nomenclatuur worden ze aangeduid met p.Cys282Tyr en p.His63Asp om de veranderingen in het HFE-eiwit aan te geven en met c.845G>A respectievelijk c.187C>G om de mutaties in het DNA aan te geven (zie ook www.hgvs.org).(5). Om reden van eenvoud zal in deze richtlijn ook gebruik worden gemaakt van de afkortingen C282Y en H63D. Deze vorm van HH wordt HFE-gerelateerde HH genoemd. Alle andere vormen van HH zijn zeldzaam tot zeer zeldzaam.(6, 7)
Deze richtlijn zal zich verder concentreren op HFE-gerelateerde HH. Andere ziektebeelden die eveneens gepaard gaan met teveel aan ijzer en/of afwijkende serumijzerparameters worden kort besproken in tabel 1. Hieronder vallen ook hoogprevalente aandoeningen als het metabool syndroom, parenchymateuze leverziekten en alcoholabusus.(7)
De afbakening van de HFE-gerelateerde vorm van HH is lastig. Immers, niet iedere drager van de mutatie ontwikkelt teveel aan ijzer en teveel aan ijzer op haar beurt leidt niet bij iedereen tot symptomen en permanente orgaanschade.(6, 8) Ook in de internationale literatuur bestaat over de definitie van HH geen consensus.(9-12) Personen met C282Y homozygotie hebben weliswaar de aanleg voor ijzerstapeling (hereditaire hemochromatose. HH), maar van deze ziekte spreken we pas als er teveel aan ijzer aangetoond is.(13)

**Tabel 1. Indeling oorzaken van teveel aan ijzer**

| | | |
|---|---|---|
| Hereditaire hemochromatose | HFE-gerelateerde hemochromatose (type 1) | C282Y homozygotie |
| | | C282Y/H63D samengestelde genotype* |
| | Non-HFE-gerelateerde HH | Type 2A hemojuveline mutaties |
| | | Type 2B hepcidine mutaties |
| | | Type 3 transferrine receptor-2 mutaties |
| | | Type 4A en 4B ferroportine mutaties |
| | Overige | Hereditair Hyperferritinemie Cataract Syndroom (HHCS) |
| | | Hemoxygenase tekort |
| | | Neonatale ijzerstapeling |
| | | BMP6 mutaties |
| Secundair teveel aan ijzer | Stoornissen in de erytrocytrijping en/of | Ineffectieve erytropoëse:<br>• Thalassemie syndromen<br>• Sideroblastaire anemieën<br>• Myeolodysplastisch syndroom<br>• Congenitale dyserytropoëtische anemieën |
| | | Soms bij toegenomen erytropoëse:<br>• Chronische hemolytische anemie |
| | Parenterale ijzertoediening (inclusief meervoudige bloedtransfusie) | |
| Mengbeeld | Verminderde beschikbaarheid van ijzer voor erytropoëse en/of verminderde ijzeracquisitie van erythroid precursor, waardoor combinatie anemie en ijzerstapeling | Aceruloplasminemie |
| | | Congenitale atransferrinemie of hypotransferrinemie |
| | | Dimetal transporter 1 (DMT1) mutaties |
| Overige stoornissen met afwijkingen in de ijzerparameters, en soms ook (milde) ijzerstapeling | Metabool syndroom | Obesitas |
| | | Hypertensie |
| | | Insuline resistentie |
| | | Non-alcoholische steatohepatitis (NASH) |
| | Acute en chronische leverziekten | Hepatitis |
| | | Porphyria cutanea tarda |
| | Alcoholabusus | |

**Dit genotype veroorzaakt vrijwel nooit een teveel aan ijzer en wordt tegenwoordig beschouwd als een dusdanig zwakke risicofactor dat een additionele factor nodig is om tot ijzerstapeling te komen.*

**Tabel 2. Kenmerken van de diverse vormen van hereditaire hemochromatose**

| Aandoening | Eiwit (gen) | OMIM type en overerving | Leeftijd | Functie van het normale eiwit | Onderscheidende kenmerken |
|---|---|---|---|---|---|
| Klassieke hereditaire hemochromatose (HH) | HFE (HFE) | Type 1 Autosomaal recessief (AR) | Volwassen | Niet goed bekend, reguleert hepcidine | Teveel aan ijzer in lever primair in de hepatocyten<br>Verhoogde transferrineverzadiging en ferritine |
| Juveniele hemochromatose | HJV (HFE2)<br><br>Hepcidine (HAMP) | Type 2A (AR)<br><br>Type 2B (AR) | Kind tot jong volwassen | BMP-coreceptor, reguleert hepcidine<br><br>Hepcidine reguleert ijzertransport uit macrofaag en intestinale epitheelcellen | Zie type 1, maar dan presentatie in de $2^e$ of $3^e$ decade<br><br>Verhoogde transferrineverzadiging en ferritine in $2^e$ of $3^e$ decade |
| TfR2 hemochromatose | TfR2 (TfR2) | Type 3 (AR) | Jong volwassen | Niet goed bekend, reguleert hepcidine | Als type 1, maar dan presentatie op jongere leeftijd ($2^e$-$4^e$ decade) |
| Ferroportin disease | Ferroportin1 (ook genoemd SLC11A3, IREG1, MTP1) | Type 4 Autosomaal dominant | Volwassen | Transmembraan export van ijzer uit intestinale epitheliale cellen en macrofagen, wordt gereguleerd door hepcidine | Type 4A: functieverlies varianten: Teveel aan ijzer in lever vooral in macrofagen, verminderde tolerantie voor flebotomie. Normale transferrineverzadiging, verhoogd ferritine.<br><br>Type 4B: Toename functie varianten: ijzer vooral in parenchym, waaronder hepatocyten, als type 1 |

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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## Pathogenese en epidemiologie van Hemochromatose

*Deze module is afkomstig uit de richtlijn 2007, en beperkt herzien zonder systematisch literatuuronderzoek.*

Hereditaire hemochromatose is een erfelijke aandoening die wordt gekenmerkt door een niet gereguleerde, bovenmatige ijzerabsorptie uit de darm terwijl het lichaam niet in staat is om de overmaat aan ijzer uit te scheiden. Dit leidt tot teveel aan ijzer in weefsels waardoor deze beschadigd kunnen raken en een deel van hun functies kunnen verliezen.
In 1996 werden twee puntmutaties beschreven in het hemochromatose(HFE)-gen, gelegen op de korte arm van chromosoom 6.(3) Bij de zogenaamde C282Y mutatie wordt in het HFE-eiwit het 282e aminozuur cysteïne vervangen door tyrosine. Bij het overgrote deel van de patiënten van Europese afkomst met het klinische beeld van hereditaire hemochromatose wordt deze mutatie in homozygote vorm gevonden.(4) Bij de H63D mutatie is het 63$^{e}$ aminozuur histidine in het HFE-eiwit vervangen door aspartaat. De aanwezigheid van deze His63Asp mutatie in hetzelfde gen op het ene allel, in combinatie met de Cys282Tyr mutatie op het andere allel wordt 'compound' heterozygotie of wel samengestelde heterozygotie genoemd. De klinische betekenis hiervan wordt steeds meer in twijfel getrokken.(3, 14) Er is daarnaast ook een groot aantal andere mutaties gevonden in het HFE-gen. De meest bekende is de S65C mutatie.(15) Zij komen echter zelden voor en de klinische betekenis is veelal niet duidelijk. Sommige mutatie lijken echter wel pathogeen te zijn.(16) Het gelijktijdig optreden van een C282Y en een H63D mutatie in één gen is zo onwaarschijnlijk dat daar klinisch geen rekening mee hoeft te worden gehouden.(17, 18)
Mutaties in het HFE-gen blijken te leiden tot hepcidineconcentraties die relatief laag zijn voor de hoeveelheid lichaamsijzer.(19-22) Aangezien hepcidine in de lever wordt gesynthetiseerd, lijkt het erop dat HFE vooral in de lever werkzaam is. Het is op dit moment niet goed bekend hoe HFE de ijzervoorraad van het lichaam detecteert, maar het lijkt erop dat HFE door de regulatie van de hepcidineconcentratie in het lichaam betrokken is bij de systemische ijzerhomeostase. Hepcidine reguleert het ijzermetabolisme door de werking van ferroportine als de transporteur van ijzer uit duodenale villicellen en macrofagen te remmen.(23) Dit model past in het beeld dat teveel aan ijzer bij HH het resultaat is van excessief transport uit de enterocyten en de macrofagen. Sinds de ontdekking van het HFE-gen hebben er opvallende ontwikkelingen plaatsgevonden in ons begrip van ijzertransport en -opslag met de beschrijving van hepcidine, hemojuvelin, TfR2 en ferroportine (Tabel 2). Veranderingen in deze eiwitten kunnen leiden tot diverse vormen van ijzerstapeling.(7, 24)
Nu het steeds duidelijker wordt dat niet HFE maar hepcidine de centrale rol in het ijzermetabolisme inneemt, kan de wisselende penetrantie van C282Y homozygotie ook wat beter worden begrepen. Bij hepcidine komen diverse multifunctionele routes bij elkaar.(19) Daarbij wordt de hepcidinesynthese ook gereguleerd door een veelheid van factoren waaronder groeifactoren, cytokines en het glucosemetabolisme.(25) In dit model bepaalt de optelsom van deze routes uiteindelijk of de ijzerhuishouding ontregelt en te veel ijzer uit de darm wordt opgenomen.
HFE-gerelateerde HH is genetisch geen zeldzame erfelijke aandoening. Van de Noord-Europese bevolking is 0,5-1,5% homozygoot, 3,5-15% heterozygoot voor de C282Y mutatie, ongeveer 20% heterozygoot voor de H63D mutatie en heeft 1-3% het samengestelde C282Y/H63D-genotype. De C282Y mutatie komt niet voor in individuen van Aziatische, Indische, Afrikaanse en Australische origine.(3, 4) De aandoening komt bij personen van Noord-Europese afkomst doorgaans, maar niet uitsluitend, tot uiting bij mannen in de vierde decade en bij vrouwen in de vijfde decade.(26, 27)

De visie op de klinische betekenis en penetrantie van C282Y homozygotie is sinds de ontdekking van het HFE-gen veranderd. In eerste instantie werd in studies van patiëntenpopulaties al snel een verband gelegd tussen klinisch beeld en gevonden mutaties. Uit nieuwere onderzoeken, waarbij genotypering plaatsvond van niet-klinische populaties, blijkt dat de meerderheid van C282Y homozygote personen wel abnormale ijzerwaarden heeft (hoge biochemische penetrantie), terwijl slechts een klein aantal van hen aan HH toe te schrijven ziektesymptomen ontwikkelt (lage klinische penetrantie) (zie ook de module ´Familieonderzoek bij Hemochromatose´).(28-32) De klinische penetrantie van C282Y homozygotie wordt voor een deel bepaald door genetische en omgevingsfactoren, zoals alcoholgebruik, virale hepatitis, ijzerinname en body mass index.(24) Daarnaast kan het klinisch tot uiting komen van hereditaire hemochromatose gemaskeerd worden door bijvoorbeeld menstruatie en ander bloedverlies, bloeddonatie, zwangerschap en geneesmiddelengebruik (maagzuurremming). Veranderingen in andere genen die coderen voor eiwitten betrokken bij de ijzerstofwisseling, zoals HFE2 en HAMP (hepcidine antimicrobieel peptide), kunnen het teveel aan ijzer verergeren bij C282Y homozygotie, hoewel dit soort combinaties van genafwijkingen zeldzaam is en niet de aanzienlijke variatie in HFE penetrantie kan verklaren.(7, 24, 33)
De geringe klinische penetrantie van C282Y homozygotie roept vragen op over de kosteneffectiviteit van voorheen gepropageerd bevolkingsonderzoek.(34) In plaats daarvan belooft detectie door middel van familiescreening en een grotere alertheid op de ziekte bij aanwezigheid van (een combinatie van) symptomen waarschijnlijk een grotere kans te geven op een vroege diagnose bij mogelijke patiënten (zie ook de modules ´Symptomatologie opname HH bij Hemochromatose´ en ´Familieonderzoek bij Hemochromatose´).(11) De clinicus staat daarmee voor de uitdaging om HH te diagnosticeren, voordat zich irreversibele weefselschade heeft ontwikkeld, terwijl tevens een voortschrijdend teveel aan ijzer moet worden onderscheiden van in toenemende mate voorkomende aandoeningen met een verhoogd serumferritinegehalte, maar vaak geen of slechts mild ijzeroverschot, zoals bij het metabool syndroom.(19)

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Diagnostiek bij Hemochromatose

De diagnostiek naar hereditaire hemochromatose wordt ingezet in de volgende situaties:

- Verdenking op HH op grond van de klinische symptomatologie van de patiënt
- Bij toeval gevonden laboratoriumuitslagen die kunnen wijzen op HH
- In het kader van familiescreening

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Symptomatologie voor opname HH in de differentiaaldiagnose bij Hemochromatose

## Uitgangsvraag

Bij welke symptomen (klachten en verschijnselen) dient HH in de differentiaaldiagnose te worden opgenomen? Verschillen deze symptomen tussen de eerste en de tweede lijn?

## Aanbeveling

| | |
|---|---|
| Geen gradering | Individuele symptomen van moeheid, buikklachten, gewrichtsklachten, diabetes mellitus, hart- en vaatziekten, impotentie of huidpigmentatie zijn geen aanleiding tot het doen van aanvullende laboratoriumdiagnostiek naar HH. Hoewel wetenschappelijk bewijs ontbreekt, valt het te overwegen bij combinaties van symptomen wel aanvullende diagnostiek te doen, aangezien op theoretische gronden de kans op HH dan groter is.<br>In navolging van internationale richtlijnen is het de mening van de werkgroep dat bij patiënten van Europese origine die worden verwezen naar de specialist met minstens 6 maanden bovenstaande onverklaarde klachten, diagnostiek naar HH middels bepaling van ijzerparameters overwogen wordt. |

| | |
|---|---|
| Sterk | Bij verdenking op een anderszins onverklaarde chronische leverziekte wordt diagnostiek naar hereditaire hemochromatose geadviseerd. |

## Conclusies

| | |
|---|---|
| Geen gradering | Algemene gezondheid, gewrichtsklachten, diabetes mellitus, moeheid, buikklachten, impotentie, hart- en vaatziekten en huidpigmentatie voorspellen afzonderlijk niet het bestaan van HH.<br>Van geen enkele van deze symptomen is bewezen dat het vaker bij HH voorkomt dan bij controles.<br><br>Asberg, 2002; Beutler, 2002; Cauza, 2005; Conte, 1998; Dubois, 1998; Ellervik, 2001; Frayling, 1998; Hramiak, 1997; Ryan, 2002; Waalen, 2002(30, 35, 42, 43, 50-52, 56, 57, 66) |

| | |
|---|---|
| Geen gradering | De voorspellende waarde van combinaties van symptomen voor het optreden van HH is nauwelijks onderzocht en toont geen duidelijke relatie tussen klachten en ijzerparameters.<br><br>Cadet, 2003(55) |

## Samenvatting literatuur

*Deze module is afkomstig uit de richtlijn 2007, en beperkt herzien zonder systematisch literatuuronderzoek.*

Zie ook de evidence tabellen. In het algemeen kan over de gevonden literatuur worden gesteld dat de bronartikelen waarnaar wordt verwezen vaak zijn geschreven voordat genetische diagnostiek beschikbaar was,

dat er geen eenduidige en soms helemaal geen definitie van hereditaire hemochromatose (HH) wordt gegeven en dat de methodologische kwaliteit veelal laag is (case reports, observationeel onderzoek zonder controlegroep, lage aantallen deelnemers en niet-geblindeerde of niet bij iedereen op dezelfde wijze toegepaste diagnostiek). Hieronder wordt de wetenschappelijke onderbouwing per symptoom beschreven. Onderzoek naar de voorspellende waarde van combinaties van symptomen werd niet gevonden. Alleen voor gewrichtsklachten werd onderzoek gevonden naar het onderscheidend vermogen van symptomen binnen een specialistische populatie. Dit onderzoek was methodologisch onvoldoende van opzet.

### Algemene gezondheid

Via populatiescreening opgespoorde C282Y homozygoten verschillen in hun algemene gezondheid niet van mensen zonder de genetische afwijking.(35) Ook in het aantal symptomen dat zij hebben, verschillen ze niet van de controlepopulatie.(30)

### Gewrichtsklachten

Vanaf 1964 zijn er talloze publicaties verschenen over de gewrichtsklachten van patiënten met HH.(36) Veel artsen die deze patiënten behandelen herkennen dit ook. In enkele publicaties werd gekeken naar het vóórkomen van gewrichtsvervangende operaties als maat voor de gewrichtsklachten.(37-40) Uit deze onderzoeken komt naar voren dat HH patiënten 2 tot 9 keer meer kans hebben op gewrichtsklachten/-operaties dan controlepersonen. Het valt hierbij op dat bij de HH patiënten deze klachten op jongere leeftijd optreden, en dat met name de MCP-gewrichten aangedaan zijn. De gewrichtsklachten treden vaak al op 8 – 9 jaar vóór het stellen van de diagnose HH. Er zijn studies die een relatie van de gewrichtsklachten met het teveel aan ijzer aangeven, maar andere, waarbij de gewrichtsklachten een vroeg optredend symptoom zijn, en de aanleiding vormen tot de diagnose HH.
In andere studies lijken gewrichtsklachten niet vaker voor te komen bij patiënten met HH dan bij mensen zonder deze aandoening,(30, 41, 42) al komt bij patiënten met ongedifferentieerde artritis mogelijk wel meer homozygotie voor de C282Y mutatie voor.(43) Over de vraag of de symptomen op jongere leeftijd optreden, verschillen de bevindingen.(30, 41, 42, 44) De lokalisaties van gewrichtsklachten (vingers of handen, polsen, heupen, knieën, enkels of rug) verschillen niet tussen patiënten met HH en mensen zonder HH.(42)
In de literatuur wordt meerdere malen gesproken over een kenmerkend klachtenpatroon, waarvan overigens wordt gezegd dat het varieert van osteoporose, artrose, pseudojicht, diffuse polsklachten tot reumatoïde artritis en dat bovendien de meeste HH patiënten niet het typische klinisch beeld hebben. Ook artritis van de metacarpophalangeale gewrichten van de tweede en derde straal, de MCP-gewrichten van de handen, wordt genoemd als kenmerkend symptoom, zowel in de literatuur als door experts. Naar deze kenmerkende symptomen is echter geen vergelijkend onderzoek verricht.(44-47) Bovendien wordt dit ook gezien bij mensen met diabetes mellitus,(48) en zware handenarbeid.(49)
Klachten die in verband gebracht kunnen worden met teveel aan ijzer, zoals gewrichtspijn, moeheid en buikpijn, komen in de algemene bevolking veel voor. Deze klachten werden in het verleden bij hoge percentages HH patiënten gerapporteerd, tot 95 % (EASL). Deze gegevens waren echter afkomstig uit patiëntengroepen die waren geselecteerd op basis van klachten, en veelal nog van vóór de ontdekking van het HFE-gen. Verder geldt voor alle publicaties dat er verschillende definities van de gewrichtsklachten worden gehanteerd: gewrichtspijn – artralgie – artrose - artropathie klinisch, dan wel radiologisch vastgesteld.

### Diabetes Mellitus (DM)

Diabetes mellitus lijkt niet vaker voor te komen bij patiënten met HH in vergelijking tot mensen zonder HH,(30, 35, 41, 50-54) hoewel dit onder slecht instelbare diabeten mogelijk wel het geval is.(55) De glucosetolerantie is gestoord bij mensen met HH. Deze is reversibel na flebotomie, zolang er geen sprake is van cirrose of DM.(56)

**Moeheid**

(Extreme) moeheid komt bij HH even vaak voor als in de controlepopulatie, maar de bevindingen verschillen over de vraag of de klachten op jongere leeftijd optreden.(30, 41) Bij vrouwen met C282Y homozygotie is er geen verband aangetoond tussen de hoogte van de ijzerparameters en moeheid.(57)

**Buikklachten en leverziekten**

Er is geen verschil in de prevalentie van buikklachten tussen C282Y homozygoten en controlepersonen.(30, 35, 42) Ook door de patiënt gerapporteerde lever- of galblaaspathologie komt even vaak voor bij HH patiënten als in de algehele populatie, maar mogelijk wel op jongere leeftijd.(41) HH patiënten hebben een relatief risico van 2,1 op het krijgen van leverpathologie, in vergelijking tot de controlepopulatie.(30) In een gezondheidscentrum bleek de prevalentie van C282Y homozygotie onder patiënten met verhoogde leverenzymen hetzelfde (bij vrouwen) of licht verhoogd (bij mannen 0,57% vs. 0,28%) ten opzichte van personen met normale leverenzymen.(58)

**Seksuele disfunctie/Infertiliteit**

Als mechanisme voor de relatie tussen HH en seksuele disfunctie wordt ijzerneerslag in zowel gonaden als hypofyse genoemd, met als gevolg niet detecteerbaar testosteron (in mannelijke patiënten). Bij vrouwen is het gevolg een lagere LH- en FSH-spiegel ijzerneerslag in de hypofyse en juist een hogere LH- en FSH-spiegel bij ijzerneerslag in de ovaria.(59) Impotentie en libidoverlies komen voor bij hemochromatose,(41, 57) maar niet vaker dan in de controlepopulatie,(30, 42) en ook niet vaker dan bij homozygoten die de diagnose HH nog niet hebben gekregen.(57) Impotentieklachten zijn voor patiënten veelal geen aanleiding om naar de dokter te gaan en zijn voor artsen ook niet de aanleiding om de diagnose HH te overwegen.(60)

**Hart- en vaatziekten**

Palpitaties worden ervaren door patiënten met HH, maar ze komen niet vaker voor dan bij controlepatiënten.(30, 42) In een casereport wordt ook decompensatio cordis genoemd als gevolg van HH.(61)

**Huidpigmentatie**

Dit is één van klassieke symptomen van HH. De klachten komen echter niet vaker voor dan in een controlepopulatie. (30, 42)

**Overige symptomen**

In de literatuur worden verder nog de volgende ziekten genoemd als passend bij of geassocieerd met HH: schildklierpathologie, maligniteiten, depressie, haaruitval. Gecontroleerd onderzoek hiernaar is echter niet beschreven.

**Combinaties van klachten**

In één studie zijn patiënten op een polikliniek Interne met een combinatie van artralgie en chronische moeheid en tevens een verhoogd ferritine vergeleken met gezonde controles. Patiënten bleken vaker C282Y homozygoot te zijn (OR 103, 95%BI 22,9-469,7), maar de relatie met ijzerstapeling blijft onduidelijk.(55)

### Casedetectie op basis van symptomen

Hoewel evidence ontbreekt, adviseert een aantal richtlijnen om diagnostiek naar HH in te zetten bij de volgende klachten: onbegrepen leverfunctiestoornissen, laat ontstane DM, onbegrepen moeheid of zwakte, vroege artropathie of artrose, onbegrepen hartziekten, huidpigmentatie en (mannen met) seksuele disfunctie.(12, 62-65)

## Overwegingen

Hoewel er geen specifieke symptomen zijn die aanleiding geven tot diagnostiek naar HH, kunnen patiënten met HH wel ernstige complicaties krijgen, die een zo vroeg mogelijke opsporing wenselijk maken.
De prevalentie van symptomatische HH is te laag om bij patiënten met één van bovengenoemde symptomen onderzoek in die richting te rechtvaardigen, aangezien het risico op foutpositieve uitslagen te hoog is. Eerst zal er meer duidelijkheid moeten zijn over symptomen die discrimineren tussen HH en andere ziekten die gepaard gaan met onbegrepen klachten. In de eerste lijn zou vooralsnog alleen een betere bekendheid met het ziektebeeld de kans op opsporing van HH mogelijk kunnen verhogen. Wetenschappelijk bewijs hiervoor ontbreekt echter.

### Klassiek beeld

Het concept dat zorgprofessionals hebben van het klassieke beeld van HH wordt sterk bepaald door de trias van Trousseau. Hierin wordt midden 19$^{e}$ eeuw de combinatie van gebruinde huid, hepatomegalie en diabetes beschreven.(67) Overigens werd hierbij destijds niet de koppeling gemaakt met ijzer. Dit sterk voortgeschreden beeld bij een teveel aan ijzer wordt tegenwoordig nauwelijks gezien, omdat patiënten zich eerder in het proces presenteren, de diagnose eerder gesteld wordt en adequate therapie wordt ingezet. Ook de trias van Brissot (3 A's: asthenie, arthropathie en aminotransferaseverhoging) is als klassiek beeld benoemd.(68)
Aanvankelijk werd hemochromatose beschreven als hypertrofische levercirrose bij diabetes mellitus.(69) De term 'hemochromatose' werd door Von Recklinghausen in 1880 geïntroduceerd.(70) Sheldon suggereerde dat het om een 'inborn error of metabolism' zou gaan.(71) Lange tijd werd hemochromatose geassocieerd met 'diabète bronzé': cirrose, diabetes en huidpigmentatie. Sinds 1964 werden gewrichtsklachten ook vaak genoemd als uiting van hemochromatose.(36) In 1975 toonde de groep van Simon aan dat het inderdaad een erfelijke aandoening was.(72) In 1996 werden de mutaties in het HFE gen door Feder et al. beschreven.(3)
Onze kijk op de diagnose hereditaire hemochromatose is in de loop der jaren sterk veranderd. Inmiddels is bekend dat de meeste mensen met het genotype homozygote C282Y uiteindelijk geen ijzerstapeling en dus ook geen orgaanschade zullen ontwikkelen. Tevens is er veel discussie over de symptomatologie van hereditaire hemochromatose. Onderzoeken naar het voorkomen van symptomen bij patiënten met hereditaire hemochromatose worden sterk bepaald door de samenstelling van de studiepopulatie. De studies voor 1996 onderzochten met name patiënten met klachten en verschijnselen zonder HFE-diagnostiek. Sinds de betreffende mutatie in het HFE-gen bekend is, heeft er ook meer onderzoek onder de algemene bevolking plaatsgevonden. Hierbij bleek dat het risico op het ontwikkelen van klachten en verschijnselen van hereditaire hemochromatose veel lager is dan aanvankelijk werd gerapporteerd. Al in de vorige richtlijn van 2007 werd besproken dat symptomen/verschijnselen afzonderlijk of in combinatie niet voorspellen voor de diagnose hereditaire

hemochromatose.

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# IJzerparameters bij Hemochromatose

## Uitgangsvraag

Welke ijzerparameters dienen te worden bepaald? Welke afkapwaarden voor ijzerparameters dienen te worden gehanteerd binnen de diagnostiek van hereditaire hemochromatose? Hoe dienen de uitslagen van de ijzerparameters te worden geïnterpreteerd?

## Aanbeveling

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|---|---|
| Geen gradering | Voor het optimaal beoordelen van de ijzerstatus wordt geadviseerd zowel de ijzerverzadingsfractie – of wel de TSAT -als ook het serumferritine te bepalen.<br>Om de TSAT te berekenen moet zowel de serumijzer- en transferrinespiegel worden bepaald.<br>Bepaling van de serumferritinespiegel wordt geadviseerd als maat voor de ijzervoorraad in het lichaam.<br>Voor het inschatten van de schadelijkheid van het ferritine moet het TSAT-percentage meegewogen worden.<br>Als afkapwaarde voor vervolgdiagnostiek naar het bestaan van HFE-gerelateerde HH wordt een transferrinesaturatie van > 45 % aangehouden.<br>Als afkapwaarde voor de serumferritinespiegel wordt verwezen naar de referentiewaarden van het eigen laboratorium.<br>Nuchtere bepaling van de transferrinesaturatie is niet nodig, alleen in twijfelgevallen moet een herhaalde bepaling nuchter worden gedaan. |

## Conclusies

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| Geen gradering | Een transferrinesaturatie van > 45% heeft een hoge sensitiviteit en specificiteit voor het opsporen van de aanleg voor HFE-hereditaire hemochromatose, maar dit afkappunt is niet zonder meer een goede maat voor klinische ziekte.<br><br>Adams, 2000; Phatak, 1998; Ryan, 2002(57, 83, 105, 106) |

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|---|---|
| Geen gradering | De variatie van de transferrinesaturatie binnen een dag is in de algemene populatie groot, maar bij patiënten met HH is de transferrinesaturatie door de dag heen steeds verhoogd. Om deze reden hoeft bloedafname niet per se nuchter plaats te vinden.<br><br>Edwards, 1989; Olssen, 1984; Witte, 1996(75, 77, 106, 107) |

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| Geen gradering | Een verhoogde TSAT is de meest gevoelige laboratoriumparameter voor de identificatie van de aanleg voor parenchymaal teveel aan ijzer en de daarmee samenhangende symptomen. |

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| Geen gradering | Het is niet bekend of een chronisch (sterk) verhoogde TSAT bij een normale ferritineconcentratie schadelijke gevolgen kan hebben. |

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| Geen gradering | Een combinatie van verhoogde TSAT en hyperferritinemie kan duiden op parenchymaal (hepatocytair en dus toxisch) teveel aan ijzer. |

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| Geen gradering | Een niet verhoogde TSAT in combinatie met hyperferritinemie is een indicatie voor teveel aan ijzer in het RES, waardoor de toxiciteit van het teveel aan ijzer wordt beperkt. Daarnaast zorgt teveel aan ijzer in het RES voor een sterkere verhoging van het serumferritine. Kortom als bij een patiënt de TSAT binnen de referentiewaarden ligt en het ferritine erboven, overschat het serumferritine (SF) de hoeveelheid lichaamsijzer en de schadelijkheid daarvan ten opzichte van een patiënt met dezelfde verhoogde ferritineconcentratie en een verhoogde TSAT. |

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| Geen gradering | In Nederland is geen draagvlak voor gebruik van de Unsaturated Iron Binding Capacity (UIBC).<br><br>Mening van de werkgroep |

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|---|---|
| Geen gradering | De klinische informatie met betrekking tot hemochromatose is voor Unsaturated Iron Binding Capacity (UIBC) en transferrinesaturatie (TSAT) gelijk.<br><br>Adams, 2000(83) |

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| Geen gradering | De ferritineconcentratie in het serum wordt niet alleen beïnvloed door de hoeveelheid lichaamsijzer.<br><br>Cavill, 1986; Halliday, 1984(78, 96, 108) |

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| Geen gradering | Door het ontbreken van prospectieve studies naar de discriminerende waarde van de ferritinespiegel voor de diagnose van HH en door de interlaboratoriumvariatie van ferritine is het niet doenlijk om een eenduidige afkapwaarde voor ferritine aan te geven. |

## Samenvatting literatuur

*Deze module is afkomstig uit de richtlijn 2007, en beperkt herzien zonder systematisch literatuuronderzoek.*

### Serumijzer

De bepaling van het serumijzer is meestal colorimetrisch. Deze methode heeft binnen de Nederlandse ziekenhuizen een interlaboratoriumvariatie van < 2,6% (Stichting Kwaliteit Medische Laboratoria, SKML; ronde 2016.4 rondzending Hormonen). De referentiewaarden zijn afhankelijk van het laboratorium waar de analyse plaatsvindt. De biologische (of wel binnen persoon) variatie is ongeveer 30%. (https://www.westgard.com/biodatabase1.htm, juni 2017). De ijzerconcentraties kennen ook een aanzienlijke binnendag variatie, met in de meeste studies hogere concentraties in de ochtend dan in de avond.(73, 74)

Bij 75% van de homozygote HH patiënten vertoont de spiegel ook schommelingen, maar de variaties zijn kleiner.(75, 76) In het algemeen kan worden volstaan met een niet-nuchtere bloedafname voor de bepaling van de serumijzerconcentratie, maar bij een licht verhoogde uitslag is het raadzaam om het onderzoek te herhalen wanneer de patiënt nuchter is (zie ook hieronder).(75, 77)
De serumijzerspiegel kan bij normale individuen voorbijgaand verhoogd zijn. Verder is het serumijzer verhoogd bij primaire ijzerstapeling of secundair aan aandoeningen van de erytropoëse, recente inname van orale ijzermedicatie, en sterk toegenomen hemolyse en weefselbeschadiging (met name levercelbeschadiging zoals dat optreedt bij acute hepatitis en chronisch leverfalen).(78)

**Transferrinesaturatie**
De transferrineverzadiging, transferrinesaturatie of ijzerverzadingsfractie geeft aan welk percentage van het serumeiwit transferrine is verzadigd met ijzer; het is geen afspiegeling van de verzadiging van het lichaam met ijzer. Er wordt in de literatuur een groot aantal methoden voor de bepaling van de transferrinesaturatie genoemd. De belangrijkste zijn:

- Berekening met behulp van de TIJBC. Hierbij wordt de gemeten serumijzerconcentratie gedeeld door de TIJBC en dit getal vervolgens vermenigvuldigd met 100.
- Berekening met behulp van transferrine. Dit is in Nederland het meest gangbaar. De serumijzerconcentratie wordt hierbij gedeeld door het serumtransferrine. Omdat 1 mol transferrine (gemiddelde molmassa 79.570 Da) 2 ijzeratomen (atoommassa 55,84 Da) bindt geldt dat voor de omrekening van serumijzer in µmol/l en transferrine in g/l ongeveer 25 µmol ijzer de bindingsplaatsen van 1 gram transferrine verzadigt. De transferrinesaturatie is dus: [(serumijzer (µmol/l) : ≈ 25) / transferrine (g/l)] x 100%.(79-81) De reden dat het aantal ijzer bindingsplaatsen niet exact geschat kan worden wordt voor een belangrijk deel toegeschreven aan de onzekere moleculaire massa van transferrine. Vandaar dat binnen Nederland het aantal µmol ijzer, dat wordt gebruikt als hoeveelheid ijzer waarmee 1 gram transferrine wordt verzadigd in de berekening van de transferrinesaturatie soms wat kan verschillen.

Het verzadigingspercentage van transferrine is normaal ongeveer 30%, maar varieert met de serumijzerspiegel, die bij gezonde mensen sterk kan schommelen (zie bovenstaand). Vaak wordt geadviseerd om bij een verhoogde waarde een tweede bepaling uit te voeren, waarbij de patiënt nuchter is en gedurende 24 uur geen vitaminepreparaten en ijzertabletten heeft ingenomen.
Verhoogde waarden van transferrinesaturatie (TSAT) worden (net als verhoogde ijzerconcentraties) gevonden bij ijzerstapeling, bij recent gebruik van ijzertabletten, bij hepatitis en bij overmatig alcoholgebruik. Verlaagde waarden worden gevonden bij ijzergebrek.
Vooral in de Angelsaksische landen wordt de afgelopen jaren gepleit voor invoering van de UIBC (Unsaturated Iron Binding Capacity). Als belangrijkste redenen worden daarbij aangevoerd de eenvoud van de test, de lagere kostprijs en het feit dat deze test in de medische wereld daar goed is ingeburgerd. De UIBC wordt berekend door het kwantificeren met behulp van ferrozine van niet-gebonden ijzer, na verzadiging van alle bindingsplaatsen van transferrine, door toevoeging van een vaste hoeveelheid exogeen ijzer. De gemeten kleurontwikkeling is proportioneel met de oorspronkelijke ijzerverzadiging van transferrine. In de Nederlandse situatie wordt vrijwel altijd de TSAT gemeten en zelden de UIBC. Bij een juiste kalibratie geven de bepaling van de UIBC en de TSAT equivalente informatie, zowel bij case-finding als bij screening, zelfs in aanwezigheid van leverfunctiestoornissen.(82-85)
Samenvattend kan worden geconcludeerd dat de klinische informatie met betrekking tot hemochromatose voor

UIBC en TSAT gelijk is. Met name bij grote screeningprogramma's zou het gebruik van de UIBC een kostenvoordeel kunnen opleveren ten opzichte van de TSAT. Bij case-finding valt dit potentiële kostenvoordeel grotendeels weg door de kleinere aantallen bepalingen. Bovendien is er binnen de Nederlandse laboratoria weinig animo voor invoering van de UIBC.
In de literatuur worden verschillende percentages opgegeven als afkapwaarde voor de transferrinesaturatie. Veelal gaat het hier om screeningsonderzoeken, waarbij een afkapwaarde wordt gekozen die sensitief genoeg is om de meeste personen met (de aanleg voor) HH te identificeren, zonder te veel foutpositieve resultaten te geven. Deze afkapwaarden in de literatuur variëren van 45 – 70%. De demografische karakteristieken van de onderzochte populatie kunnen de afkapwaarde voor de transferrinesaturatie en de prevalentie van HH beïnvloeden. Bij een relatief hoge afkapwaarde van 62% meet men 40% van de homozygote vrouwen niet positief, terwijl dit bij bijna 100% van de mannen wel het geval is. Om in de situatie van casedetectie geen relevante afwijkende waarden te missen adviseren verschillende auteurs een TSAT afkapwaarde van 45% bij nuchtere bepaling. Bij deze afkapwaarde wordt 98% van de homozygoten correct geïdentificeerd, terwijl 22% heterozygoten bij deze grens als positief werd gelabeld.(57, 86, 87) In het onderzoek van Adams et al. werd bij een afkapwaarde van 45% bij mannen een sensitiviteit van 100% en een specificiteit van 95% gevonden en bij vrouwen een sensitiviteit van 64% in combinatie met een specificiteit van 95%.(83) Phatak et al. hanteerden 45% als primaire actiegrens bij het onderzoek naar HH onder 16.031 patiënten van huisartsen. De EASL International Consensus Conference on Hemochromatosis adviseert een afkapwaarde voor de transferrinesaturatie van 45%, niet noodzakelijk nuchter afgenomen. Er wordt in sommige onderzoeken onderscheid gemaakt tussen mannen en (premenstruele) vrouwen.
Aanwijzingen dat een hoge transferrine saturatie bijdraagt aan parenchymaal teveel aan ijzer en weefselschade komen voort uit studies, die laten zien dat bij een transferrinesaturatie boven de 70%, ijzer vrij kan komen in de circulatie.(88-90) Preklinische studies laten zien dat dit zogenoemde non transferrin bound iron (NTBI) en zijn labiele (redox actieve) component, Labile Plasma Iron (LPI), potentiele toxische vormen van ijzer zijn die snel worden opgenomen in parenchymale cellen en kunnen bijdragen aan oxidant gemedieerde orgaanschade.(91) De bepaling van NTBI en LPI zijn momenteel echter nog onvoldoende robuust voor gebruik in de kliniek. Daarnaast ontbreken klinische studies waarin de onafhankelijke meerwaarde van de meting van deze toxische ijzermarkers is aangetoond.
Voor de eenvoud van de vuistregel wordt in deze richtlijn gekozen voor één TSAT afkapwaarde van 45% voor beide geslachten. De transferrinesaturatie is een goede maat voor detectie van de aanleg voor (HFE-gerelateerde) HH, maar het afkappunt is niet zonder meer een maat voor klinische ziekte. Daarbij zijn er ook geen gegevens over de sensitiviteit en specificiteit van de TSAT voor klinische ziekte.

**Ferritine**

Ferritine is een oplosbaar eiwit met een holle kern. In de cel wordt $Fe^{2+}$ geoxideerd tot $Fe^{3+}$ en in de kern van het ferritine opgeslagen. Ferritine kan ongeveer 4500 ijzeratomen in de kern bevatten. Op deze manier is ijzer in een niet-toxische vorm in de cel opgeslagen. De synthese van ferritine wordt gestimuleerd door ijzer. In tegenstelling tot cellulair ferritine is plasma ferritine geglycolyseerd en ijzerarm. Plasma ferritine concentratie is een afspiegeling van de ijzerconcentratie van zowel reticulo-endotheliale als parenchymale ijzervoorraden.(92) Echter voor een bepaalde hoeveelheid lichaamsijzer, zijn de plasma ferritine concentraties hoger bij aandoeningen waarbij het ijzer vooral in het reticulo-endotheliale systeem (RES, zoals bij patiënten die bloedtransfusies krijgen) zit vergeleken met aandoeningen waarbij het ijzer vooral in het parenchym zit (zoals bij HH).(93)

Voor de bepaling van ferritine worden immunochemische methoden toegepast. In 2016 vond de SKML (rondzending hormonen 2016.4) een relatief hoge tussen-laboratorium-variatiecoëfficiënt van 11%. Het vermoeden bestaat dat dit toegeschreven kan worden aan onvoldoende standaardisatie van de ferritinebepaling (wereldwijd), omdat sommige bepalingen niet gekalibreerd zijn tegen de WHO standaard.(94). Het bovenstaande betekent dat een ferritine van 20 µg/l binnen een laboratorium of tussen Nederlandse ziekenhuislaboratoria kan worden gemeten tussen 18 en 22 µg/l of een ferritine van 200 µg/l tussen 178 en 220 µg/l. De referentiewaarden worden echter per laboratorium vastgesteld en verschillen tussen de laboratoria. Vanwege de grote tussen-laboratorium-variatie van de ferritinebepaling, wordt geadviseerd de referentiewaarden van het eigen laboratorium te hanteren.
Daarnaast zijn de referentiewaarden echter vaak vastgesteld in het verre verleden. Overgewicht, non alcoholische steatohepatitis (NASH) en het metabool syndroom zijn geassocieerd met hyperferritinemie. Met de toename van overgewicht in de laatste 2 decennia in de algemene bevolking zouden de normaalwaarden theoretisch sterk toegenomen moeten zijn. De door veel laboratoria gebruikte (oudere) referentiewaarden zijn daarmee eerder streefwaarden geworden dan referentiewaarden.
Verhoogde waarden van ferritine worden gevonden bij teveel aan ijzer, bloedtransfusie, ontstekingsprocessen, solide en hematologische maligniteiten, sommige vormen van chronische hemolyse, leverziekten (alcohol, virusinfecties, geneesmiddelentoxiciteit, M. Gaucher), het metabool syndroom, en non alcoholische steatohepatitis.(95-102)
Een hoge TSAT faciliteert (toxisch) parenchymaal teveel aan ijzer. De combinatie van een hoge TSAT en ferritine wordt daarom gezien bij aandoeningen met parenchymaal teveel aan ijzer zoals bij HH en anemieën met teveel aan ijzer, maar kan ook worden gezien bij chronische leveraandoeningen. Een normale TSAT in combinatie met een verhoogde ferritine weerspiegelt vaak een situatie waarbij het lichaamsijzer grotendeels in het RES is opgeslagen. Hierbij is het teveel aan ijzer op zichzelf klinisch vaak minder zorgelijk.(103)
De ferritinespiegel speelt een rol bij de besluitvorming over de in te zetten behandeling. Voor de afkapwaarden van de serumferritinespiegel worden in de literatuur ook diverse waarden genoemd. Er zijn geen prospectieve studies waarin onderzocht is wat in de populatie de best discriminerende waarden van het ferritine zijn. Bovendien zijn de referentiewaarden van ferritine per laboratorium verschillend. Deze verschillen kunnen worden toegeschreven aan verschillen in de gebruikte immunochemische meetmethode, maar vermoedelijk ook aan verschillen in de populatie aan de hand waarvan de referentiewaarden zijn vastgesteld.
Voor het vaststellen van verhoogde ferritinewaarden wordt geadviseerd uit te gaan van de referentiewaarden voor mannen en pre- en postmenopauzale vrouwen van het eigen laboratorium.

**Serumtransferrine en totale ijzerbindingscapaciteit**
Transferrine is een glycoproteïne. Het bestaat uit twee domeinen, elk met een bindingsplaats voor $Fe^{3+}$. Door deze binding wordt ijzer in een niet-toxische vorm via het bloed getransporteerd. Voor de bepaling van transferrine worden immunochemische methoden toegepast. De interlaboratoriumvariatie is gemiddeld 3,3% (SKML, ronde 2016.4 rondzending hormonen). Ook de referentiewaarden verschillen niet of nauwelijks tussen de Nederlandse laboratoria waar de analyse plaatsvindt. De transferrine wordt nog in enkele Nederlandse laboratoria benaderd door de totale ijzerbindingscapaciteit (TIJBC).
Transferrine is een negatief acutefase eiwit en is dus verlaagd bij ontstekingen en maligniteiten. Lage plasmaspiegels worden ook gezien bij afgenomen synthese in het geval van chronische leverziekten en ondervoeding, bij eiwitverlies zoals bij het nefrotisch syndroom en bij homozygote of heterozygote pathogene

defecten in het gen dat codeert voor transferrine. Ook bij ziekten met een teveel aan ijzer zoals hereditaire en secundaire vormen van hemochromatose is het plasma transferrine verlaagd. Plasmatransferrine is verhoogd tijdens zwangerschap en bij ijzerdeficiëntie.

### Vaststellen van pathologische ijzerstatus

Om na te gaan of er bij een persoon sprake is van teveel aan ijzer kan in eerste instantie aan de hand van biochemisch bloedonderzoek een indruk over de ijzerstatus worden verkregen. Daartoe worden het serumijzer, de transferrinespiegel of de totale ijzerbindingscapaciteit, en de serumferritinespiegel bepaald en de transferrineverzadiging berekend.(9)

### Interpretatie

De gecombineerde bepaling van serumijzer, transferrine, transferrinesaturatie en serumferritine verschaft een simpele en betrouwbare eerste vaststelling van de hoeveelheid en verdeling van het ijzer in het lichaam.(102)
Deze richtlijn concentreert zich op HFE-gerelateerde HH. Andere ziektebeelden die eveneens gepaard gaan met teveel aan ijzer en/of afwijkende serumijzerparameters dienen fenotypisch zoveel mogelijk te worden uitgesloten, alvorens genetisch te gaan testen voor HFE-gerelateerde HH. Bij hyperferritinemie en/of verhoogde TSAT moeten verworven oorzaken worden uitgesloten (tabel 1), waaronder anemieën met teveel aan ijzer, het hyperferritinemie cataract syndroom (HHCS), leverziekten en de combinatie van aandoeningen die het metabool syndroom vormen.(95, 97-101, 104)
Een normale of licht verhoogde TSAT in combinatie met een verhoogd serumferritine kan suggestief zijn voor HHCS, aceruloplasminemie of ferroportineziekte. Tevoren dient uiteraard een secundaire acutefasereactie en aandoeningen die met het metabool syndroom samenhangen te zijn uitgesloten. (7, 104)
Als secundaire oorzaken zijn uitgesloten, moet diagnostiek van erfelijke oorzaken van HH worden overwogen.

## Verantwoording

Laatst beoordeeld : 28-10-2018
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Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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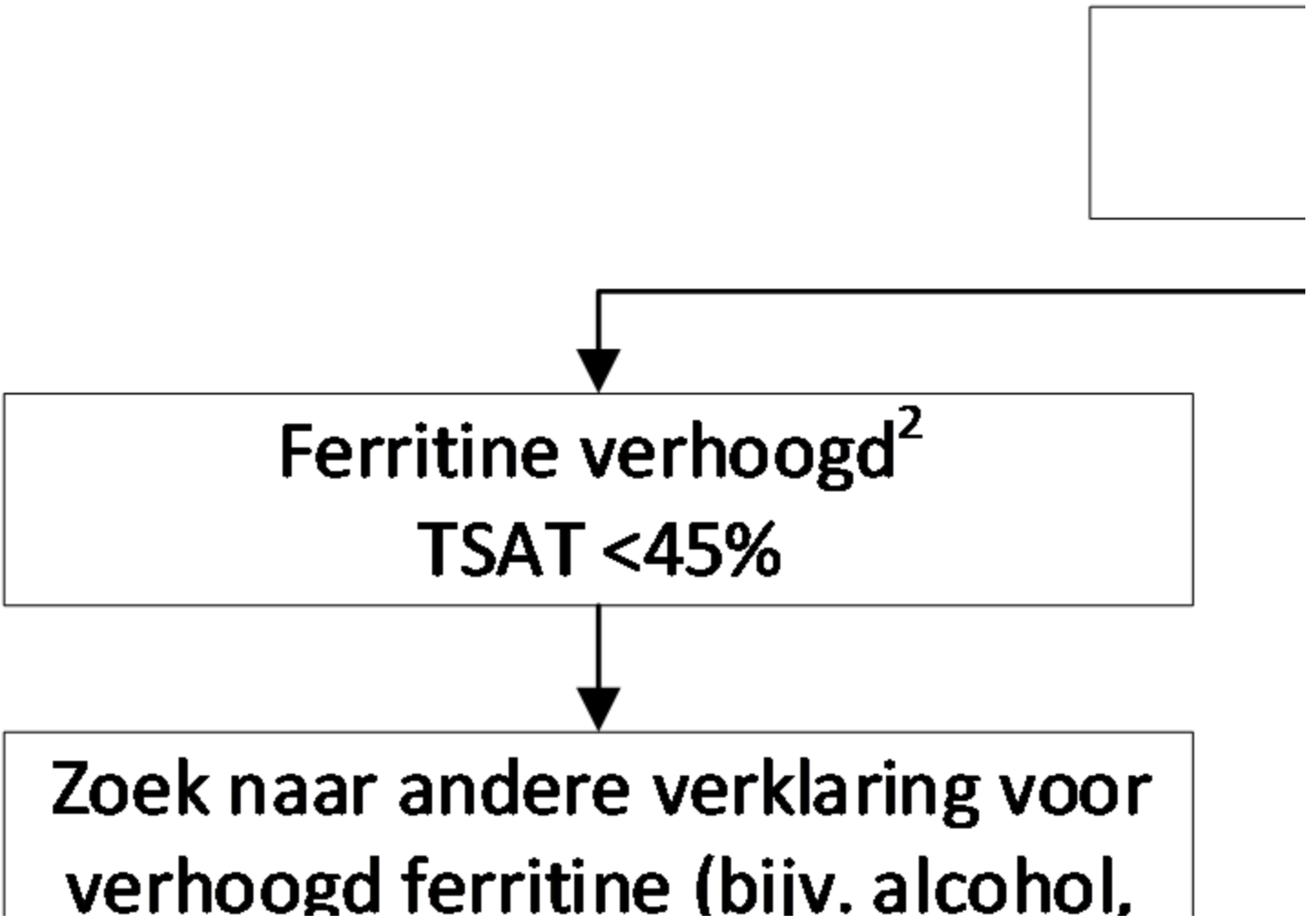
# Genetisch onderzoek bij Hemochromatose

## Uitgangsvraag

Wat is de indicatie voor genetisch onderzoek? Wanneer, welke genen, door wie, welke mutaties, welke volgorde? Hoe moet genetisch onderzoek worden geïnterpreteerd?

## Aanbeveling

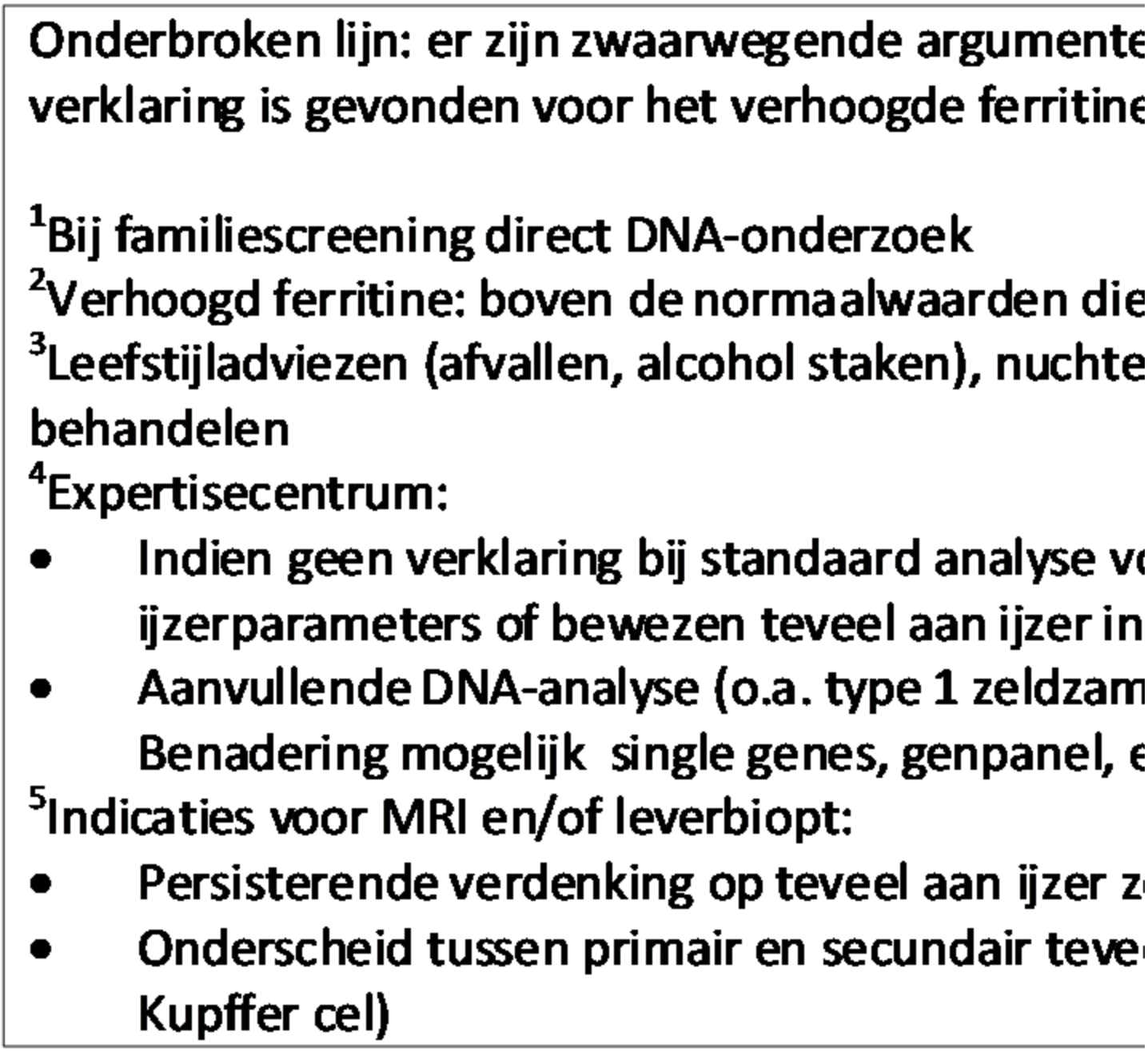
| | |
|---|---|
| Geen gradering | Onderzoek van HFE-mutaties dient te worden verricht bij alle patiënten (van kaukasische afkomst) met verhoging van transferrinesaturatie > 45% en serumferritine boven de normaalwaarde van het laboratorium voor leeftijd en geslacht, waarbij andere oorzaken van verhoogde ijzerparameters zijn uitgesloten.<br>Bij alternatieven (i) geen mutaties, (ii) heterozygoot voor C282Y, (iii) compound heterozygotie (iv) heterozygoot voor H63D en (v) homozygoot voor H63D: zie flowchart.<br>(*: onderzoek van het gen op zeldzame mutaties, anders dan C282Y en H63D)<br><br>Zie flowchart: |



steatose, leverziekte)

*Zie tabel 4.2*

**Bij geen verklaring en blijvend verhoogd ferritine**


Onderbroken lijn: er zijn zwaarwegende argumente
verklaring is gevonden voor het verhoogde ferritine

[1]Bij familiescreening direct DNA-onderzoek
[2]Verhoogd ferritine: boven de normaalwaarden die
[3]Leefstijladviezen (afvallen, alcohol staken), nuchte
behandelen
[4]Expertisecentrum:
- Indien geen verklaring bij standaard analyse v
ijzerparameters of bewezen teveel aan ijzer in
- Aanvullende DNA-analyse (o.a. type 1 zeldzam
Benadering mogelijk single genes, genpanel, e

[5]Indicaties voor MRI en/of leverbiopt:
- Persisterende verdenking op teveel aan ijzer z
- Onderscheid tussen primair en secundair teve
Kupffer cel)

**Inleiding**

*Deze module is afkomstig uit de richtlijn 2007, en beperkt herzien zonder systematisch literatuuronderzoek.*

De ziekte 'idiopathische' hemochromatose veranderde in 'hereditaire' hemochromatose (HH) met de waarneming, rond 1975, dat de aandoening opvallend frequent voorkwam bij broers en zussen van patiënten en bij kinderen uit consanguïne huwelijken. Tevens bleek uit segregatieanalyse van stambomen dat de ziekte autosomaal recessief overerft. Genetisch onderzoek bij patiënten met biochemische of klinische verdenking op HH werd pas mogelijk met de ontdekking, door Michel Simon en medewerkers, dat hemochromatose

geassocieerd was met HLA serotype A3. In een Deense studie bij HH patiënten was het relatieve risico (in vergelijking met een normale populatie) op HLA-A3 10,9 en op HLA-B7 4,1. Bij patiënten met een klinisch kennelijk homozygote vorm van HH werden daarna vele verschillende HLA haplotypen waargenomen die overigens identiek waren bij 'sibs' (broers en zussen) die eveneens klinische of biochemische expressie van teveel aan ijzer hadden. HLA typering had derhalve geen betekenis voor de diagnostiek van HH bij patiënten maar wel bij familieonderzoek. Daarbij bleek overigens dat er grote verschillen bestonden in de fenotypische expressie van HH, zelfs bij personen met dezelfde HLA haplotypen.(109, 110)
Genetisch onderzoek als een zinvolle aanvulling van de diagnostiek bij ijzerstapeling werd pas mogelijk na isolatie van een met hemochromatose geassocieerd gen (HFE) in 1996.(3) Bij patiënten met de kenmerken van HH bleek een mutatie van het HFE-gen te bestaan die resulteerde in een 845G→A verandering (van cysteïne naar tyrosine bij residu 282 van het HFE-eiwit): de C282Y mutatie. Dit genotype werd bij 52-100% van de patiënten met het fenotype van HH gevonden.(4, 111, 112) Van de niet-C282Y homozygote patiënten was een aantal compound heterozygoot voor C282Y en een tweede HFE mutatie, n.l. met een 187C→G verandering, resulterend in een H63D mutatie.(113) Overigens wordt compound heterozygotie tegenwoordig eerder als risicofactor beschouwd dan als genetische aanleg.(114) De prevalentie van de H63D-mutatie is hoog in populaties van Noord-Europese afkomst (ongeveer 20%), terwijl de C282Y prevalentie in deze populaties ongeveer 10% is. Bij C282Y heterozygoten en H63D homozygoten wordt doorgaans geen teveel aan ijzer gevonden. Naast genoemde HFE-mutaties worden sporadisch nog andere pathologische mutaties gevonden in het HFE-gen.
De afgelopen jaren is gebleken dat mutaties in een aantal andere genen verantwoordelijk zijn voor de non-HFE vormen van HH. Het betreft eiwitten die een rol spelen als ijzertransporter of ijzersensor zoals transferrinereceptor-2 (TfR2), hemojuveline (HJV), hepcidine (HAMP), ferroportine (FPN) en recentelijk BMP6.(24, 115) De genetische afwijkingen die leiden tot HH zijn hierdoor behoorlijk gecompliceerd geworden.

## Conclusies

| | |
|---|---|
| Geen gradering | Homozygotie voor de C282Y mutatie van het HFE-gen is bewijzend voor de aanleg voor de ziekte HH, maar geeft geen indicatie of er ook teveel aan ijzer zal optreden en kan de ernst van teveel aan ijzer en weefselschade niet voorspellen. |

## Samenvatting literatuur

Voor de plaatsbepaling van genetisch onderzoek zijn vier overwegingen van belang: (i) bij alle vormen van HH bestaat de behandeling uit aderlatingen, (ii) momenteel is alleen diagnostiek van HFE mutaties algemeen beschikbaar, (iii) voor het bij HH obligate familieonderzoek moeten de mutaties van de proband bekend zijn en (iv) indien bij mensen met slechts geringe biochemische tekenen van teveel aan ijzer homozygotie voor de C282Y mutatie gevonden wordt, zal dat richting geven aan de planning van toekomstige controles.
Hoewel strikt genomen klinische en biochemische parameters bepalend zijn voor al dan niet instellen van behandeling met aderlatingen, zal onderzoek naar mutaties van het HFE-gen, op grond van bovenstaande overwegingen, moeten plaatsvinden bij alle patiënten met de combinatie van een verhoogde transferrinesaturatie, boven 45%, en een verhoogd ferritine (zie de module ´IJzerparameters bij Hemochromatose´). Indien onderzoek plaatsvindt op jeugdige leeftijd of bij vrouwen die nog menstrueren, dan kan het ferritine nog laag zijn maar met kans op een aanzienlijke stijging in een volgende levensfase.

Een derde mutatie S65C, met een lage allelfrequentie van 1,6-2,0% heeft een klein maar consistent effect op de ijzerparameters in combinatie met de C282Y.(15, 116, 117) Tot nu toe zijn er echter geen overtuigende bewijzen dat S65C is geassocieerd met HH. Dit tezamen met de lage allelfrequentie maakt dat er onvoldoende argumenten zijn om ook voor S65C te testen om de aanwezigheid van HH te bevestigen.(114)
Alleen de interpretatie van onderzoek naar de veel voorkomende mutaties van het HFE-gen wordt hier besproken.
De mogelijkheden zijn: (i) geen mutaties, (ii) heterozygoot voor C282Y, (iii) homozygoot voor C282Y, (iv) heterozygoot voor H63D, (v) homozygoot voor H63D, (vi) compound heterozygoot voor C282Y/H63D. Alleen de bevinding (iii) past bij HH type 1. Andere afwegingen bij het inzetten van vervolgdiagnostiek zoals aanvullend DNA onderzoek, leverbiopsie, lever MRI worden besproken in de modules ´IJzer in de lever: leverbiopsie bij Hemochromatose´, ´IJzer in de lever: MRI bij Hemochromatose´ en ´Diagnostisch vervolgonderzoek Hemochromatose´.

## Overwegingen

De allelfrequentie van de bekende HFE-mutaties is zeer laag bij niet-kaukasiërs. Derhalve is onderzoek naar C282Y- en H63D-mutaties niet zinvol bij patiënten in deze groep. Andere mutaties in het HFE-gen en mutaties in andere genen die betrokken zijn bij hemochromatose komen niet exclusief bij kaukasiërs voor.
Het wordt geadviseerd om DNA-onderzoek van patiënten met vermoeden van HH type 1 (voor zeldzame mutaties) en type 2-4 te laten uitvoeren in formele expertise centra (in Nederland is dit het Radboudumc expertise centrum zeldzame aandoeningen van de ijzerstofwisseling dat onderdeel is van het Europese reference netwerk (ERN) EuroBloodNet (https://www.eurobloodnet.eu/subnetworks.php; https://www.radboudumc.nl/expertisecentra/ijzerstofwisselingsziekten). Websites voor aanvragen van genanalyse: http://www.radboud-ironcenter.com/diagnostics/dna-diagnostics/ of https://order.radboudumc.nl/genetics. (zie ook de module ´Diagnostisch vervolgonderzoek Hemochromatose´)

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Compound heterozygotie en teveel aan ijzer bij Hemochromatose

## Uitgangsvraag

Is compound heterozygotie (Cys282Y en H63D) in het HFE gen voldoende om goed gedocumenteerd teveel aan ijzer te kunnen verklaren?
Is compound heterozygotie een verklaring voor teveel aan ijzer?

P Patiënten met vastgesteld teveel aan ijzer
I Positieve test compound heterozygotie in HFE gen
C Negatieve test compound heterozygotie in HFE gen
O Diagnose hereditaire hemochromatose

P Patiënten compound heterozygoot
I -
C Patiënten wildtype
O Teveel aan ijzer

P Patiënten met teveel aan ijzer
I -
C Patiënten zonder teveel aan ijzer
O Gen onderzoek met als uitslag compound heterozygoot

De setting voor deze uitgangsvraag is de tweedelijns gezondheidszorg in Nederland.

## Aanbeveling

| | |
|---|---|
| Sterk | Wanneer een compound heterozygoot C282Y/H63D genotype is vastgesteld wordt geen familieonderzoek naar deze mutaties geadviseerd. |

## Inleiding

*Deze module is nieuw in deze richtlijn.*

Wanneer DNA analyse wordt gedaan naar hereditaire hemochromatose is een aantal uitslagen mogelijk: homozygotie voor wildtype (allel zonder mutatie), C282Y of H63D; heterozygotie wildtype/C282Y of wildtype/H63D of C282Y/H63D. Met name deze laatste variant C282Y/H63D, ook wel compound heterozygotie genoemd, geeft aanleiding tot discussie.
Een groot deel van de Nederlandse bevolking (1-3%) is compound heterozygoot C282Y/H63D. Vanuit het oogpunt van gezondheidszorg en preventie is het van groot belang om te bepalen of deze personen een significant verhoogd morbiditeitsrisico hebben. Vervolgens is de vraag of dit risico groot genoeg is om familieonderzoek naar compound heterozygoten te rechtvaardigen.

## Conclusies

| | |
|---|---|
| ZEER LAAG | Er is onvoldoende bewijs dat compound heterozygotie leidt tot klinisch relevant teveel aan ijzer.<br><br>*Neghina, 2011(134); Gurrin, 2009 (126)* |

## Samenvatting literatuur

*Beschrijving studies*
Van 23 artikelen werd de volledige tekst bestudeerd.(118-140) Tabellen met studiekarakteristieken van de beoordeelde studies zijn te vinden bij de aanverwante producten.
Neghina et al. publiceerden een systematische review met meta-analyses.(134) Studies die over dezelfde uitgangsvraag gingen en al dan niet opgenomen waren in de review van Neghina et al. zijn na bestudering van de volledige tekst van de artikelen geëxcludeerd.(118-121, 123, 125, 127-130, 132, 133, 136-140). Ook bleek een aantal artikelen bij bestudering van de volledige tekst van het artikel niet aan te sluiten bij de uitgangsvraag.(122, 124, 131, 135)
Uiteindelijk bleven alleen de systematische review van Neghina et al. en het artikel van Gurrin et al. over voor beantwoording van de uitgangsvraag.(126, 134)

*Kwaliteit van het bewijs*
Een samenvatting van de kwaliteit van bewijs per uitgangsvraag is te vinden bij de aanverwante producten. De review van Neghina et al. kent een goede search- en selectiestrategie, maar een kwaliteitsbeoordeling van de geïncludeerde studies ontbreekt. Er zijn daarom twijfels over de kans op vertekening en bovendien is er waarschijnlijk sprake van indirect bewijs, omdat er studies zijn geïncludeerd met niet-kaukasische populaties. Ook is er sprake van grote heterogeniteit in de meta-analyses en van forse imprecisie.(134) De studie van Gurrin et al. kent een lange follow-up, maar geen vergelijking met gezonde volwassenen zonder genmutatie, hetgeen de interpretatie beperkt maakt.(126)

*Inhoudelijk resultaat*
In de systematische review van Neghina et al. zijn 43 patiënt-controle onderzoeken opgenomen met in totaal 9.986 patiënten met verdenking teveel aan ijzer (verhoogde serum ijzermarkers, of verhoogde serum ijzermarkers geassocieerd met verhoogde lever ijzer index en/of andere verhoogde ijzerwaarden in leverbiopt, of flebotomie, bij afwezigheid van andere oorzaken) en 25.492 controles aanwezig.(134) Hierin werden de volgende associaties gevonden:

**Tabel 1. Associatie tussen genotypen en vermoeden van of bevestigd teveel aan ijzer(134)**

| Genotype | Associatie met vermoeden van teveel aan ijzer (OR (95%BI)) | Associatie met bewezen teveel aan ijzer (OR (95%BI)) |
|---|---|---|
| C282Y homozygoot | 289,1 (45,7-1830,1) | 1297,7 (796,7-2114,2) |
| C282Y/H63D | 15,5 (5,7-42,1) | 42,0 (26,6-66,2) |
| C282Y/WT | 2,7 (1,1-6,4) | 5,4 (3,7-8,0) |
| H63D/H63D | 3,3 (1,0-10,8) | 7,3 (4,7-11,5) |

Gurrin et al. gebruikten data uit een groot Australisch prospectief cohortonderzoek. Uit de data selecteerden zij patiënten met compound heterozygotie en HFE wild-type. In de tekst van het artikel beschrijven de auteurs dat zij ook vergelijken met een selectie uit de normale bevolking, maar die gegevens staan in het artikel niet beschreven. De follow-up van het onderzoek is 12 jaar, waarbij baseline en follow-up vergeleken worden voor wat betreft serumferritinewaarden en transferrinesaturatie. Deze blijken gedurende de follow-up niet significant te wijzigen, behalve voor vrouwen die bij baseline premenopauzaal en bij follow-up postmenopauzaal waren; bij hen steeg de serumferritineconcentratie. Uiting van ziekte (bijvoorbeeld artritis, vermoeidheid en leveraandoeningen) verschilde niet significant tussen compound heterozygoten en wild-type. Slechts bij één patiënt was sprake van gedocumenteerd teveel aan ijzer.(126)

## Zoeken en selecteren

Voor deze uitgangsvraag is in Medline gezocht naar literatuur op 8 november 2016. De literatuur is vervolgens geselecteerd op basis van onderwerp (sluit het artikel aan bij de uitgangsvraag?) en studiekenmerken (ten minste systematisch opgezet onderzoek). De volledige literatuursearch en literatuurselectie zijn weergegeven in de zoekverantwoording.

## Overwegingen

Diverse studies laten zien dat er een licht verhoogd risico is voor compound heterozygoten op teveel aan ijzer. Het is echter onduidelijk hoeveel patiënten gebaat zouden zijn bij vroegdiagnostiek en welke winst er precies voor hen te behalen is. Hierbij speelt een rol dat, anders dan bij de C282Y homozygoten, andere factoren zoals metabool syndroom en alcoholgebruik een belangrijkere rol spelen bij het ontstaan van klachten. Compound heterozygotie lijkt een geringe risicofactor te zijn voor klinische HH. Hoewel precieze getalsmatige berekening niet mogelijk is zouden zeer veel onderzoeken moeten worden verricht, waaronder relatief duur genetisch onderzoek, om relatief beperkte morbiditeit te voorkomen. Tevens is de vraag in hoeverre de morbiditeit in deze subgroep echt te voorkomen is aangezien er meestal sprake is van genoemde comorbiditeit.
Omdat de publicaties die zijn verschenen sinds de vorige versie van de richtlijn laten zien dat compound heterozygotie alleen niet voldoende is om klinische verschijnselen te krijgen, maar dat het ontstaan daarvan afhankelijk is van genoemde andere factoren zoals metabool syndroom en alcoholgebruik, wordt er nu geen advies meer gegeven om eerste graadsverwanten genetisch te onderzoeken naar het voorkomen van compound heterozygotie.
In een recente richtlijn van de Europese Molecular Quality Network (EMQN) wordt geen duidelijk advies gegeven over wel of niet screenen van eerstegraads verwanten van C282Y/H63D compound heterozygoten.(114)

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# IJzer in de lever: leverbiopsie bij Hemochromatose

## Uitgangsvraag

Wanneer is een leverbiopsie nodig om de diagnose te stellen en hoe dient deze te worden geïnterpreteerd?

## Aanbeveling

| | |
|---|---|
| Geen gradering | Een leverbiopsie wordt niet aanbevolen voor bevestiging van de diagnose HH.<br>Leverbiopsie kan een plaats hebben voor beoordeling van de mate van leverschade indien de serumferritineconcentratie > 1000 µg/l bedraagt. |

## Conclusies

| | |
|---|---|
| Geen gradering | De leverbiopsie is zelden nodig om een diagnose HH te bevestigen.<br><br>Chapman, 1994; George, 1996; Moodie, 2002; Powell, 2005(11, 141-143) |

| | |
|---|---|
| Geen gradering | De leverbiopsie is geschikt om de mate van leverschade vast te stellen (mate van fibrose/cirrose).<br>De fibroscan is een non-invasieve manier om leverschade vast te stellen. De fibroscan is echter niet gevalideerd voor hereditaire hemochromatose. |

## Samenvatting literatuur

*Deze module is afkomstig uit de richtlijn 2007, en beperkt herzien zonder systematisch literatuuronderzoek.*

De diagnostiek van HH is relatief eenvoudig, betrouwbaar en weinig invasief op basis van biochemisch en genetisch onderzoek. Een leverbiopsie daarentegen kan gepaard gaan met complicaties, en heeft daarom in principe geen plaats in de diagnostiek van HH. Uitsluitend indien aan de diagnose wordt getwijfeld, zoals bij een gecombineerde klinische etiologie bij presentatie van de patiënt kan een leverbiopsie een plaats hebben.(11, 141-143) Wel wordt HH incidenteel vastgesteld indien in een leverbiopt als toevalsbevinding een hepatocellulair patroon van teveel aan ijzer wordt gevonden.
Lokalisatie van aankleuring in vooral de hepatocyten heeft een matige positief voorspellende waarde voor het stellen van de diagnose HH.(144) Een reticulo-endotheliaal patroon voorspelt echter de afwezigheid van HH betrouwbaar.(144)
Bij patiënten met HH kan een biopt van de lever worden genomen om de hoeveelheid opgeslagen ijzer te bepalen en om de mate van leverschade vast te stellen. Beide geschieden door een semi-kwantitatieve histochemische kleuring die door een patholoog wordt geëvalueerd. De mate van teveel aan ijzer in de lever wordt bepaald met een Perlskleuring. De mate van aankleuring is een betrouwbare maat voor de hoeveelheid ijzer en wordt in 4 klassen ingedeeld.(145-147) De gouden standaard voor de ijzerbepaling in de lever, de droogijzerbepaling heeft als nadeel in vergelijking met de Perlskleuring dat het niet met een naaldbiopt kan worden gedaan. Er is meer materiaal voor nodig.

De belangrijkste vorm van leverschade bij HH is levercirrose. Levercirrose kan op basis van klinische en serologische parameters (serumferritine) worden vastgesteld met een sensitiviteit van 100%, echter de specificiteit is ongeveer 70%.(148-151) Levercirrose wordt voorafgegaan door een in de tijd toenemende fibrose. De mate van fibrose wordt in een leverbiopt bepaald door een histochemische kleuring op collageen (bij voorkeur van Giesson) die semi-kwantitatief wordt afgelezen door een patholoog. Een biopt heeft bij voorkeur minimaal 10 portadriehoekjes. Er is geen alternatief voor een leverbiopt voor de bepaling van de mate van fibrose. Wel zijn er algoritmes (inclusief fibroscan) in ontwikkeling, die echter nog onvoldoende zijn gevalideerd. Aangezien de kans op ernstige leverschade minder dan 1% is bij een serumferritine van minder dan 1000 µg/l is pas vanaf dat niveau een leverbiopt relevant voor stadiëring van de leverziekte.(150, 151) De ernst van leverenzymstoornissen speelt geen rol bij de indicatie voor een leverbiopt.

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# IJzer in de lever: MRI bij Hemochromatose

## Uitgangsvraag

Is er een plaats voor MRI in de diagnostiek van HFE-gerelateerde HH?

Hoe dient het MRI-onderzoek te worden uitgevoerd?

## Aanbeveling

| | |
|---|---|
| *Geen gradering* | Een schatting van de hoeveelheid ijzer in de lever door middel van MRI kan overwogen worden bij patiënten met biochemische criteria voor een teveel aan ijzer, die bij DNA onderzoek geen HH hebben én geen alternatieve verklaring hebben voor een verhoogde ferritine (zoals alcohol, steatose, leverziekte).<br>Ter bepaling van het ijzergehalte zijn een tweetal methoden beschikbaar waarbij de website van Rennes (https://imagemed.univ-rennes1.fr/en/mrquantif/online_quantif.php) beide methoden gratis aanbiedt en waarbij de relaxometriemethode als voorkeursmethode door de website wordt geadviseerd.<br>De richtlijnwerkgroep erkent de voordelen van de T2-relaxometrie, maar onthoudt zich een specifieke voorkeur voor een bepaalde MRI-techniek, aangezien hier geen literatuuronderzoek naar verricht is. |

## Conclusies

| | |
|---|---|
| Geen gradering | Met MRI kan op non-invasieve wijze, een ijzerbepaling van de lever worden verkregen.<br><br>Alustiza, 2004; Gandon, 1994; Gandon, 2004(158-160) |

## Samenvatting literatuur

*Deze module is afkomstig uit de richtlijn 2007, en beperkt herzien zonder systematisch literatuuronderzoek.*

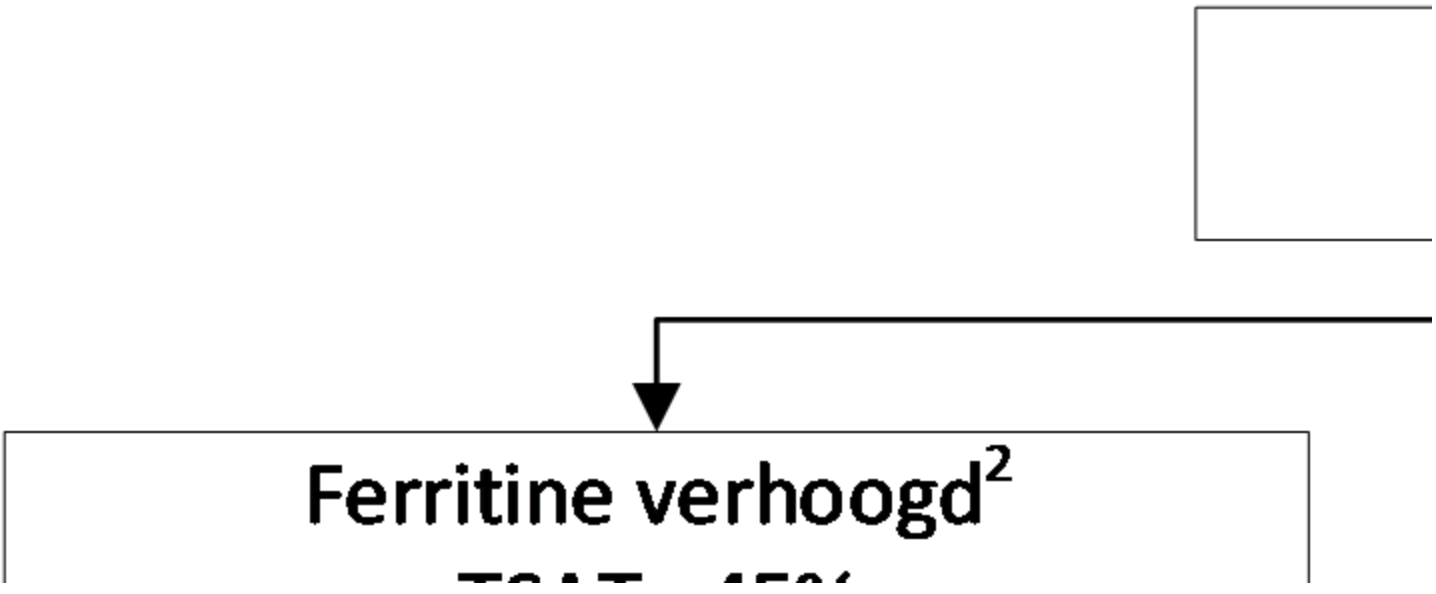
De precieze rol van MRI naar de diagnostiek van hereditaire hemochromatose blijft onduidelijk. Er is door verschillende richtlijnen en auteurs geen eenduidige consensus over het gebruik van MRI in de diagnostiek naar hereditaire hemochromatose.(106, 152-154)
Dit lijkt mede ingegeven doordat de MRI ook (mild) verhoogde leverijzerconcentraties kan geven door andere oorzaken dan HH, zoals bij steatose, hepatitis, overmatig alcoholgebruik en secundaire hemochromatose.
Als toepassing van het gebruik van MRI worden in de literatuur onder andere genoemd:

- Als aanvullende diagnostiek bij een hoog ferritine en een TSAT >45% maar een negatieve genetische test;
- Als aanvullende diagnostiek bij een TSAT <45%;
- Ter bevestiging van de diagnose;
- Ter kwantificatie van de ernst;
- Voor meting van het effect van therapie.(106, 152-154)

MRI is een geschikte methode om het ijzergehalte van de lever op een non-invasieve manier te bepalen (144-149). Het bestaan en de ernst van eventueel bijkomende fibrose en cirrose van het leverparenchym kunnen niet met MRI worden vastgesteld (145). Een andere beperking van MRI is dat niet alleen ijzer in de hepatocyt wordt gemeten, maar ook in de Kupffercellen. Dit laatste is niet indicatief voor hereditaire hemochromatose. Idealiter wordt ook de hoeveelheid ijzer in de milt bepaald als maat voor ijzerload in het reticulo-endotheliale systeem.
Er bestaan verschillende methoden om met MRI een leverijzerconcentratie te bepalen. Deze methoden zijn hoofdzakelijk gebaseerd op signaal intensiteits ratio's (SIR) of relaxometrie. De zogenaamde SIR methoden zijn gebaseerd op een ratio van de signaalintensiteit tussen de lever en structuren welke geen ijzerstapeling laten zien, zoals de paraspinale spieren.
Relaxometrie methoden zijn gebaseerd op de verkorting van de T2 tijden door het paramagnetische effect van ijzer waarbij ijzer een verlaagde signaalintensiteit geeft.(155) Voordelen zijn een hoge correlatie tussen gemeten waarden en leverbiopsieën. Een ander voordeel is dat de techniek toepasbaar is op andere organen zoals het hart en de milt. Belangrijke nadelen zijn dat er geen eenduidige consensus is over het gebruikte MRI protocol en de data-analyse. Daarbij kunnen deze protocollen niet op alle MRI apparaten toegepast worden en is de meer geavanceerde data-analyse niet altijd voorhanden.
De methode van Rennes is de meest gebruikte methode en online beschikbaar (https://imagemed.univ-rennes1.fr/en/mrquantif/online_quantif.php). Op de website worden software en MRI protocollen beschikbaar gesteld om gebruik te kunnen maken van de relaxometrie methode welke de voorkeur heeft. Ook is er een online calculator voor de SIR-methode. Deze SIR-methode is gestandaardiseerd, reproduceerbaar en breed toepasbaar in vrijwel elk ziekenhuis. Nadelen zijn dat sommige studies laten zien dat er een overschatting lijkt van de leverijzerconcentratie bij met name lagere waarden. Verder kunnen waarden tot maximaal 350 µmol/g (20 mg/g) gemeten worden.(156, 157)

### Overwegingen

De leden van de werkgroep zijn van mening dat er een beperkte rol voor de MRI is in de diagnostiek naar hereditaire hemochromatose. Een MRI kan overwogen worden indien er na initiële HFE-diagnostiek geen verklaring gevonden wordt voor het persisterend verhoogde ferritine (zie flowchart).




TSAT <45%
Zoek naar andere verklaring voor verhoogd ferritine (bijv. alcohol, steatose, leverziekte)
Zie tabel 4.2
Bij geen verklaring en blijvend verhoogd ferritine

Onderbroken lijn: er zijn zwaarwegende argumente
verklaring is gevonden voor het verhoogde ferritine

[1]Bij familiescreening direct DNA-onderzoek
[2]Verhoogd ferritine: boven de normaalwaarden die
[3]Leefstijladviezen (afvallen, alcohol staken), nuchte
behandelen
[4]Expertisecentrum:

- Indien geen verklaring bij standaard analyse v
  ijzerparameters of bewezen teveel aan ijzer in
- Aanvullende DNA-analyse (o.a. type 1 zeldzam
  Benadering mogelijk single genes, genpanel, e

[5]Indicaties voor MRI en/of leverbiopt:

- Persisterende verdenking op teveel aan ijzer z
- Onderscheid tussen primair en secundair teve
  Kupffer cel)

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Diagnostisch vervolgonderzoek bij Hemochromatose

## Uitgangsvraag

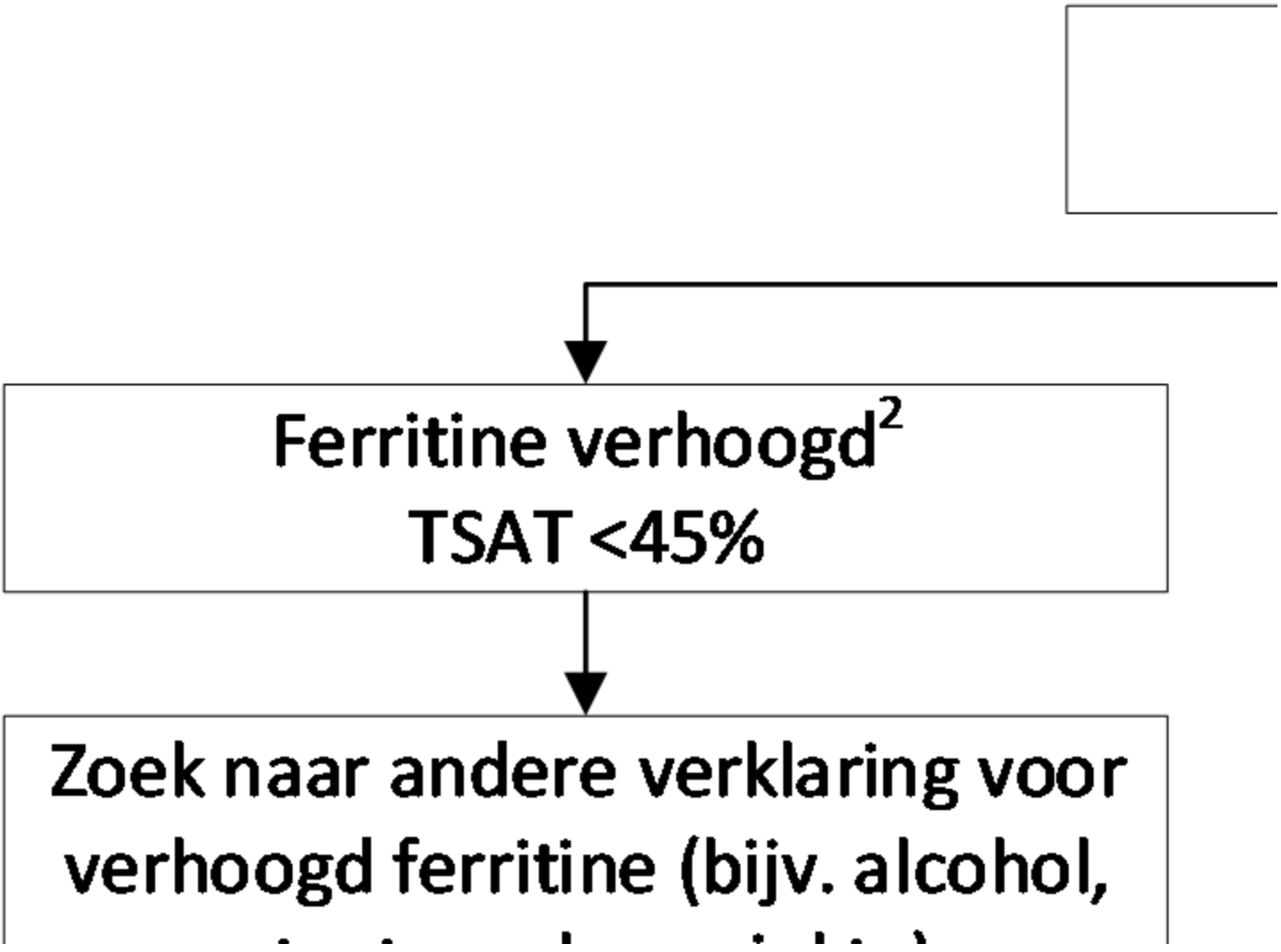
Welk diagnostisch vervolgonderzoek (diagnostisch aderlaten, specifiek genetisch onderzoek, MRI als tussenstap) is geïndiceerd wanneer bij een klinische verdenking hereditaire hemochromatose DNA onderzoek (HFE, exon 2 of 4) geen verklaring heeft opgeleverd?

P Patiënten met klinische verdenking HH, na DNA-onderzoek
I Diagnostisch aderlaten, Aanvullend genetisch onderzoek, MRI
C -
O Diagnostische accuratesse

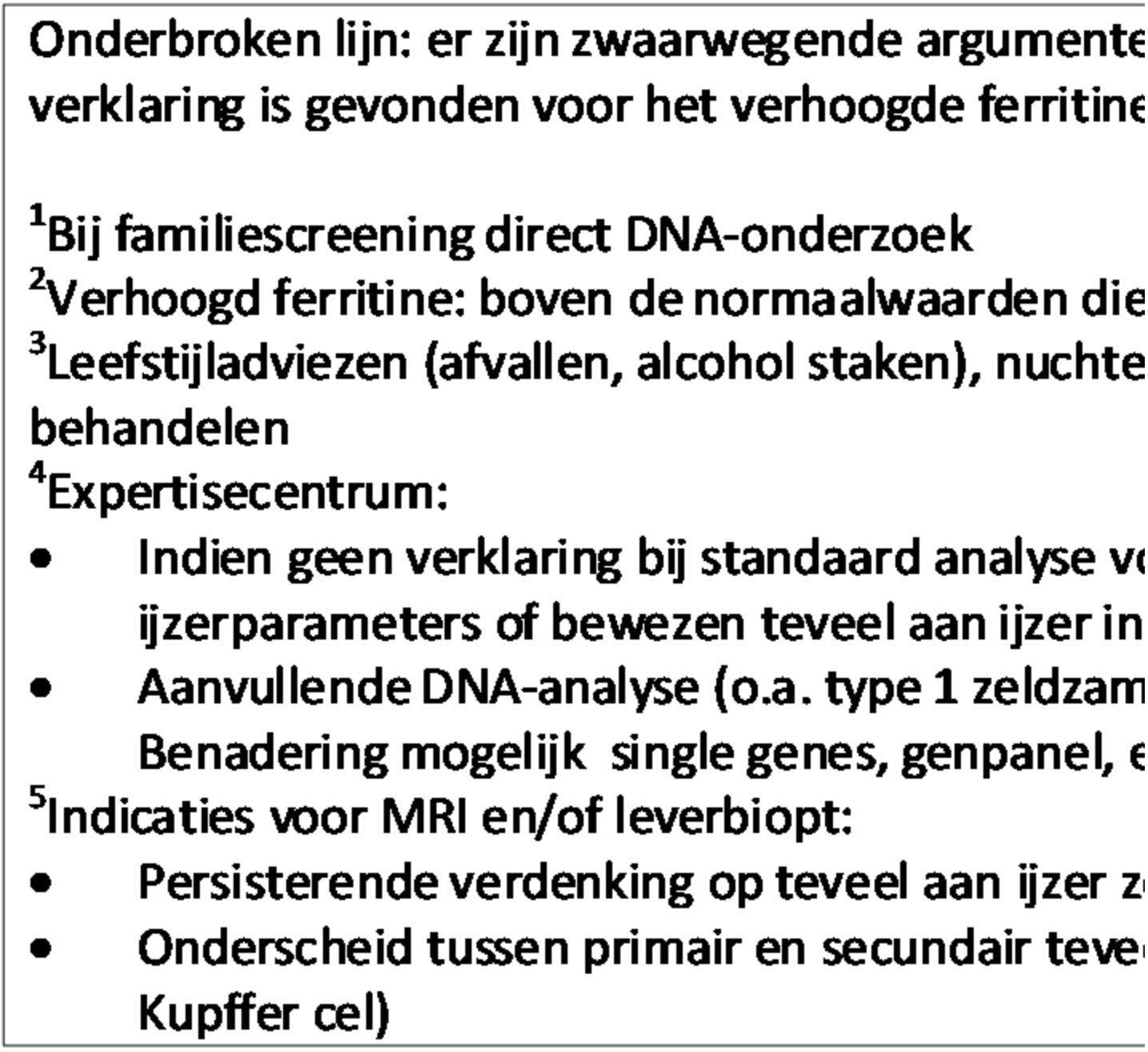
De setting voor deze uitgangsvraag is de tweedelijns gezondheidszorg in Nederland.

## Aanbeveling

Zwak (zie flowchart)




steatose, leverziekte)
Zie tabel 4.2
Bij geen verklaring
en blijvend verhoogd ferritine




**Inleiding**

*Deze module is nieuw in deze richtlijn.*

Bij een toenemend aantal patiënten worden bij het onderzoek naar de ijzerstatus afwijkende, verhoogde uitslagen gezien. Het is in de praktijk niet altijd meteen vast te stellen of deze uitslagen secundair zijn aan andere ziekten/aandoeningen, dan wel bij een vorm van teveel aan ijzer passen.
Alvorens de diagnostiek naar hereditaire hemochromatose in te zetten, moeten aandoeningen als metabool syndroom, hematologische ziekten, hepatitis e.d. als mogelijke oorzaak voor de gevonden afwijkingen worden uitgesloten. Bij een transferrinesaturatie van meer dan 45 procent en een serumferritine spiegel boven de

referentiewaarde geldend in het betreffende ziekenhuis, wordt diagnostiek naar hereditaire hemochromatose aanbevolen.
Hieronder wordt verstaan: aanvullend DNA-onderzoek door middel van sequencing van het gehele HFE-gen en de genen betrokken bij HH types 2-4. Daarnaast zijn er recent enkele genen ontdekt zoals het eerder genoemde BMP6 (module ´Genetisch onderzoek bij Hemochromatose´) die ook worden onderzocht. Dit onderzoek wordt aangeduid met de term 'panel hemochromatose (HFE, HFE2, HAMP, TFR2, SLC40A1, BMP6, FTL, IRE-FTH1)' en wordt aangeboden in het expertisecentrum ijzerstofwisselingsziekten, in Nijmegen, stichting klinisch genetisch centrum Nijmegen, Radboudumc UMC. Indien ook dit geen diagnose oplevert kan in overleg met het expertisecentrum nog vervolgonderzoek worden verricht door middel van diagnostische whole exome sequencing (WES), eventueel gevolgd door research WES, waarbij met informed consent van de patiënt naar het hele exoom wordt gekeken. Websites: http://www.radboud-ironcenter.com/diagnostics/dna-diagnostics/ of https://order.radboudumc.nl/genetics.

## Conclusies

| | |
|---|---|
| | Het is niet bekend wat de diagnostische accuratesse is van diagnostisch aderlaten bij patiënten met de klinische verdenking HH, voor het stellen van de diagnose HH.<br><br>*Geen evidence beschikbaar* |

| | |
|---|---|
| ZEER LAAG | Bij patiënten met hyperferritinemie kan met MRI-onderzoek de leverijzerconcentratie worden gemeten. In de literatuur worden verschillende afkapwaarden met verschillende diagnostische accuratesse besproken. De werkgroep concludeert dat als de uitslag boven de pragmatisch gestelde grens van 100 µmol/g komt, er waarschijnlijk sprake is van teveel aan ijzer. De oorzaak daarvan is daarmee nog niet vastgesteld.<br><br>*Alustiza, 2004; St Pierre, 2005; Castiella, 2011; Kreeftenberg, 2000; Sarigianni, 2015(157, 158, 169, 172, 173)* |

| | |
|---|---|
| ZEER LAAG | Aanvullend genetisch onderzoek kan bij sommige patiënten met verdenking op HH op basis van serum ijzerparameters maar zonder verklarende C282Y homozygotie en andere oorzaken voor teveel aan ijzer, bijdragen om de diagnose te stellen.<br><br>*Bryant, 2009(162)* |

## Samenvatting literatuur

*Beschrijving studies*
Van 16 artikelen werd de volledige tekst bestudeerd.(157, 158, 161-174) Na bespreking van de conceptteksten in de werkgroep werd nog een recent artikel toegevoegd.(175) Tabellen met studiekarakteristieken van de beoordeelde studies zijn te vinden bij de aanverwante producten.

Eén artikel, dat door de auteurs als systematisch onderzoek wordt bestempeld, bleek niet-systematisch onderzoek te betreffen, en is daarom alsnog geëxcludeerd.(174) Eén artikel over het vergelijken van een magnetische ijzer detector susceptometer met MRI voor het kwantificeren van ijzerstapeling is eveneens bij lezing van de volledige tekst geëxcludeerd, omdat dit niet relevant is voor het beantwoorden van de uitgangsvraag.(167) De systematische review van Bryant et al. uit 2009 en die van Cooper uit 2008 bleken gebaseerd te zijn op dezelfde gegevens als de review van Bryant et al. uit 2008 en zijn daarom afgevallen.(163, 165) Een artikel van Gallego et al. bleek bij bestudering van de volledige tekst te gaan over de epidemiologie van hereditaire hemochromatose bij verschillende genotypen, maar geeft geen informatie over de diagnosestelling en valt daarom af.(166) Een artikel over het voorspellen van de waarschijnlijkheid van C282Y homozygotie op basis van transferrine saturatie en ferritineconcentratie sluit eveneens niet aan bij de uitgangsvraag en is geëxcludeerd na bestudering van de volledige tekst van het artikel.(170) Het artikel van Cherfane et al. gaat over misdiagnose op basis van verhoogde ijzerwaarden en sluit niet aan bij de voor deze uitgangsvraag voorgestelde diagnostische interventies.(164) Het artikel van Przygodzki et al. gaat over de diagnostische waarde van leverbiopten; een diagnostische methode die bij voorkeur niet wordt toegepast. (171)
Er bleven na selectie op basis van de volledige tekst van het artikel 9 artikelen over voor beantwoording van de uitgangsvraag.(157, 158, 161, 162, 168, 169, 172, 173, 175). Deze artikelen kunnen onderverdeeld worden in twee thema's, die afzonderlijk zullen worden behandeld:

- MRI: 6 artikelen(157, 158, 169, 172, 173, 175)
- Specifiek genetisch onderzoek: 3 artikelen(161, 162, 168)

Over de diagnostische accuratesse van diagnostisch aderlaten voor het stellen van de definitieve diagnose hereditaire hemochromatose werd geen evidence gevonden.

*Kwaliteit van het bewijs*
Een samenvatting van de kwaliteit van bewijs per uitgangsvraag is te vinden bij de aanverwante producten.

**MRI**
De kwaliteit van de evidence is zeer laag. De zes artikelen bevatten alle een grote kans op vertekening van de resultaten. Ook zijn er problemen met de generaliseerbaarheid van de resultaten. Zo zijn de deelnemers aan de studies van Alustiza et al., Castiella et al. en Runge et al. niet allemaal patiënten met (verdenking) hemochromatose.(157, 158, 175) En ook bevatten veel studies patiënten uit een niet-kaukasische populatie, waarmee ze mogelijk niet vergelijkbaar zijn met de Nederlandse situatie.(157, 158, 172, 173) Ook in de systematische review van Sarigianni et al. zijn niet alleen patiënten met (verdenking) hemochromatose opgenomen.(172) Er is dus sprake van indirect bewijs. Vanwege onvergelijkbaarheid van de studies is het niet mogelijk om een meta-analyse van de resultaten te maken.

**Aanvullend genetisch onderzoek**
De kwaliteit van de evidence is zeer laag. De drie artikelen bevatten alle een grote kans op vertekening van de resultaten, bijvoorbeeld omdat er geen sprake is van een vergelijkende studie.(168) Ook zijn er mogelijk problemen met de generaliseerbaarheid van de resultaten naar de Nederlandse populatie; er is dus sprake van indirect bewijs.(161) Ook is er sprake van beperkte beschrijving van methoden en resultaten, zodat de betrouwbaarheid van het onderzoek moeilijk in te schatten is.(162) Aanvullend sequencing onderzoek van het gehele HFE gen en genen betrokken bij HH types 2-4 zoals gepubliceerd na de literatuursearch kan alsnog een

genetische diagnose opleveren en heeft in die gevallen vanzelfsprekend een hogere kwaliteit van bewijs.(16)

*Inhoudelijk resultaat*

**MRI**

Het onderzoek van Alustiza et al. onder 112 patiënten laat zien dat dat met behulp van MRI-onderzoek de diagnose HH gesteld kan worden, wanneer vergeleken wordt met een leverbiopt (waarbij in dit artikel de leverijzerconcentratie leidend is voor het stellen van de diagnose HH). Bij een afkapwaarde van de leverijzerconcentratie van 85 µmol/g is de sensitiviteit 86% en de specificiteit 100%. Bij een afkapwaarde van 40 µmol/g is de sensitiviteit 100% en de specificiteit 81%.(158) Ook het onderzoek van Castiella et al. onder 171 patiënten laat zien dat MRI van waarde kan zijn voor het stellen van de diagnose HH. Bij een afkapwaarde van 170 µmol/g is de sensitiviteit 69% en de specificiteit 100%; bij een afkapwaarde van 60 µmol/g is de sensitiviteit 100% en de specificiteit 75%. De auteurs geven hierbij aan dat de Rennes methode die zij gebruikt hebben de neiging heeft tot overschatting van het teveel aan ijzer.(157) De studie van Kreeftenberg et al. onder 23 patiënten waarin MRI met een biopt werd vergeleken heeft als resultaat een correlatie van 0,929. De auteurs geven aan dat kwantitatieve beoordeling alleen mogelijk is bij ernstige teveel aan ijzer in de lever en zij concluderen dat een biopt nodig blijft.(169) Sarigianne et al publiceerden een systematische review over de diagnostische accuratesse van MRI om teveel aan ijzer in de lever te bepalen bij ondermeer patiënten met hereditaire hemochromatose. Ook in deze review bleek meta-analyse van de resultaten niet mogelijk vanwege heterogeniteit van de data. De gevonden sensitiviteit varieerde van 0,00 tot 1,00 (mediaan 0,94) en de gevonden specificiteit van 0,50 tot 1,00 (mediaan 0,89). Ook deze auteurs concluderen dat er sprake is van zwak bewijs.(172) Het onderzoek van St. Pierre et al. ten slotte bepaalde de diagnostische accuratesse van MRI bij 105 patiënten in vergelijking met een leverbiopt. Ook in deze studie werden verschillende afkapwaarden geëvalueerd. Bij een drempelwaarde van bijvoorbeeld 1,8 mg/g (32 µmol/g) werd een sensitiviteit van 0,94 en een specificiteit van 1,00 gevonden voor het overschrijden van de bovennormale grens voor leverijzerconcentratie.(173) Het nadien toegevoegde onderzoek van Runge et al. vergeleek drie manieren om middels MRI-onderzoek de leverijzerconcentratie te bepalen.(175) In dit retrospectieve onderzoek werden 114 patiënten geïncludeerd die MRI-onderzoek naar bepaling van de leverijzerconcentratie ondergingen, van wie 12% met de indicatie hemochromatose. De auteurs concluderen dat de R2*-bepaling de methode van eerste keus is, vanwege de grote diagnostische accuratesse en de goede uitvoerbaarheid.

**Specifiek genetisch onderzoek**

Bryant et al. publiceerden een systematische review waarmee zij de klinische validiteit en bruikbaarheid van genetisch onderzoek voor de diagnostiek van hereditaire hemochromatose hebben geëvalueerd. In dit onderzoek werden 11 patiënt-controle onderzoeken geïncludeerd met in totaal 1518 patiënten en 2119 controles, waarbij DNA-onderzoek met ‘diagnostiek op andere wijze’ (niet duidelijk omschreven) werd vergeleken en de definitie van HH varieerde. De auteurs vonden een sensitiviteit die varieert van 72% tot 100% en een specificiteit die varieert van 99% tot 100%. Er zijn in deze studie geen gegevens gevonden over de klinische bruikbaarheid van de test (ten aanzien van bijvoorbeeld morbiditeit en mortaliteit).(162)
Een recenter onderzoek gaat in op de specifieke techniek van het onderzoek, waar bij 212 bloed samples het gebruik van PCR met a-fosforothioaat-gemedieerde primer extensie en colorimetrische bepaling werd vergeleken met ‘restriction fragment length polymorphism’. De diagnostische accuratesse voor mutaties is hierbij als volgt: haplotype mutaties: sensitiviteit 0,98 en specificiteit 1,00, en voor de detectie van het fenotype

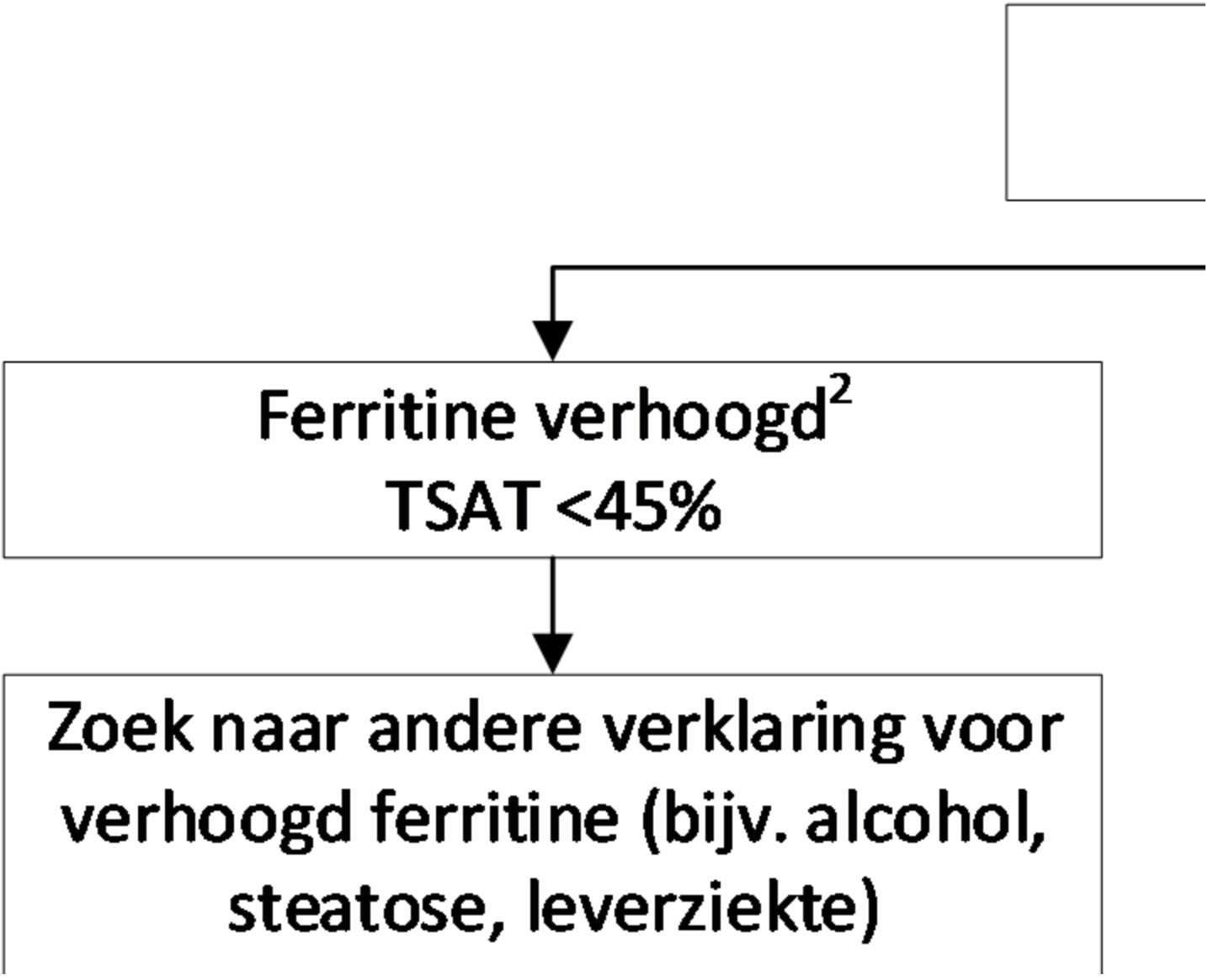
is de sensitiviteit in dit onderzoek 1,00 en de specificiteit ook 1,00.(161) Kingston et al. ten slotte beschreven de resultaten van een niet vergelijkend onderzoek waarbij zij keken naar PCR en analyse met GeneScans van 5327 bloed samples. Zij komen niet met resultaten die deze uitgangsvraag kunnen beantwoorden.(168)

### Zoeken en selecteren

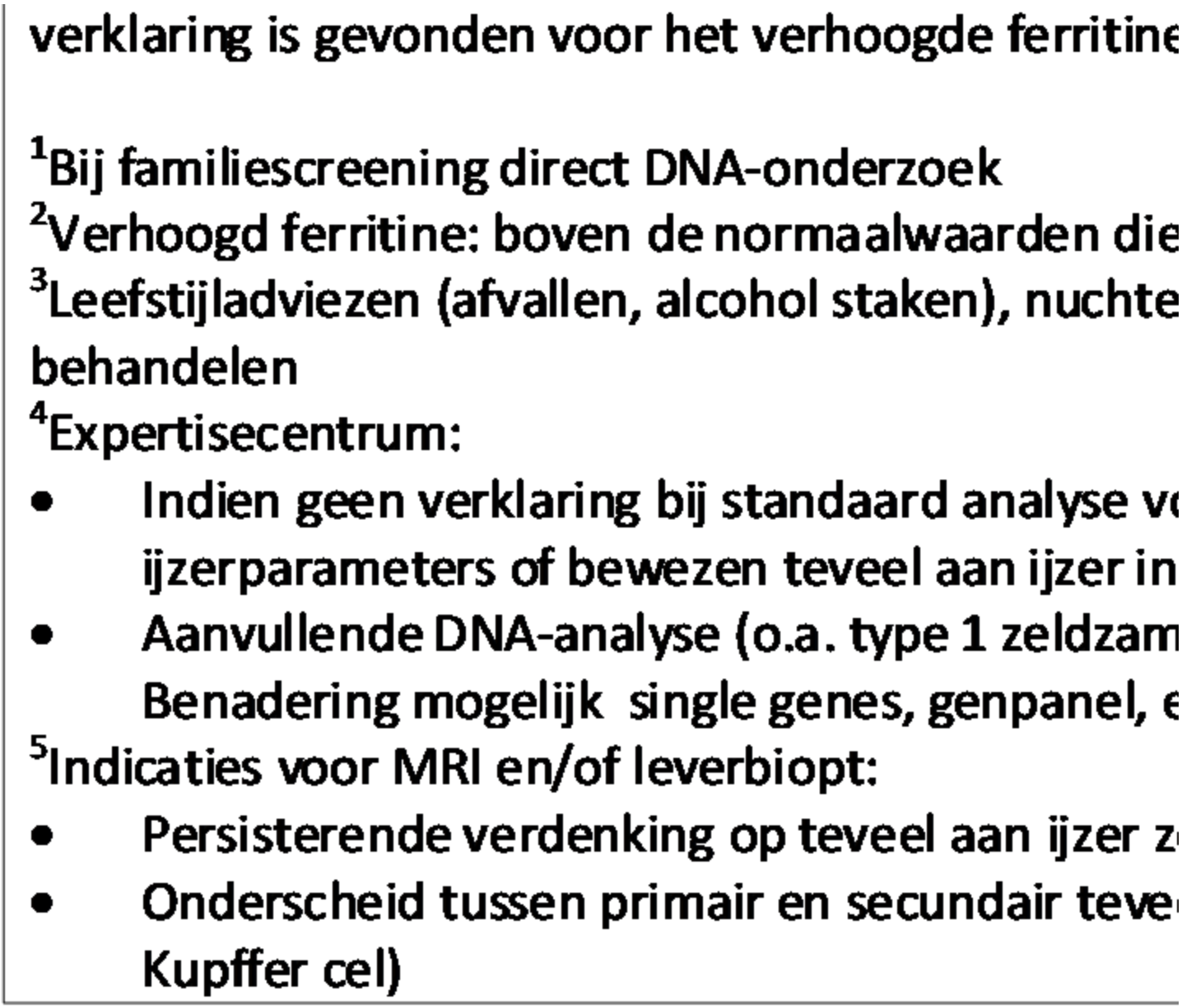
Voor deze uitgangsvraag is in Medline gezocht naar literatuur op 8 november 2016. De literatuur is vervolgens geselecteerd op basis van onderwerp (sluit het artikel aan bij de uitgangsvraag?) en studiekenmerken (ten minste systematisch opgezet onderzoek). De volledige literatuursearch en literatuurselectie zijn weergegeven in de zoekverantwoording.

### Overwegingen

De algehele kwaliteit van het bewijs is zeer laag. Voor het onderzoek naar de oorzaak bij een patiënt met hyperferritinemie is het volgende stroomdiagram als hulpmiddel voor de behandelende arts opgesteld.




Zie tabel 4.2
Bij geen verklaring
en blijvend verhoogd ferritine
Onderbroken lijn: er zijn zwaarwegende argumente


verklaring is gevonden voor het verhoogde ferritine

[1]Bij familiescreening direct DNA-onderzoek
[2]Verhoogd ferritine: boven de normaalwaarden die
[3]Leefstijladviezen (afvallen, alcohol staken), nuchte
behandelen
[4]Expertisecentrum:
- Indien geen verklaring bij standaard analyse v
  ijzerparameters of bewezen teveel aan ijzer in
- Aanvullende DNA-analyse (o.a. type 1 zeldzam
  Benadering mogelijk single genes, genpanel, e

[5]Indicaties voor MRI en/of leverbiopt:
- Persisterende verdenking op teveel aan ijzer z
- Onderscheid tussen primair en secundair teve
  Kupffer cel)

Hyperferritinemie is niet alleen een uiting van een toegenomen ijzervoorraad, maar kan ook door andere aandoeningen worden veroorzaakt. Een overzicht van de DD staat in tabel 1. Bij analyse van hyperferritinemie zullen dus meerdere aandoeningen overwogen moeten worden. De transferrinesaturatie speelt hierbij een belangrijke rol. Als deze <45 % bedraagt, is de kans op teveel aan ijzer door een onderliggende genetische aanleg voor hereditaire hemochromatose nagenoeg uitgesloten. Als er sprake is van een verhoogd ferritine en transferrineverzadiging zonder homozygotie voor de C282Y mutatie, kan worden overwogen om het ferritine en de transferrineverzadiging te volgen in combinatie met leefstijladviezen. Bij een ferritine > 1000 µg/l en geen verklaring op basis van de leefstijl, lijkt het aangewezen om sneller vervolgonderzoek in te zetten. Op proef aderlaten zonder diagnose wordt niet als standaard beleid geadviseerd aangezien er geen bewijs dan wel streefwaardes zijn voor deze setting, terwijl aderlaten wel een medisch invasieve behandeling is.

Bij blijvend verhoogde waarden kan een MRI-onderzoek worden verricht om de leverijzerconcentratie te bepalen. Anders dan bij secundaire hemochromatose waar de MRI wordt gebruikt om te bepalen of er een behandelindicatie is voor de ijzerstapeling, wordt de MRI hier gebruikt om te bepalen of nader onderzoek naar hereditaire hemochromatose gewenst is. Het is niet mogelijk om op basis van evidence concrete afkapwaarden te benoemen. Om de clinicus toch een handvat te geven, zijn navolgend enige suggesties genoemd. Bij waarden < 100 µmol Fe/g droog levergewicht is de kans op een schadelijke overmaat aan ijzer zeer klein.(12, 136) Bij mensen met het metabool syndroom of radiologische afwijkingen voor steatosis hepatis worden deze ijzerwaarden vaak gezien op de MRI. Als de uitslag > 100 µmol Fe/g droog levergewicht bedraagt kan er zeer wel sprake zijn van een schadelijke overmaat aan ijzer en lijkt uitgebreid genetisch onderzoek een logische vervolgstap om te komen tot een diagnose en de daarvoor optimale behandeling. Dit geldt vooral als de nieuwe MRI relaxometrie wordt gebruikt en er daarbij geen aanwijzingen zijn voor steatosis hepatis of ijzerstapeling in de milt.
Er zijn verschillende stroomdiagrammen gepubliceerd waarbij het leverbiopt en de MRI telkens een andere positie krijgen in de diagnostiek. Het leverbiopt is een invasief onderzoek met zeldzame, maar potentieel ernstige complicaties. Het leverbiopt heeft echter als voordeel dat op een directe wijze onderzoek gedaan kan worden naar de verdeling van ijzer in de lever (parenchym- of Kupffercellen), er gekeken kan worden naar andere leverziekten (steatose, auto-immuunhepatitis) en er een uitspraak gedaan kan worden over fibrose/beginnende cirrose. In de praktijk wordt het leverbiopt alleen ingezet bij verdenking op leverschade of een onderliggende leverziekte. De afweging of een MRI of een leverbiopt de juiste stap is, zal per casus afgewogen dienen te worden.
Bij problemen in het diagnostisch onderzoek naar de oorzaak voor een verhoogd ferritine, kan men voor verdere advisering contact opnemen met het expertisecentrum van het Radboudumc te Nijmegen.

**Tabel 1. Differentiaal diagnose verhoogd ferritine bij normale TSAT (<45%) (176)**

*Serumferritine 300 tot 1000 µg/l**
Metabool syndroom/niet-alcoholische leververvetting
Alcohol
Ontstekingsreactie
Maligniteit
M. Gaucher

*Serumferritine 1000 tot 5000 µg/l**
Alcoholisch leverlijden
Virale hepatitis
Secundaire ijzerstapeling
Multipele bloedtransfusies
Ineffectieve erytropoëse
Ferroportin Type 4A HH (zeldzaam)
Aceruloplasminemie
Hereditaire hyperferritinemie – cataract syndroom (HHCS)

*Serumferritine > 5000 µg/l**
Adult-onset M. Still
HLH/MAS
Fulminant leverlijden

** De afkapwaarden voor serumferritine zijn afkomstig uit het artikel van Beaton(176)*

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Behandeling bij Hemochromatose

*Deze module is afkomstig uit de richtlijn 2007, en beperkt herzien zonder systematisch literatuuronderzoek.*

De behandeling van teveel aan ijzer bestaat uit het onttrekken van ijzer. De mogelijkheden zijn flebotomie, erytrocytaferese of in zeldzame gevallen het gebruik van ijzerbindende chelatoren. Bij hereditaire hemochromatose is flebotomie over het algemeen de standaardbehandeling. Daarnaast kan de opname van ijzer mogelijk worden verminderd door toepassing van leefstijladviezen of gebruik van protonpompremmers. Dit is additief op de standaardbehandeling met flebotomie. Flebotomie heeft om praktische redenen, geringere kosten en minder bijwerkingen de absolute voorkeur boven ijzerchelatie, die vooral een plaats heeft bij de behandeling van secundaire hemochromatose zoals optreedt bij thalassemieën en andere ijzerstapelende anemieën. Bij patiënten bij wie om cardiovasculaire redenen aderlaten onwenselijk is kan het gebruik van erytrocytaferese of chelatie als alternatief voor het aderlaten worden overwogen.
Over het nut van het onttrekken van ijzer zijn geen direct vergelijkende studies beschikbaar. Er zijn wel studies die laten zien dat veronderstelde complicaties van teveel aan ijzer deels reversibel zijn (afname leverschade, cardiomyopathie, hypogonadotroop hypogonadisme en glucose-intolerantie) of vertraagd kunnen worden door flebotomie (leverfibrose), hetgeen de zin van ijzeronttrekking ondersteunt.(177) Ook gewrichtsklachten kunnen reversibel zijn, maar veel minder evident. In een op een vragenlijst gebaseerd onderzoek van McDonnell had 43,5% van de respondenten gewrichtsklachten, waarbij verbetering optrad bij 9,2%, terwijl er bij 34% een toename van klachten was ondanks ijzeronttrekking.(41) Het behandelen van hemochromatose met flebotomie kan regressie geven van levercirrose en oesofagusvarices. Milman liet zien dat adequaat met flebotomie behandelde patiënten een significant betere overleving hadden.(178) Dit gold zelfs voor patiënten met cirrose of insulineafhankelijke diabetes mellitus. Niederau et al. hebben patiënten langdurig (mediaan > 14 jaar) gevolgd en vonden een relatie tussen ernst van teveel aan ijzer en overleving.(179, 180) Een verminderde overleving werd veroorzaakt door levercelcarcinoom, cardiomyopathie, levercirrose en diabetes mellitus.(60, 178-180)
De intensiteit van behandeling met flebotomie is empirisch bepaald, en bestaat uit een depletiefase van eenmaal per week 450-500 ml. Veelal wordt op geleide van het Hb, het hematocriet en de serumferritineconcentratie besloten wanneer flebotomie kan worden uitgesteld of stopgezet (zie ook de module ´Indicatie erytrocytaferese bij Hemochromatose´). In de onderhoudsfase moet vervolgens met een beperkt aantal behandelingen per jaar worden voorkomen dat de ijzerconcentratie opnieuw stijgt.
In de volgende paragrafen worden de start- en streefwaarden van behandeling besproken, alsmede de indicatie voor erytrocytaferese en leefstijladviezen. Tot slot volgt een module over de mogelijkheid tot bloeddonatie.

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Starten met aderlaten bij Hemochromatose

## Uitgangsvraag

Is er een duidelijke grens aan te geven van ferritine (bij bewezen hemochromatose en los van klachten/schade) waarboven starten met aderlaten geïndiceerd is?

P Patiënten met diagnose hereditaire hemochromatose die nog niet zijn behandeld
I Aderlaten vanaf verschillende afkappunten
C -
O Voorkomen eindorgaanschade (overleving, diabetes mellitus, levercirrose, hartfalen), klachten (bijv. gewrichtsklachten)

De setting voor deze uitgangsvraag is de tweedelijns gezondheidszorg in Nederland.

## Aanbeveling

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|---|---|
| Zwak | Het wordt aanbevolen te starten met aderlaten bij patiënten met genetisch vastgestelde hereditaire hemochromatose én een serumferritineconcentratie boven de bovengrens van de referentiewaarden van het lokale laboratorium. |

## Inleiding

*Deze module is nieuw in deze richtlijn.*

Flebotomie is een veilige behandeling van HH. Echter het bewijs dat dit winst oplevert voor een patiënt wat betreft levensverwachting is eigenlijk alleen geleverd voor mensen met een risico op levercirrose. Er zijn ook studies die aantonen dat flebotomie leidt tot afname van moeheid, serum transaminases concentratie, en huidpigmentatie en daarnaast leidt tot verbetering van het histopathologische stadium van fibrose.(177-179) Een ferritineconcentratie hoger dan 1000 µg/l wordt bij patiënten die homozygoot zijn voor de C282Y variant algemeen beschouwd als een goede risicoschatting voor de ontwikkeling van cirrose en overlijden.(148, 150, 181) (42, 182) Het is in Nederland op dit moment echter gebruikelijk om patiënten met een serum ferritineconcentratie juist boven de bovengrens van het referentiegebied van het eigen laboratorium met flebotomie te laten starten. Mogelijk is er met dit beleid sprake van overbehandeling.

## Conclusies

| | |
|---|---|
| LAAG | Er is beperkt bewijs beschikbaar over de ideale drempel voor het starten met aderlaten bij patiënten met HH.<br><br>*Barton, 2012; Ong, 2017 (182, 185)* |

## Samenvatting literatuur

*Beschrijving studies*

Van 4 artikelen werd de volledige tekst bestudeerd. Tabellen met studiekarakteristieken van de beoordeelde studies zijn te vinden bij de aanverwante producten.(182, 183, 186, 187)
Het artikel van Ong et al. bleek bij bestudering van de volledige tekst om een studieprotocol te gaan, waarin wordt beschreven dat de auteurs een multicenter randomized controlled trial gaan uitvoeren door bij patiënten met matig verhoogde serum ferritine symptomen en ziektekenmerken te vergelijken tussen groepen die al dan niet worden behandeld.(187) De resultaten zijn zeer recent gepubliceerd en in de tekst 'van bewijs naar aanbeveling' toegevoegd.(185)
Er bleven na selectie op basis van de volledige tekst van het artikel 3 artikelen over voor beantwoording van de uitgangsvraag.

*Kwaliteit van het bewijs*
Een samenvatting van de kwaliteit van bewijs per uitgangsvraag is te vinden bij de aanverwante producten. De resterende studies kennen een grote kans op vertekening. Het eerste onderzoek betreft een niet-vergelijkend onderzoek onder slechts 9 personen en bovendien is het relatief oud.(186) Het tweede onderzoek betreft een retrospectieve analyse van 2 cohortonderzoeken. Deze beide studies kennen een grote kans op vertekening van de resultaten vanwege de opzet van de studie, en bovendien is het niet duidelijk of de studie van Barton tevoren geplande analyses betreft.(182) Ook is er sprake van indirectheid, omdat de patiënten in de geïncludeerde studies mogelijk niet vergelijkbaar zijn met de Nederlandse situatie.

*Inhoudelijk resultaat*
De studie van Barton et al. onderzocht voorspellende factoren voor een serum ferritine concentratie > 1000 µg/l en het relatieve risico van teveel aan ijzer op de mortaliteit. In dit onderzoek werden 2 cohortonderzoeken retrospectief geanalyseerd, waarin in totaal 422 C282Y homozygote patiënten met HH behandeld werden met flebotomie. De follow-up van deze cohorten patiënten is niet duidelijk vermeld, maar het staat vast dat ten minste een aantal jaren is teruggekeken. De auteurs rapporteren dat de gemiddelde overleving na de diagnose 13,2 jaar betreft (sd 7,3). Als factoren die onafhankelijk geassocieerd zijn met serum ferritine > 1000 µg/l bij de diagnose benoemen de auteurs de volgende: geslacht, leeftijd, verhoogde serum concentratie ALT/AST, vervette lever, sterke alcoholconsumptie, chronische virushepatitis, cirrose, diabetes en cardiomyopathie. Een serum ferritine concentratie > 1000 µg/l bij diagnose was geassocieerd met een verhoogd risico op overlijden (RR in de ene cohortstudie: 5;4 (95%BI: 2,2-13,1); in de andere cohortstudie 4,9 (95%BI: 1,1-22,0)).(182)
De studie van Bolan et al. betrof een oud, maar prospectief, niet-vergelijkend cohortonderzoek. Bij 9 patiënten, die 61 tot 535 weken werden gevolgd werd onderzocht of MCV als indicator kon worden gebruikt voor de flebotomiebehandeling bij patiënten met hereditaire hemochromatose. De auteurs rapporteren dat de MCV-waarde steeg gedurende de inductiebehandeling, waarna deze stabiel werd. Tijdens de onderhoudsbehandeling werd gericht op een MCV-waarde 5-10% onder de preflebotomie waarde waarbij het Hb > 13 g/dl bleef. De transferrine saturatie bleef daarmee < 35% en het mediane flebotomie interval was 7,5 weken.(186) De resultaten van dit onderzoek lijken niet zo relevant voor beantwoording van de uitgangsvraag.
In het onderzoek van Morrison et al. werden klinische en laboratoriumparameters onderzocht met als doel om gevorderde fibrose te voorspellen bij patiënten met HH. In dit onderzoek werden 182 patiënten met HH geïncludeerd, van wie er 22% fibrose of cirrose had. De auteurs vonden een sterke associatie tussen een serum ferritine concentratie < 1000 µg/l en de afwezigheid van cirrose of fibrose. Er werd geen associatie gevonden tussen cirrose of fibrose en leeftijd bij diagnose, leeftijd, of genotype. Normale serum aminotransferase was wel

geassocieerd met afwezigheid van fibrose of cirrose. Wanneer serum ferritine ≥ 1000 µg/l als diagnostische test voor het aantonen van 'bridging' fibrose of cirrose zou worden gebruikt, dan geeft dit een sensitiviteit van 0,97 (95%BI: 0,953-0,997) en een specificiteit van 0,65 (95%BI: 0,581-0,719).(181)
Aanvullend aan het systematische literatuuronderzoek werd de volgende informatie door de werkgroep ingebracht: Bardou-Jacquet et al. onderzochten in 2015 in het Franse LOGIFER-cohort de overleving en doodsoorzaken van 1085 behandelde C282Y homozygote patiënten die 8,3 jaar (sd 3,9) gevolgd werden. Patiënten met initiële ferritine concentraties > 2000 µg /l hadden een verhoogde mortaliteit, en patiënten met een ferritine tussen de bovengrens van normaal en 1000 µg/l hadden een lagere mortaliteit vanwege verminderde cardiovasculaire en extrahepatische kanker gerelateerde mortaliteit.(188) Sommige lezers waren het met deze conclusie eens.(189) In een ingezonden brief op dit artikel geven andere echter de beperkingen van deze studie aan en roepen ze op tot een gecontroleerde klinische studie die de noodzaak van behandeling van matig verhoogde ferritine concentratie moet onderzoeken.(190) Deze gecontroleerde studie is de Mi-Iron trial.(185)
In de recent gepubliceerde Mi-iron trial zijn HH-patiënten met verhoogde TSAT en ferritine tussen de 300 µg/l en ferritine 1000 µg/l gerandomiseerd over de behandelde en de controlegroep en respectievelijk behandeld met 3-wekelijkse erytrocytaferese en plasmaferese, tot ferritines < 300 µg/l en met zodanig aantal behandelingen dat met een ferritinedaling van 120 µg/l per behandeling een ferritine < 300 µg/l zou worden gehaald. Geen van de patiënten had leverfibrose. Na afloop van de behandelingen waren er significante verbeteringen in de moeheid-score (patient-reported Modified Fatigue Impact Scale (MFIS) score) in de behandelde ten opzichte van de controlegroep. Ook in het cognitieve onderdeel van de 'moeheid-score' waren er significante verbeteringen in de behandelde groep in vergelijking met de controlegroep. Er waren geen verschillen in de veranderingen in de fysieke en psychosociale componenten van de 'moeheid-score' tussen de groepen. Tot slot was de reductie in plasma F2-isoprostanes, een biomarker voor cellulaire oxidatieve schade aan lipiden, groter in de behandelde dan in de controlegroep. De auteurs van de studie en het bijbehorende editorial concluderen dat de resultaten suggereren dat normalisatie van serumferritine door ijzerdepletie gezondheidswinst oplevert voor alle patiënten met HH en verhoogde serumferritineconcentraties.(184, 185)
Een meta-analyse van de resultaten was niet mogelijk.

## Zoeken en selecteren

Voor deze uitgangsvraag is in Medline gezocht naar literatuur op 8 november 2016. De literatuur is vervolgens geselecteerd op basis van onderwerp (sluit het artikel aan bij de uitgangsvraag?) en studiekenmerken (ten minste systematisch opgezet onderzoek). Op verzoek van de werkgroep zijn een paar artikelen, gevonden bij uitgangsvraag 5, toegevoegd. (181, 183-185) De volledige literatuursearch en literatuurselectie zijn weergegeven in de zoekverantwoording.

## Overwegingen

Aderlaten is een relatief eenvoudige behandeling. Daarnaast laat de hierboven beschreven en zeer recent afgeronde Mi-iron trial zien dat het behandelen van ferritine concentraties tussen bovengrens van normaal en 1000 µg/l op korte termijn leidt tot significante verbeteringen in de 'patient-reported Modified Fatigue Impact Scale (MFIS)' score. Bovendien adviseren internationale richtlijnen te behandelen wanneer ferritine hoger is dan de bovengrens van de referentiewaarden.(106, 153)

De meting van serumferritine is (in ons land) niet optimaal gestandaardiseerd (zie de module ´IJzerparameters bij Hemochromatose´). Hierdoor kunnen de resultaten van ferritinemetingen en dus ook de referentie ranges voor ferritine van de verschillende laboratoria van elkaar verschillen.
Praktische handvatten ten aanzien van Hemoglobine (Hb):

- Indien het Hb minder dan 0,5 mmol/l onder de ondergrens van het referentiegebied voor het betreffende geslacht van het lokale laboratorium is, kan de flebotomie gewoon doorgang vinden tenzij de patiënt symptomatologie heeft.
- Indien het Hb te laag is op basis van een POCT meting en de flebotomie daarom zou worden afgelast, overweeg dan eerst een normale Hb-bepalingdoor middel van venapunctie.
- Fors dalend Hb tijdens de flebotomiecyclus moet de behandelaar prikkelen om de diagnose hemochromatose te heroverwegen, dan wel te beoordelen of er een gecombineerd probleem speelt. Vaak speelt een foliumzuurdeficiëntie een rol en kan de flebotomiecyclus simpel worden hervat met foliumzuursuppletie. Overweeg hervatting met kleiner volume en/of een lagere frequentie.

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Streefwaarde ferritine bij Hemochromatose

## Uitgangsvraag

Wat is de streefwaarde van het ferritine (tijdens de onderhoudsfase) voor aderlaten en kan TSAT hier een rol in spelen om individueel maatwerk te leveren?

P Patiënten met diagnose hereditaire hemochromatose die nog niet zijn behandeld
I Aderlaten vanaf verschillende afkappunten
C -
O Voorkomen eindorgaanschade (overleving, diabetes mellitus, levercirrose, hartfalen), klachten (bijv. gewrichtsklachten)

De setting voor deze uitgangsvraag is de tweedelijns gezondheidszorg in Nederland.

## Aanbeveling

| | |
|---|---|
| Zwak | Na adequate ijzerdepletie kan standaard een onderhoudsbehandeling worden gegeven, waarna behandeling alleen wordt gestart als de ferritine concentratie boven de bovengrens van normaal stijgt. Indien bij patiënten desondanks de TSAT boven de 70% blijft of wanneer bij de aan hereditaire hemochromatose toegeschreven klachten of symptomen blijven bestaan, is er ruimte voor maatwerk. |

## Inleiding

*Deze module is nieuw in deze richtlijn.*

Bij het schrijven van de oude Nederlandse richtlijn in 2007 bestond internationaal nog de gewoonte om in de depletiefase een serumferritineconcentratie van < 50 µg/l na te streven. Bewijs hiervoor bestond echter niet. Daarnaast heeft de oude Nederlandse richtlijn ervoor gekozen om in de fase die volgt op de depletiefase -te weten de onderhoudsfase - een streefwaarde van < bovengrens van normaal aan te houden op grond van theoretische overwegingen. Anno 2018 gelden die overwegingen nog steeds en kunnen als volgt opgesomd worden. Een lage ferritinewaarde verhoogt de kans op anemie, maar ook op andere ijzergebrek gerelateerde klachten. Ten tweede kan beredeneerd worden met de huidige kennis ten aanzien van het hepcidine dat bij lage ferritinewaarden en verhoogde erytropoëse het hepcidine alleen maar zal dalen met als gevolg dat ijzer nog eenvoudiger uit het dieet wordt opgenomen.(191, 192) Ten derde is het onwaarschijnlijk dat een ferritineconcentratie tot de bovenwaarde van normaal tot ijzerstapeling leidt. Vanuit pathofysiologisch perspectief is het mogelijk beter om een combinatie van TSAT en ferritinewaarden streefwaarden te hanteren. In deze module worden aanbevelingen voor deze streefwaarden onderbouwd.

## Conclusies

| | |
|---|---|
| ZEER LAAG | Op basis van de literatuur search is er geen hard bewijs voor een optimale streefwaarde van het ferritine voor het aderlaten in de depletie- en onderhoudsfase, en voor TSAT als biomarker om individueel maatwerk te leveren. |

| | |
|---|---|
| ZEER LAAG | Een langdurige blootstelling aan een TSAT> 50% in de onderhoudsfase van behandeling van HH is mogelijk geassocieerd met (verergering van) gewrichtsklachten, vermindering van het libido en belastbaarheid.<br><br>*Bardou-Jacquet 2017* |

## Samenvatting literatuur

*Beschrijving studies*
Van 9 artikelen werd de volledige tekst bestudeerd. Tabellen met studiekarakteristieken van de beoordeelde studies zijn te vinden bij de aanverwante producten.(181-183, 186, 187, 193-196)
Het artikel van Ong et al. bleek bij bestudering van de volledige tekst om een studieprotocol te gaan. Hierin wordt beschreven dat de auteurs een multicenter randomized controlled trial gaan uitvoeren, waarbij symptomen en ziektekenmerken bij patiënten met matig verhoogde serum ferritine vergeleken worden tussen groepen die al dan niet worden behandeld. Dit lijkt een uiterst relevante studie voor deze uitgangsvraag, maar de resultaten ervan zijn nog niet bekend.(187) Dit artikel is daarom geëxcludeerd. Het artikel van Liu et al. is eveneens geëxcludeerd, omdat dit geen systematisch onderzoek betreft, ondanks dat de auteurs het tegendeel beweren.(195) Ook andere van de gevonden artikelen bleken bij bestudering van de volledige tekst niet relevant voor beantwoording van de uitgangsvraag. (182) (186) (194) (196)
Er bleven na selectie op basis van de volledige tekst van het artikel 2 artikelen over voor beantwoording van de uitgangsvraag.(183, 193)

*Kwaliteit van het bewijs*
Een samenvatting van de kwaliteit van bewijs per uitgangsvraag is te vinden bij de aanverwante producten. De kans op vertekening van de resultaten is erg groot, vanwege het niet vergelijkende design en de retrospectieve opzet van een aantal geïncludeerde studies. Bovendien zijn de methoden in een aantal studies beperkt beschreven. Ook is er waarschijnlijk sprake van indirect bewijs, omdat het onderzoek bij niet-kaukasische patiënten betreft. De studie van Bardou-Jacquet tenslotte is een prospectief cohortonderzoek, met een zeer grote uitval en een beperkt aantal variabelen.(183)

*Inhoudelijk resultaat*
Bardou-Jacquet et al. includeerden 266 patiënten met hereditaire hemochromatose onder onderhoudsbehandeling in hun prospectieve onderzoek.(183) De gemiddelde follow-up in dit onderzoek was 13,4 jaar, waarbij werd gekeken naar associaties tussen enerzijds een verhoogde transferrinesaturatie (≥ 50%) en serumferritine (≥ 50 µg/l) en anderzijds klachten en symptomen. De auteurs concludeerden dat langdurig verhoogd serumferritine (2,5 jaar) en transferrinesaturatie (8 jaar) geassocieerd waren met gewrichtssymptomen en verminderde mogelijkheden tot sporten en werken, en verminderd libido.

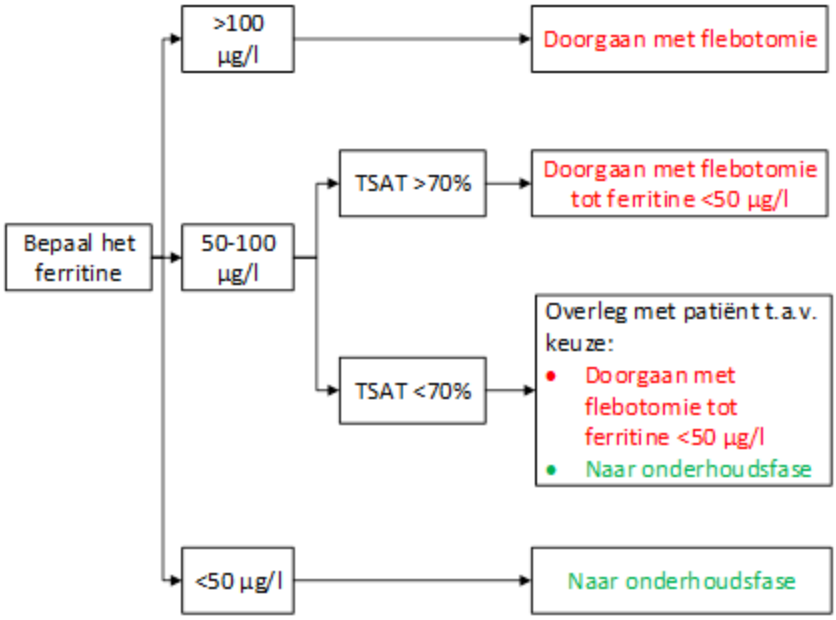
Adams et al. onderzochten bij 100 C282Y homozygoten of er een drempelwaarde van ijzerstapeling is die leidt tot cirrose. De auteurs rapporteren dat bij patiënten met cirrose de leverijzerconcentratie hoger is dan bij patiënten zonder cirrose. Een optimale drempel van de lever ijzerconcentratie stellen zij op 283 µmol/g. Bij die afkapwaarde is de sensitiviteit 0,85 en de specificiteit 0,84 voor het voorspellen van cirrose. De auteurs concluderen dat teveel aan ijzer in de lever geassocieerd is met cirrose, maar dat ook andere factoren van belang zijn. De relevantie van dit artikel voor het beantwoorden van deze uitgangsvraag is beperkt, omdat er leverijzerwaarden nodig zijn.(193)
Een meta-analyse van de gevonden resultaten was niet mogelijk, vanwege heterogeniteit in opzet en uitkomstmaten van de studies.

## Zoeken en selecteren

Voor deze uitgangsvraag is in Medline gezocht naar literatuur op 8 november 2016. De literatuur is vervolgens geselecteerd op basis van onderwerp (sluit het artikel aan bij de uitgangsvraag?) en studiekenmerken (ten minste systematisch opgezet onderzoek). Op verzoek van de werkgroep is een artikel, verschenen na de literatuursearch toegevoegd.(183) De volledige literatuursearch en literatuurselectie zijn weergegeven in de zoekverantwoording.

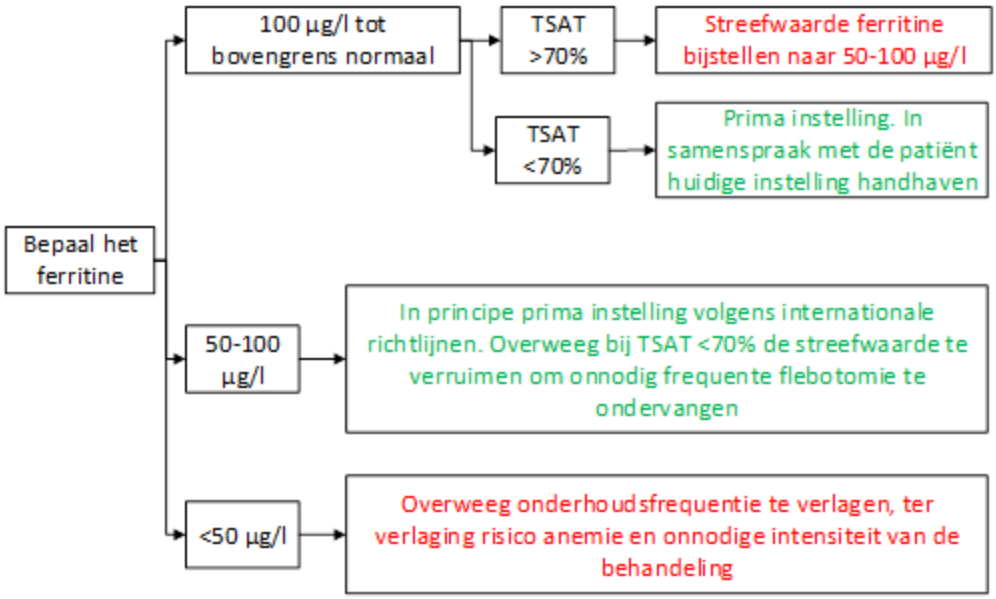
## Overwegingen

Er zijn geen data over het optimale streefwaarden tijdens de onderhoudsfase.
Alhoewel in de uitgangsvraag alleen de streefwaarde voor de onderhoudsfase wordt benoemd, geeft de werkgroep hier ook een handvat voor streefwaarden tijdens de depletiefase.
In de bestaande internationale richtlijnen wordt voor **de depletiefase** geadviseerd te streven naar een ferritine < 50 µg/l, maar bewijs daarvoor is nihil.(106, 153) Het streven naar een dergelijk lage ferritineconcentratie heeft als nadeel dat er een risico op ijzergebrek en anemie ontstaat. Sommige patiënten houden klachten van complicaties na de depletiefase. Er is beschreven dat bijvoorbeeld leverfibrose reversibel is met aderlaten. Derhalve zou dit reden kunnen zijn om te streven naar een lagere streefwaarde van ferritine bij patiënten met klachten, mits de patiënt aderlating goed verdraagt en het Hb voor aanvang van de aderlating niet verlaagd is. De recente studie van Bardou-Jacquet laat zien dat langdurige blootstelling aan een TSAT>50% een mogelijk verhoogde kans op complicaties geeft.(183) Tevens zijn er aanwijzingen dat een TSAT> 70% leidt tot (toxisch) NTBI vorming (niet transferrine gebonden ijzer), maar ook dat het streven naar een normalisatie van TSAT een grotere kans geeft op het ontstaan van een anemie na aderlaten.(88, 197) (198) Anderzijds lijkt de daling in het ferritine beter te correleren met de hoeveelheid onttrokken ijzer dan daling in TSAT. Om die reden is er iets voor te zeggen om het advies met betrekking tot de streefwaarden te baseren op een combinatie van streefwaarden voor ferritine en TSAT en daarbij individueel maatwerk te leveren.




*Figuur 1. Indicatie streefwaarden tijdens depletiefase behandeling*

Tijdens de **onderhoudsfase** adviseren internationale richtlijnen om te streven naar een ferritine tussen de 50 en 100 µg/l.(106, 153) In de Nederlandse richtlijn van 2007 is ervoor gekozen voor een advies waarbinnen het mogelijk wordt om het ferritine op te laten lopen naar de bovengrens van normaal. Dit heeft als voordeel dat er minder aderlatingen in de tijd nodig zijn, omdat de vicieuze cirkel van aderlaten, ferritinedaling en hepcidinedaling met daardoor snelle reaccumulatie van de ijzervoorraden in de tijd kan worden voorkomen. Bij klachten en/of TSAT> 70% wordt een lagere waarde van ferritine nagestreefd, mits dit niet leidt tot anemie en de patiënt de behandeling goed verdraagt.




*Figuur 2. Indicatie streefwaarden ferritine tijdens onderhoudsfase behandeling*

## Verantwoording

Laatst beoordeeld : 28-10-2018

Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Indicatie erytrocytaferese bij Hemochromatose

## Uitgangsvraag

Wanneer bestaat de voorkeur voor erytrocytaferese in plaats van aderlaten (medische indicatie)?

P Patiënten met hereditaire hemochromatose (initiële fase, eventueel ook onderhoudsfase)
I Erytrocytaferese
C Aderlaten
O Bijwerkingen, efficiëntie (tijdswinst en ferritinedaling), kosteneffectiviteit

De setting voor deze uitgangsvraag is de tweedelijns gezondheidszorg in Nederland.

## Aanbeveling

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|---|---|
| Zwak | Naast ontijzering middels flebotomieën is erytrocytaferese een technisch goed alternatief. Op individuele basis zal een arts met een patiënt kunnen kiezen voor de meest optimale ontijzeringstherapie. |

## Inleiding

*Deze module is nieuw in deze richtlijn.*

Aderlatingen van 500 ml per keer, uitgevoerd 1x per 1-2 weken, vormen al sinds jaar en dag de standaardbehandeling voor de ontijzering van de patiënt met HH. Deze behandeling is intensief en wordt niet door alle patiënten even goed verdragen. Zo zijn daar klachten als moeite met het aanprikken van geschikte aders, maar ook duizeligheid en collapsen die de behandeling voor een patiënt zeer onaangenaam maken. Daarnaast is er natuurlijk de tijdsbelasting. Omdat de aderlatingen veelal in de ziekenhuizen gedurende werktijd gebeurt kan dit voor actief aan het arbeidsleven deelnemende patiënten en hun werkgevers een forse kostenpost zijn.
Ook voor de onderhoudsbehandeling zijn er zowel lichamelijke als sociaal/maatschappelijke hindernissen, met als gevolg dat op den duur een aantal patiënten zich aan de therapie onttrekt. Het is daarom goed te weten dat er alternatieve mogelijkheden voor ontijzering zijn en in de overwegingen om daarvoor te kiezen de pro's en contra's van de alternatieve in vergelijking met de standaardbehandeling mee te wegen.

## Conclusies

| | |
|---|---|
| ZEER LAAG | Erytrocytaferese is effectief om teveel aan ijzer te verminderen bij patiënten met hereditaire hemochromatose en kan vanuit maatschappelijk perspectief kosteneffectief zijn in vergelijking met aderlaten, ondanks dat de directe kosten van erytrocytaferese hoger zijn. Voor het gehele behandeltraject is een verschil in effectiviteit en bijwerkingen met aderlaten niet aangetoond.<br><br>*Rombout-Sestrienkova, 2012; Sundic, 2014(201, 202)* |

## Samenvatting literatuur

*Beschrijving studies*
Van 5 artikelen werd de volledige tekst bestudeerd. Tabellen met studiekarakteristieken van de beoordeelde studies zijn te vinden bij de aanverwante producten.(199-203)
Vanwege de beschikbaarheid van experimenteel onderzoek is besloten de retrospectieve niet-vergelijkende studie van Poullin et al. niet nader te analyseren.(200)

*Kwaliteit van het bewijs*
Een samenvatting van de kwaliteit van bewijs per uitgangsvraag is te vinden bij de aanverwante producten. De beide RCT's zijn zeer beperkt in omvang en niet geblindeerd, hetgeen de resultaten sterk kan vertekenen. Er is sprake van enige inconsistentie in de resultaten. Een meta-analyse van de resultaten was daarom niet mogelijk.

*Inhoudelijk resultaat*
Rombout-Sestrienkova et al. onderzochten in een niet geblindeerde randomized controlled trial de verschillen tussen erytrocytaferese eens per 2 weken 300-800 ml erytrocyten en flebotomie eens per week 500 ml bloed (200-250 ml erytrocyten). In dit Nederlandse onderzoek werden 38 nieuwe patiënten met hereditaire hemochromatose geïncludeerd en er werd gekeken naar het aantal behandelingen dat nodig was tot het serum ferritine £ 50 µg/l was. Daarbij kwamen geen verschillen tussen beide groepen naar voren in hematologische en biochemische variabelen voor en aan het eind van de behandeling. Bij aderlaten bleken gemiddeld 27 behandelingen nodig, bij erytrocytaferese waren dat er gemiddeld 9. De behandelduur bij aderlaten was gemiddeld 33,7 weken en bij erytrocytaferese was dat 19,6 weken. Bij aderlaten was het behandelingsinterval kleiner, het totale verwijderde volume groter, de totale ijzerverwijdering groter en de ijzerverwijdering per procedure lager dan bij erytrocytaferese. Er was geen significant verschil in bijwerkingen. De kosten per procedure zijn bij aderlaten lager, en dat geldt ook voor de gemiddelde kosten voor de totale behandeling. Bij aderlaten zijn de kosten voor verloren productie echter hoger.(201)
Sundic et al. voerden eveneens een niet geblindeerde randomized controlled trial uit, waarbij zij bestudeerden of snellere daling van ferritine en transferrine saturatie mogelijk is met erytrocytaferese in vergelijking met aderlaten bij patiënten met hereditaire hemochromatose. In dit onderzoek werd 62 weken behandeld met erytrocytaferese eens per 2 weken 400 ml erytrocyten of flebotomie eens per week 200-220 ml erytrocyten. De beide groepen bleken vergelijkbaar in de tijd om de ferritine concentratie te laten dalen tot < 50 µg/l. Ook was er geen verschil in daling van de transferrine saturatie, bijwerkingen en totale behandelduur. De materiaalkosten waren bij erytrocytaferese hoger dan bij aderlaten.(202)
Een recent verschenen Cochrane systematische review heeft geen andere studies dan bovenstaande geïncludeerd.(204)

## Zoeken en selecteren

Voor deze uitgangsvraag is in Medline gezocht naar literatuur op 8 november 2016. De literatuur is vervolgens geselecteerd op basis van onderwerp (sluit het artikel aan bij de uitgangsvraag?) en studiekenmerken (ten minste systematisch opgezet onderzoek). De volledige literatuursearch en literatuurselectie zijn weergegeven in de zoekverantwoording.

## Overwegingen

Er bestaat geen voorkeur voor de ontijzering bij patiënten met HH voor aderlatingen in hoge frequentie dan wel erytrocytaferese. Wel is het zo dat erytrocytaferesebehandeling over het algemeen meer op maat is gesneden dan de huidige praktijk van flebotomie. De werkgroep pleit ervoor ook flebotomie op maat aan te bieden (variatie in afnamevolume per keer op geleide van bijvoorbeeld lichaamsgewicht, en variatie in bijvoorbeeld naalddikte). De keuze tussen flebotomie en erytrocytaferese zal gebaseerd zijn op individuele patiëntkarakteristieken, zoals neiging tot collaps bij een flebotomie, ervaren ongemak en comorbiditeit. Bij cardiovasculair lijden lijkt erytrocytaferese beter verdragen te worden dan een hoge frequentie aderlatingen. (205) Ook organisatorische factoren kunnen een rol spelen bij het maken van een keuze tussen deze vormen van ijzeronttrekking, waaronder tijdsinvestering van de patiënt, reistijd van en naar de behandeling, duur van de behandeling en knelpunten in de vergoedingensystematiek. De behandeling wordt niet in alle ziekenhuizen gegeven. Misschien moet de patiënt daarom langer reizen of veranderen van ziekenhuis danwel behandelend arts om deze therapie te ondergaan.
Een andere manier om de behandellast voor de patiënt te beperken is door het verminderen van de ijzeropname. Leefstijladviezen en protonpompremmers kunnen hier mogelijk een rol spelen (zie ook de module ´Bloeddonatie bij Hemochromatose´).

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Leefstijladviezen bij Hemochromatose

## Uitgangsvraag

Zijn er leefstijladviezen te geven voor mensen met hereditaire hemochromatose?

## Aanbeveling

| | |
|---|---|
| Geen gradering | Bij dieetadviezen dient een lichte afname van de frequentie van aderlaten te worden afgewogen tegen de kans op een lage therapietrouw en een verminderde kwaliteit van leven. Als pa-tiënten eraan hechten zelf een bijdrage te willen leveren aan het verminderen van ijzerstapeling is het eten van (veel) rood vlees en het consumeren van vitamine C-rijke vruchten en dranken tijdens de maaltijd af te raden.<br>Patiënten met verhoogde ijzerparameters wordt aangeraden zich tijdens de depletiefase te onthouden van alcohol en in zijn algemeenheid terughoudend te zijn met het nuttigen van alcoholhoudende dranken.<br>De werkgroep onthoudt zich van een aanbeveling over het gebruik van protonpompremmers in het algemeen. De reden hiervoor is het gebrek aan evidence voor de effecten van protonpompremmers bij patiënten met HH op de lange termijn. In individuele gevallen kunnen arts en patiënt samen een afweging van de voor- en nadelen maken over het gebruik van protonpompremmers om de ijzeropname te verminderen. |

## Conclusies

| | |
|---|---|
| Geen gradering | IJzer in het dieet verhoogt het lichaamsijzer bij C282Y homozygoten, met als gevolg dat een hogere frequentie van aderlaten nodig is.<br><br>*Walters, 1975; Olsson, 1997(208, 218)* |

| | |
|---|---|
| Geen gradering | Bevolkingsstudies tonen een relatie tussen een hoge ijzerinname, hoge transferrineverzadiging en mortaliteit. Het is niet duidelijk of dit primair is toe te schrijven aan de individuen met aanleg voor hereditaire hemochromatose (C282Y homozygoten).<br><br>*Mainous, 2004(219)* |

| | |
|---|---|
| Geen gradering | Alcohol heeft een additief toxisch effect op de lever.<br><br>*Adams, 1991; 1996; Niederau, 1985; Scotet, 2003(60, 212, 214, 215)* |

| | |
|---|---|
| Geen gradering | Het eten van (veel) rood vlees en het consumeren van vitamine C-rijke vruchten of dranken tijdens de maaltijd lijkt geassocieerd met een hoge ijzeropname.<br><br>*Bezwoda, 1976; Hutchinson, 2008; Lynch, 1989; Mainous, 2004; Milward, 2008; Moretti, 2013 (206, 210, 211, 219-221)* |

| | |
|---|---|
| Geen gradering | Er zijn aanwijzingen dat het gebruik van een protonpompremmer de opname van ijzer uit de voeding vermindert en daarmee het aantal benodigde flebotomieën bij patiënten met hemochromatose verlaagt.<br><br>*Hutchinson, 2012;(216) Van Aerts, 2016 (222)Vanclooster, 2017(211, 216)* |

## Samenvatting literatuur

*Deze module is nieuw in deze richtlijn.*

Er is een aantal onderzoeken gepubliceerd naar het effect van de samenstelling van voeding en dranken op de ijzeropname bij patiënten met HH.(206, 207) De resultaten van de verschillende onderzoeken zijn niet altijd eenduidig, maar een aantal bevindingen lijkt in dit verband relevant.

<u>IJzeropname</u>
*IJzer in voeding*
Walters et al. onderzochten de ijzeropname bij 15 HH patiënten vergeleken met 52 controles, na het consumeren van kippensoep verrijkt met ijzer. De ijzeropname in de patiëntengroep was significant hoger dan in de controlegroep, met name bij de patiënten met een relatief laag ferritinegehalte in het serum. Olsson et al. bestudeerden het toevoegen van ijzer aan voeding (standaard in Zweden tot 1995).(208) Bij 16 mannen die in verband met HH onderhoudsbehandeling met aderlatingen kregen, werd de ijzerabsorptie gemeten voor en na het stoppen van de met ijzer verrijkte voeding. De opname van ijzer verminderde met 0,65 mg/dag (van 4,27 naar 3,63 mg/dag), waardoor het interval tussen de aderlatingen kon worden verlengd van 59 naar 69 dagen zonder dat zich ijzergebreksanemie ontwikkelde.

*Dierlijk (heem) ijzer versus plantaardig (non-heem) ijzer*
Bezwoda et al. onderzochten het effect van dierlijk ijzer in de vorm van lamsvlees versus plantaardig ijzer in tarwe in een groep van 12 hemochromatose patiënten vergeleken met twee controlegroepen (n=30), allen met ferritine gehalte lager dan 25 µg/liter. De opname van plantaardig ijzer in de patiëntengroep bedroeg 36,4 %, vergeleken met 5,8% resp. 18,9 % in de controlegroepen. De opname van dierlijk ijzer in de patiëntengroep bedroeg 37,1 %, vergeleken met 31,6 resp. 29,8 % in de controlegroepen. Lynch et al. onderzochten het effect van plantaardig en van dierlijk ijzer in hamburgers bij 15 HH patiënten vergeleken met twee controlegroepen (n=97). Zowel de opname van het plantaardige als het dierlijke ijzer was groter in de patiëntengroep dan in de controlegroepen, met name bij patiënten met lagere ferritinegehaltes. De opname van dierlijk ijzer is groter dan van plantaardig ijzer. Mainous et al. hebben in een 12 jaar durende cohortstudie (n=9252) het effect van hoge ijzerconsumptie en het eten van rood vlees bestudeerd. Zij vonden een relatie tussen hoge ijzerinname, hoge transferrineverzadiging en mortaliteit (HR 2,9 (95% BI 1,39-6,04)) en idem voor het eten van rood vlees (HR 2,26

(95% BI 1,45-3,52)). Cade et al. publiceerden een prospectieve studie in een groep van 6.779 35-69-jarige vrouwen.(209) Bij postmenopauzale vrouwen die een heem-rijk voedingspatroon hadden en homozygote HFE-drager waren werden de hoogste ferritinewaarden gevonden.

Versterken ijzeropname

*Vitamine C en citrusvruchten*

Milward et al. onderzochten het effect van de consumptie van twee of meer stuks fruit per dag (geen citrusvruchten) op de ijzerstatus van 2232 gezonde Australische burgers.(210) Zij vonden een 20 % reductie van de ferritine spiegels vergeleken met de consumptie van één stuks fruit onafhankelijk van de aan-of afwezigheid van een HFE-genotype. Een dergelijk beschermend effect werd niet gevonden met citrusvruchten. Lynch et al. onderzochten het effect van 100 mg vitamine C (in sinaasappelsap) op de opname van ijzer uit een standaard maaltijd. In een groep van 22 C282Y/wild type was de opname 9,2 % vergeleken bij 3,4 % in een controlegroep van 75 personen. De auteurs beschrijven dat dit de hypothese ondersteunt dat heterozygoten meer ijzer opnemen wanneer er een extra stimulus is (vitamine C) dan gezonde vrijwilligers. Hutchinson et al. onderzochten het effect van 260 mg vitamine C (in sinaasappelsap) en vonden een hogere ijzeropname in een groep van 12 HH patiënten en 10 ijzerdeficiënte patiënten vergeleken met twee groepen van in totaal 21 controles.(211)

Verminderen ijzeropname

*Alcohol*

Alcohol heeft een additief hepatotoxisch effect. Adams et al. vonden in 105 patiënten met HH frequenter cirrose in leverbiopten bij de 15% patiënten met een alcoholconsumptie van meer dan acht glazen/dag, zonder dat er tussen de twee groepen een verschil was in ijzerconcentratie en leverijzerindex.(212) Deze studie laat een significant verschil in overleving zien, mogelijk op basis van cirrose en niet alcoholgebruik op zichzelf. Cirrose is in eerdere studies de belangrijkste factor gebleken die gecorreleerd is met mortaliteit.(213, 214)
Een studie naar het effect van excessief alcoholgebruik in 33 (8,7% van de bestudeerde populatie) C282Y-homozygoten werd uitgevoerd door Scotet et al.(215) Zij vonden in deze subgroep hogere parameters voor ijzer, ijzerverzadiging en ferritine, verhoogde leverenzymen (ALAT en ASAT) en meer huidpigmentatie.

*Protonpompremmers*

Hutchinson et al. voerden een beperkt onderzoek uit om te bestuderen of protonpompremmers de ijzeropname remmen. In dit onderzoek werden 15 patiënten met HH retrospectief geanalyseerd, waarbij werd gevonden dat het aantal flebotomieën per jaar voor gebruik van een protonpompremmer gemiddeld 2,5 keer per jaar was en tijdens gebruik van een protonpompremmer 0,5 keer per jaar. 'IJzerprovocatie' in het prospectieve deel van dit onderzoek onder 14 patiënten liet zien dat gebruik van protonpompremmers leidde tot minder opname van ijzer uit de voeding.(199)
Van Aerts et al. analyseerden in een retrospectief onderzoek 57 patiënten met hereditaire hemochromatose, van wie er bij 12 data waren voor en tijdens gebruik van protonpompremmers en bij 9 data tijdens gebruik van protonpompremmers. Patiënten bleken voordat zij protonpompremmers gebruikten gemiddeld 3,17 flebotomiebehandelingen nodig te hebben en tijdens gebruik van protonpompremmers 0,50 behandelingen per jaar.(203)
Vanclooster et al. analyseerden in een dubbelblind placebo-gecontroleerd gerandomiseerd onderzoek de waarde van protonpompremmers op de frequentie van flebotomie bij patiënten met HH.(216) In dit onderzoek werden 30 patiënten met C282Y homozygote HH gerandomiseerd tussen pantoprazol 40 mg/dag en placebo

gedurende 12 maanden. Bij serumferritine > 100 µg/l werd flebotomie uitgevoerd. In de groep die een protonpompremmer gebruikte werden in de studieperiode gemiddeld 1,27 flebotomieën uitgevoerd per persoon, in de placebogroep waren dit er gemiddeld 2,60 (p=0,0052). De auteurs concluderen dat gebruik van een protonpompremmer de frequentie van flebotomie kan verlagen.
In een longitudinaal cohortonderzoek in de Verenigde Staten werd de associatie tussen gebruik van protonpompremmers en overlijden onderzocht. (217) In de vergelijking al dan niet gebruik van protonpompremmers werden 2.886.879 personen geïncludeerd met een mediane follow-up van 5,71 jaar. De gecorrigeerde hazard ratio voor overlijden was 1,23 (95%BI: 1,22-1,24). Dat wil zeggen dat in de groep met gebruik van protonpompremmers ongeveer een kwart meer sterfte was. Een oorzaak voor deze sterfte wordt in het artikel niet gegeven.

## Zoeken en selecteren

Deze module is geschreven op basis van verkennend literatuuronderzoek en consensus in de werkgroep.

## Overwegingen

De vraag is in hoeverre adviezen zijn te geven. De overmaat van ijzerabsorptie bij hemochromatose patiënten (0,5 tot 1,0 mg/dag) kan worden gecorrigeerd door ijzeronttrekking middels aderlatingen (200-250 mg ijzer/500 cc bloed). Maar minder ijzeropname is zeker beter. Men dient op te passen voor multivitaminepreparaten en voor geneesmiddelen verrijkt met ijzer. Voor patiënten met HH is het eten van rood vlees een bron van ijzer met een hoge biologische beschikbaarheid (heem ijzer). Het vermijden van vitamine C-rijke vruchten en dranken bij de maaltijd is verstandig. Het gebruik van alcoholhoudende dranken dient beperkt te zijn, met name tijdens de depletiefase. Het is echter niet duidelijk of het voordeel van deze dieetadviezen, namelijk een mogelijke afname in de frequentie van aderlaten, opweegt tegen de afname van de kwaliteit van leven die het kan teweegbrengen.
In internationale richtlijnen wordt aanbevolen geen rauwe schaaldieren te eten ter preventie van infectie met Vibrio vulnificans en de grotere gevoeligheid hiervoor bij mensen met ijzerstapeling. Voor mensen die in Nederland verblijven wordt dit risico zeer beperkt geacht. De wereldreiziger wordt afgeraden rauwe schaaldieren te consumeren.

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Bloeddonatie bij Hemochromatose

## Uitgangsvraag

Zijn patiënten met hereditaire hemochromatose geschikt als bloeddonor?

## Aanbeveling

| | |
|---|---|
| Geen gradering | In Nederland mag bloed van patiënten met HH gebruikt worden voor transfusiedoeleinden als aan de specifieke voorwaarden hiervoor (zie overwegingen) is voldaan. |

## Conclusies

| | |
|---|---|
| Geen gradering | Er zijn aanwijzingen in de beschikbare studies dat het bloed van hemochromatosepatiënten die aan de normale criteria voor bloeddonorschap voldoen geen extra risico met zich meebrengt.<br><br>*De Buck, 2012; Winters, 2017 (223, 224)* |

## Samenvatting literatuur

*Deze module is nieuw in deze richtlijn.*

In een systematische review van De Buck et al. uit 2012 werden 6 observationele onderzoeken opgenomen over de veiligheid van bloeddonatie door patiënten met hemochromatose.(223) Hierbij werden patiënten met hemochromatose vergeleken met patiënten zonder hemochromatose. Hierbij zijn geen aanwijzingen gevonden dat erytrocytenconcentraties afkomstig van patiënten met hemochromatose zonder complicaties van ijzerstapeling niet aan de voorwaarden voor normale bloeddonaties zouden voldoen, of dat bloed afkomstig van patiënten met hemochromatose een risico voor ontvangers met zich mee zou brengen. De resultaten van dit onderzoek zijn bevestigd in de systematische review van Winters et al.(224)

## Zoeken en selecteren

Deze module is geschreven op basis van verkennend literatuuronderzoek en consensus in de werkgroep.

## Overwegingen

In Nederland is Sanquin de organisatie die door de minister als enige uitvoerende organisatie voor donatie van bloed is aangewezen. Vanaf 27 juni 2016 zijn personen met HH welkom als bloeddonor maar onder voorwaarden:

1. Absolute contra-indicaties voor bloedafname bij Sanquin:

- Hart- en vaatziekten: ernstige hartritmestoornissen, linker hoofdcoronairarterie stenose, ernstige aortastenose, angina pectoris, decompensatio cordis, CVA of TIA in anamnese;
- Neurologische ziektebeelden: epileptisch insult binnen 3 maanden voorafgaand aan donatie;
- Infectieziekten: HBV, HCV, HIV-1/2, HTLV-I/II of andere ziektekiemen.

2. Voorwaarden die voor alle donoren gelden:

- Personen moeten bij aanmelden jonger zijn dan 65 jaar en mogen niet meer doneren als ze ouder zijn dan 70 jaar;
- Mannen mogen maximaal 5 keer per jaar doneren, vrouwen mogen maximaal 3 keer per jaar doneren;
- Personen die doneren moeten minimaal een gewicht hebben van 50 kg;
- Personen die willen doneren mogen na 1980 geen bloedtransfusie hebben gehad of bloedproducten hebben ontvangen;
- Personen die willen doneren mogen geen orgaan- of weefseltransplantatie hebben ondergaan;
- Personen die willen doneren mogen tussen 1-1-1980 en 31-12-1996 niet 6 maanden of langer aanwezig zijn geweest in het Verenigd Koninkrijk;
- Personen die willen doneren mogen geen drugsgebruik met behulp van spuiten hebben gehad;
- Personen die willen doneren mogen geen diabetes hebben die met insuline injecties wordt behandeld;
- Van personen die willen doneren en die aan een chronische of ernstige ziekte lijden of hebben geleden zal nadere informatie worden gevraagd;
- Een en ander staat altijd ter beoordeling van de keuringsarts van Sanquin.

3. Specifieke voorwaarden voor personen met HH:

- Aanmelding als donor moet worden gedaan door de behandelend arts;
- Donatie kan slechts plaatsvinden in de onderhoudsfase en als het ferritinegehalte < 100 µg/l is;
- Jaarlijks dient door de behandelend arts een bewijs van voortzetting met een recente ferritinebepaling te worden verstrekt;
- De behandelaar blijft verantwoordelijk voor begeleiding en controle van zijn patiënt;
- Voorafgaand aan elke bloedafname wordt de donor door een keuringsarts van Sanquin beoordeeld. Voor criteria zie website Sanquin.

Als voldaan wordt aan de algemene en specifieke voorwaarden en het bloed voor donatie kan worden gebruikt, worden geen onkosten in rekening gebracht bij derden.
Kan het bloed niet worden gebruikt voor transfusiedoeleinden dan worden de kosten van bloedafname in rekening gebracht bij het ziekenhuis waaraan de behandelend arts die voor de verwijzing verantwoordelijk is, is verbonden. (aderlating €73,20, erytrocytaferese €271,80 prijspeil 2017).
Voor nadere informatie wordt verwezen naar de website van Sanquin.

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Familieonderzoek bij Hemochromatose

Deze module is opgedeeld in twee submodules:

- Genetisch familieonderzoek bij Hemochromatose
- Logistiek familieonderzoek bij Hemochromatose

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Genetisch onderzoek bij familieleden bij Hemochromatose

## Uitgangsvraag

Wat is het minimale relatieve risico op morbiditeit voor familieleden om genetisch onderzoek te rechtvaardigen?

P Familieleden van patiënten met hereditaire hemochromatose
I -
C -
O Relatieve risico op morbiditeit bij positieve en negatieve testuitslag van genetisch onderzoek

De setting voor deze uitgangsvraag is de tweedelijns gezondheidszorg in Nederland.

## Aanbeveling

Antwoord op uitgangsvraag
Het geschatte minimale a priori risico van 1% op ernstige morbiditeit zoals levercirrose bij eerste graadsverwanten wordt hoog genoeg bevonden om familieonderzoek naar C282Y homozygotie te rechtvaardigen.

| | |
|---|---|
| Zwak | Het wordt aanbevolen om eerstegraads verwanten van homozygoten vanaf de leeftijd van 18 jaar genetisch te onderzoeken naar het voorkomen van C282Y homozygotie.<br>Dit advies geldt voor alle broers en zussen van een index patiënt.<br>Voor kinderen van C282Y homozygote patiënten geldt hetzelfde advies, maar is genetisch onderzoek niet zinvol wanneer de partner van deze patiënt niet van kaukasische komaf is. Bij niet-kaukasiërs wordt de C282Y mutatie namelijk zelden of nooit aangetoond.<br>Ook voor ouders van C282Y homozygote patiënten kan genetisch onderzoek aangewezen zijn. Hoge leeftijd kan echter een reden zijn om hiervan af te zien.<br>Nieuw geïdentificeerde homozygoten dienen gevolgd te worden d.m.v. controle ijzerparameters iedere 3 jaar. Bij afwijkende waarden wordt behandeld conform adviezen in de module´ Behandeling bij Hemochromatose´. |

## Inleiding

*Deze module is nieuw in deze richtlijn.*

Hereditaire hemochromatose is, zoals de naam aangeeft, een erfelijke ziekte gebaseerd op een teveel aan ijzer. Dit teveel aan ijzer is goed te behandelen met eenvoudige therapie. Daarmee kan morbiditeit en mortaliteit in de toekomst voorkomen worden. De klachten waarmee een teveel aan ijzer zich in een vroege, reversibele fase m.b.t. morbiditeit, presenteert zijn aspecifiek of geheel afwezig, wat vroege herkenning bemoeilijkt. Eerstegraads familieleden hebben een hogere kans dan de gemiddelde bevolking op teveel aan ijzer. Screening (presymptomatisch onderzoek) van deze familieleden zou een vroege herkenning van HH kunnen vereenvoudigen en daarbij morbiditeit en mortaliteit kunnen voorkomen. Omdat teveel aan ijzer onder de 18

jaar bij HFE gerelateerde HH vrijwel is uitgesloten zijn screeningsadviezen alleen van toepassing bij personen die 18 jaar of ouder zijn. Onder eerste graadsverwanten wordt verstaan 'sibs' (broers en zussen), ouders en kinderen.

## Conclusies

| | |
|---|---|
| ZEER LAAG | Het risico op klinische hemochromatose bij familieleden van patiënten met hereditaire hemochromatose is verhoogd, maar de hoogte van dit risico is niet goed bekend.<br><br>*Aleman, 2011; Bulaj, 2000; Elmberg, 2013; Jacobs, 2007; Jacobs, 2009; McCune, 2006; Nelson, 2001; Watkins, 2008(37, 140, 225, 226, 229, 230, 232, 233)* |

## Samenvatting literatuur

*Beschrijving studies*
Van 14 artikelen werd de volledige tekst bestudeerd. Tabellen met studiekarakteristieken van de beoordeelde studies zijn te vinden bij de aanverwante producten.(37, 118, 119, 140, 225-234)
Het artikel van Adams et al. bleek een case report met opinion paper te zijn in plaats van een systematisch opgezet onderzoek en werd daarom geëxcludeerd.(119) De studie van El-Serag et al. was een kosteneffectiviteitsstudie waarbij verschillende screeningsstrategieën werden geëvalueerd. Hierbij werd niet gekeken naar het risico op morbiditeit; daarom werd ook dit artikel bij bestudering van de volledige tekst geëxcludeerd.(227) De systematische reviews van Jin et al. en Rasmussen et al. bleken niet aan te sluiten bij de uitgangsvraag en zijn na bestudering van de volledige tekst alsnog geëxcludeerd.(234) (231)
Er bleven na selectie op basis van de volledige tekst van het artikel 10 artikelen over voor beantwoording van de uitgangsvraag.(37, 118, 140, 225, 226, 228-230, 232, 233)

*Kwaliteit van het bewijs*
Een samenvatting van de kwaliteit van bewijs per uitgangsvraag is te vinden bij de aanverwante producten. De kwaliteit van de evidence is zeer laag. Er is een grote kans op vertekening van de resultaten in de bestudeerde studies, bijvoorbeeld vanwege de retrospectieve of de niet vergelijkende opzet. Bovendien werd in een aantal studies de methodologie beperkt beschreven, zodat niet gecontroleerd kan worden hoe de kwaliteit van de studie is. Ook is er soms sprake van vertekening door selectie, omdat een deel van de patiënten in de studie niet het vervolgonderzoek (=screening/presymptomatisch onderzoek) heeft gehad. Ook is er in een aantal studies sprake van onderzoek in niet-kaukasische populaties, zodat de resultaten mogelijk niet extrapoleerbaar zijn naar de Nederlandse situatie. Er is dus sprake van indirect bewijs.

*Inhoudelijk resultaat*
Een meta-analyse van de gevonden resultaten was niet mogelijk, vanwege sterke heterogeniteit in de opzet van de studies.
Acton et al. onderzochten 526 specimens van patiënten die verwezen waren voor genetisch onderzoek. Dit betrof retrospectief onderzoek onder een geselecteerde groep patiënten, waarbij de auteurs concludeerden dat testen op HFE-mutaties zinvol is bij familie van patiënten met HH om HH bij familie te kunnen ontdekken.

Inderdaad vinden de onderzoekers dat genmutaties in HFE-genen bij familieleden van patiënten meer voorkomen dan bij de algemene bevolking, maar over morbiditeit bij die familieleden doen de onderzoekers geen uitspraak.(118)
In het onderzoek van Aleman et al. werden de symptomen en prognose van patiënten met HH onderzocht, waarbij onderscheid werd gemaakt in de wijze van ontdekken van de hemochromatose: bij reguliere check-up, vanwege familiescreening, vanwege een leveraandoening, vanwege artralgie of vanwege overige symptomen. De groep patiënten bij wie de HH via familie screening aan het licht was gekomen kende een lagere mortaliteit in vergelijking met de andere groepen, ook was er sprake van minder mortaliteit ten gevolge van leveraandoeningen in vergelijking met de groep die vanwege leveraandoeningen was gediagnostiseerd. Mogelijk is er hierbij wel sprake van leadtime bias.(225)
Bulaj et al. vergeleken symptomen en de conditie van patiënten met HH met die van hun familieleden. In dit onderzoek onder 184 patiënten en 214 homozygote familieleden van patiënten werd gevonden dat de transferrinesaturatie bij mannen vaak vergelijkbaar was. Bij vrouwen was de transferrinesaturatie bij familieleden lager dan bij patiënten. Teveel aan ijzer in de lever en cirrose kwamen het meest voor bij patiënten met klinische symptomen, maar kwamen ook voor bij familieleden.(226)
Elmberg et al. bepaalden de morbiditeit ten gevolge van artropathie bij patiënten met HH en hun verondersteld heterozygote familieleden en vergeleken dit met de algemene bevolking. Hierbij includeerden zij 3531 patiënten, 11.794 eerstegraads verwanten, 1305 partners van patiënten en bij elke groep 10 keer zoveel gematchte controles. Bij patiënten met hereditaire hemochromatose was er een verhoogde kans op alle vormen van artritis en gewrichtsvervangende ingrepen. Bij eerstegraads verwanten (verondersteld heterozygoot) en partners van patiënten werd er geen enkel verhoogd risico vastgesteld.(37)
Gleeson et al. onderzochten symptomen en signalen van hemochromatose bij 209 C282Y homozygote volwassenen, die geïdentificeerd werden via familieonderzoek. Zij vonden dat het serum ferritine bij 53% van de mannen en bij 29% van de vrouwen verhoogd was. Een verhoogde transferrine saturatie index werd gevonden bij 58% van de mannen en bij 46% van de vrouwen. Afwijkingen in leverfuncties werden gezien bij 32% van de mannen en 6% van de vrouwen. Bij een beperkt deel van de patiënten werd een leverbiopt gedaan (waarschijnlijk op indicatie). Bij 42% van deze biopten werd er histologisch leverstapeling in de lever vastgesteld.(228)
Jacobs et al. publiceerden een onderzoek waarin zij determinanten identificeerden die van invloed waren op een teveel aan ijzer bij eerstegraads verwanten van C282Y homozygote patiënten met hereditaire hemochromatose. In dit onderzoek werden 224 patiënten, 428 broers en zussen, 241 kinderen en 66 ouders van patiënten geïncludeerd. Een verhoogde transferrinesaturatie werd gevonden bij 93% van de patiënten, 33% van de broers en zussen, 25% van de kinderen en 20% van de ouders van patiënten. Een verhoogd serumferritine werd gezien bij 86% van de patiënten, 36% van de broers en zussen, 17% van de kinderen en 27% van de ouders van patiënten. Er werd een statistisch significante relatie tussen het genotype en verhoogde transferrinesaturatie bij eerstegraads familieleden gevonden voor de volgende mutaties: C282Y homozygoot en C282Y/H63D. Een statistisch significante relatie tussen genotype en verhoogde serumferritine concentratie werd eveneens gevonden bij de genotypen C282Y en C282Y/H63D.(230)
In een ander onderzoek van Jacobs et al. werd de morbiditeit en mortaliteit van eerstegraads verwanten van C282Y homozygote patiënten met hereditaire hemochromatose vergeleken met die van de algemene bevolking. In dit onderzoek werden 735 eerstegraads verwanten van patiënten vergeleken met 735 personen uit de algemene bevolking. Zij vonden een slechtere algemene gezondheid, een hoger gebruik van medicatie gerelateerd aan HH (bijv. antireumatica) en meer aan HH gerelateerde aandoeningen bij eerstegraads

familieleden dan bij de algemene bevolking. Ook werd een hoger aantal personen met verhoogde transferrinesaturatie en verhoogd serumferritine gevonden bij deze groep. Een verschil in mortaliteit werd niet gezien.(229)
Mc Cune et al onderzochten de relatieve bijdrage van HFE, andere genetische factoren en exogene factoren op teveel aan ijzer bij 56 C282Y homozygote patiënten en 165 eerstegraads verwanten. Bij verwanten van patiënten bleek C282Y homozygotie de grootste risicofactor voor teveel aan ijzer. Bij compound heterozygoten was er een grotere kans op diabetes, hypertensie en hartziekten dan bij mensen zonder mutatie. Eer werd geen relatie gevonden tussen de mate van teveel aan ijzer en de ernst van de morbiditeit. De auteurs concluderen dat C282Y sterk gerelateerd is aan teveel aan ijzer, maar een lage klinische penetrantie heeft.(232)
Nelson et al. onderzochten de kans op ziekte bij familieleden van patiënten met hereditaire hemochromatose. In dit onderzoek werden 279 homozygote broers en zussen van patiënten, 1265 niet-homozygote broers en zussen en 1338 partners van patiënten geïncludeerd. Zij vonden bij homozygote broers en zussen een hogere kans op diabetes, artritis en hepatoom. Er werd geen statistisch significante relatie gevonden met het optreden van kanker, hartaandoeningen en een beroerte.(233)
Watkins et al. ten slotte onderzochten de biochemische en klinische penetrantie van hereditaire hemochromatose bij eerstegraads familieleden van patiënten met HH. Bij deze familieleden was genetische hemochromatose vastgesteld. In deze studie werden 63 patiënten geïncludeerd, waaruit duidelijk werd dat de biochemische penetrantie weliswaar hoog, maar de klinische penetrantie laag is.(140)

## Zoeken en selecteren

Voor deze uitgangsvraag is in Medline gezocht naar literatuur op 8 november 2016. De literatuur is vervolgens geselecteerd op basis van onderwerp (sluit het artikel aan bij de uitgangsvraag?) en studiekenmerken (ten minste systematisch opgezet onderzoek). De volledige literatuursearch en literatuurselectie zijn weergegeven in de zoekverantwoording.

## Overwegingen

Diverse studies laten zien dat er voor C282Y homozygoten een verhoogde kans is op biochemische afwijkingen en op klachten. Hoe groot deze kans is, is moeilijk aan te geven.
De geschatte kans op een ernstige complicatie zoals levercirrose bedraagt voor C282Y homozygoten 4%, dus voor broers en zussen van een homozygoot a priori 1% (1/4 x 4%). Voor ouders of kinderen is de a priori kans minimaal 0,2%.(235). De EMQN die in 2016 eenzelfde studie publiceerde komt tot dezelfde conclusie.(114)
Publicaties die zijn verschenen sinds de vorige versie van de richtlijn laten zien dat compound heterozygotie alleen niet voldoende is om klinische verschijnselen te krijgen, maar dat het ontstaan daarvan afhankelijk is van andere factoren zoals metabool syndroom en alcoholgebruik. Daarom wordt familieonderzoek naar compound heterozygotie niet meer aanbevolen.(114)

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Logistiek familieonderzoek bij Hemochromatose

## Uitgangsvraag

Hoe directief en door wie moeten familieleden van patiënten met hereditaire hemochromatose en C282Y homozygotie worden benaderd?

Hoe is de follow-up bij familieleden met een positieve uitslag van het familieonderzoek?

## Aanbeveling

| | |
|---|---|
| Geen gradering | Met patiënten met hereditaire hemochromatose en C282Y homozygotie dienen erfelijkheidsaspecten en familieonderzoek te worden besproken (zie voor andere mogelijkheden de overwegingen bij deze module). Zo nodig kan verwezen worden naar een afdeling klinische genetica. Familieleden zouden door de patiënt zelf geïnformeerd moeten worden over de mogelijkheid van onderzoek naar de aanleg voor HH, in eerste instantie door middel van DNA onderzoek.<br>Bij alle nieuw geïdentificeerde homozygoten dient onderzoek naar teveel aan ijzer te worden gedaan door middel van bloedonderzoek.<br>Indien er geen afwijkingen zijn, dient dit iedere 3 jaar te worden herhaald. |

## Overwegingen

*Deze module is afkomstig uit de richtlijn 2007, en beperkt herzien zonder systematisch literatuuronderzoek.*

Er kan voor gekozen worden om de proband (eerste familielid gediagnosticeerd met homozygote C282Y HH) de familieleden te laten informeren met het advies om zich bij de huisarts te melden om onderzoek te verrichten naar de aanleg voor HH. Het lijkt zinvol om de proband enige hulp te bieden door gezamenlijk een inventarisatie te maken van de eerstegraads familieleden die benaderd zouden moeten worden en hun huisartsen, en een brief met algemene informatie mee te geven c.q. te sturen naar die familieleden en een informatiebrief naar hun huisartsen. De logistiek voor dergelijk familieonderzoek is beschikbaar op een afdeling klinische genetica waarover ieder academisch ziekenhuis beschikt. De genetisch consulenten van deze afdelingen hebben expertise in het verrichten van dit type onderzoek. De meeste grote en middelgrote perifere ziekenhuizen hebben tegenwoordig spreekuren die worden gehouden door klinisch genetici en genetisch consulenten uit de academische ziekenhuizen waardoor de praktische bereikbaarheid voor vrijwel iedere patiënt en zijn of haar familie uitstekend is. Eventueel kan de huisarts van een familielid zelf DNA onderzoek inzetten. De interpretatie van het onderzoek is eenvoudig. Alleen wanneer het familielid C282Y homozygoot blijkt te zijn dient hij/zij te worden verwezen naar een internist/hematoloog of afdeling klinische genetica voor verder familieonderzoek (als nieuwe proband met nieuwe eerstegraads verwanten). Bij alle andere uitslagen zoals heterozygotie C282Y of homozygoot normaal hoeft geen vervolgonderzoek bij het familielid of zijn ouders/kinderen plaats te vinden. Alle nieuw geïdentificeerde homozygoten krijgen het advies om onderzoek naar teveel aan ijzer te laten verrichten. Indien er geen afwijkingen zijn dient dit onderzoek iedere 3 jaar te worden herhaald. Dit onderzoek (ferritine, TSAT) kan door de huisarts worden verricht. De patiënt dient zich iedere 3 jaar bij de huisarts te melden voor bloedonderzoek van ferritine en transferrinesaturatie. Wanneer de waardes normaal zijn komt

patiënt 3 jaar later terug voor herhaling van het onderzoek. Wanneer TSAT en eventueel ferritine verhoogd zijn dient de patiënt te worden verwezen naar een internist, internist-hematoloog of MDL-arts voor verdere controles c.q. behandeling.
Voor het afsluiten van bijvoorbeeld levensverzekeringen of arbeidsongeschiktheidsverzekeringen mag de verzekeraar in bepaalde omstandigheden vragen of de betrokkene erfelijkheidsonderzoek heeft laten verrichten. Nu DNA onderzoek mogelijk is, maakt dit de situatie voor familieleden van een HH patiënt in alle gevallen gunstiger. Vroeger was er in theorie voor ieder familielid een verhoogde kans om HH te krijgen. Nu kunnen de personen die de aanleg hebben, worden geïdentificeerd. Voor hen is er eenvoudige preventieve behandeling beschikbaar. Voor de familieleden die de aanleg niet hebben, is een verhoogd risico uitgesloten. In vergelijking met de tijd dat er nog geen DNA onderzoek mogelijk was, lijkt de situatie met betrekking tot het te verzekeren risico dus verbeterd, omdat de kans voor familieleden om klachten van HH te krijgen kan worden verkleind. Omdat teveel aan ijzer onder de 18 jaar bij HH vrijwel is uitgesloten zijn screeningsadviezen alleen van toepassing bij personen die 18 jaar of ouder zijn.

Kosten
Wanneer DNA onderzoek naar de aanleg voor HH wordt ingezet, via de huisarts, internist/hematoloog of via een afdeling genetica, zullen de kosten daarvan ten laste van de patiënt komen zodat het eigen risico van de patiënt zal worden aangesproken. Het DNA onderzoek in de academisch genetische laboratoria kent een tarief van 516,49 Euro (eind 2017). Sommige laboratoria in perifere ziekenhuizen bieden dit onderzoek aan voor een lagere prijs.
Alleen met DNA onderzoek kan definitief worden bepaald of iemand wel of niet de aanleg voor HH heeft. Wanneer de patiënt goed geïnformeerd is over de kans op klinische verschijnselen zou deze er uit oogpunt van kostenbesparing voor kunnen kiezen om in plaats van DNA onderzoek ijzerparameters te laten bepalen door de huisarts. Dergelijk onderzoek kost ongeveer 15 Euro. Dit zal dan wel iedere 3 jaar moeten worden herhaald. Wanneer dit afwijkend is kan alsnog voor genetisch onderzoek worden gekozen.
Wanneer een C282Y homozygote patiënt twee of meer kinderen heeft is het kosteneffectief om de partner te testen op dragerschap van de C282Y mutatie. Als de partner geen drager is hoeft bij de kinderen geen onderzoek te worden verricht omdat er dan geen kans is op C282Y homozygotie.

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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# Orgaanschade bij Hemochromatose

## Uitgangsvraag

Wat is de kans op orgaanschade (m.n. de lever) bij het stellen van de diagnose HH en zijn er factoren die hierop van invloed zijn (prognostisch), (bijv. ferritine <1000 µg/l en bij ferritine > 1000 µg/l, alcoholgebruik, overgewicht, virale infecties) en hoe toon je die aan (echo, MRI, fibroscan, leverbiopsie, virusserologie)?

Wat is de kans op orgaanschade als gevolg van HH en hoe stel je deze vast? Hoe dient follow up te geschieden na het stellen van orgaanschade?

P Patiënten met diagnose hereditaire hemochromatose
I -
C -
O Kans op eindorgaanschade (levercirrose, hepatocellulair carcinoom) en prognostische factoren

Wat te doen met patiënten bij wie schade is vastgesteld en hoe moet de follow-up dan geregeld zijn?

Welke follow up dient er gedaan te worden, indien er sprake is van orgaanschade als gevolg van hereditaire hemochromatose?

P Patiënten met hereditaire hemochromatose en eindorgaanschade
I Specifieke follow-up
C -
O Progressie eindorgaanschade (morbiditeit en/of mortaliteit door eindorgaanschade (bijv. hepatocelulair carcinoom en gedecompenseerde levercirrose, ook schade aan gewrichten en hart)

De setting voor deze uitgangsvraag is de tweedelijns gezondheidszorg in Nederland.

## Aanbeveling

| | |
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| Sterk | Wanneer de diagnose hereditaire hemochromatose is gesteld wordt geadviseerd op orgaanschade te onderzoeken middels klinische en niet-invasieve testen. Met name bij een ferritine >1000 µg/l wordt extra aandacht geadviseerd voor het uitsluiten van leverfibrose en -cirrose. |

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| Sterk | Bij patiënten met cirrose als gevolg van hereditaire hemochromatose wordt screening op hepatocellulair carcinoom geadviseerd middels echografie van de lever, conform de richtlijnen van de AASLD en de EASL. Er is geen plaats meer voor standaard alfafoetoproteïne bepaling. Wanneer er verdenking is op orgaanschade van de lever, zoals een cirrose dan wel een andere primaire leverziekte, is verwijzing naar de MDL-arts geïndiceerd. |

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| Zwak | Er is onvoldoende conclusief bewijs dat hereditaire hemochromatose kan leiden tot artropathie. Desondanks wordt alertheid op hereditaire hemochromatose als mogelijke oorzaak geadviseerd met name bij artropathie op jonge leeftijd en artropathie van de MCP (2e tot 5e straal) gewrichten. |

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| Zwak | Hoewel sterk wetenschappelijk bewijs ontbreekt voor associatie tussen hereditaire hemochromatose en een aantal aandoeningen zoals diabetes mellitus en schildklierziekten, wordt de clinicus geadviseerd om alert te zijn op klachten/verschijnselen die hierbij kunnen passen en zo nodig hier diagnostiek naar in te zetten. |

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|---|---|
| Zwak | Er zijn geen specifieke adviezen t.a.v. follow-up en behandeling van orgaanschade die is opgetreden als gevolg van hereditaire hemochromatose. Verwezen wordt naar de desbetreffende richtlijnen. |

## Inleiding

*Deze module is nieuw in deze richtlijn.*

Hereditaire hemochromatose is een ziekte die wordt gekarakteriseerd door progressieve ijzerstapeling die op termijn kan leiden tot orgaanschade, met name levercirrose. Doel van vroegtijdige diagnose en behandeling is het voorkomen dan wel beperken van orgaanschade.
Aanvankelijk werd hemochromatose beschreven als hypertrofische levercirrose bij diabetes mellitus.(69) De term ‘hemochromatose’ werd door Von Recklinghausen in 1880 geïntroduceerd.(70) Sheldon suggereerde dat het om een ‘inborn error of metabolism’ zou gaan.(71) Lange tijd werd hemochromatose geassocieerd met ‘diabète bronzé’: cirrose, diabetes en huidpigmentatie. Sinds 1964 werden gewrichtsklachten ook vaak genoemd als uiting van hemochromatose.(36) In 1975 toonde de groep van Simon aan dat het inderdaad een erfelijke aandoening was.(72) In 1996 werden de mutaties in het HFE gen door Feder et al. beschreven.(3)
Onze kijk op de diagnose hereditaire hemochromatose is in de loop der jaren sterk veranderd. Inmiddels is bekend dat de meeste mensen met het genotype homozygote C282Y uiteindelijk geen ijzerstapeling en dus ook geen orgaanschade zullen ontwikkelen. Tevens is er veel discussie over de symptomatologie van hereditaire hemochromatose. Onderzoeken naar het voorkomen van symptomen bij patiënten met hereditaire hemochromatose worden sterk bepaald door de samenstelling van de studiepopulatie. De studies voor 1996 onderzochten met name patiënten met klachten en verschijnselen zonder HFE diagnostiek. Sinds de betreffende mutatie in het HFE gen bekend is, heeft er ook meer onderzoek onder de algemene bevolking plaatsgevonden. Hierbij bleek dat het risico op het ontwikkelen van klachten en verschijnselen van hereditaire hemochromatose veel lager is dan aanvankelijk werd gerapporteerd. Al in de vorige richtlijn van 2007 werd besproken dat symptomen/verschijnselen afzonderlijk of in combinatie niet voorspellen voor de diagnose hereditaire hemochromatose.

## Conclusies

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| ZEER LAAG | Een hoge lever ijzerconcentratie lijkt bij nieuw gediagnostiseerde patiënten met hereditaire hemochromatose geassocieerd met het optreden van fibrose.<br><br>*Adams, 2006(236)* |

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|---|---|
| ZEER LAAG | Bij patiënten met hereditaire hemochromatose en cirrose is de kans op het krijgen van een hepatocellulair carcinoom verhoogd.<br><br>*Beaton, 2006(255)* |

| | |
|---|---|
| ZEER LAAG | Er is geen solide bewijs voor een causaal verband tussen hereditaire hemochromatose en specifieke symptomen of aandoeningen (waaronder diabetes mellitus, gewrichtsklachten, schildklieraandoeningen, hart- en vaatziekten, seksuele dysfunctie), behalve leverfibrose/cirrose.<br><br>*Asberg, 2002; Donnelly, 2010; Ellervik, 2007; Moczulski, 2001; Rong, 2012; Ross, 2003; Shizukuda, 2006(237, 240, 241, 248, 250) (245, 247)* |

| | |
|---|---|
| | Het is niet bekend welke follow-up het meest effectief is bij patiënten met hereditaire hemochromatose indien eindorgaanschade is vastgesteld. |

## Samenvatting literatuur

*Beschrijving studies*
Eerste uitgangsvraag: Van 21 artikelen werd de volledige tekst bestudeerd. Tabellen met studiekarakteristieken van de beoordeelde studies zijn te vinden bij de aanverwante producten.(179, 214, 236-254)
Een aantal artikelen is na bestudering van de volledige tekst van het artikel afgevallen omdat het artikel niet aansloot bij de uitgangsvraag.(179, 214, 238, 239, 242-244, 246, 252-254) Twee artikelen van Shizukuda et al. vielen af omdat zij dezelfde patiëntenpopulatie beschreven als een derde artikel van Shizukuda et al.(249, 251)
Er bleven na selectie op basis van de volledige tekst van het artikel 10 artikelen over voor beantwoording van de uitgangsvraag.(236, 237, 240, 241, 244, 245, 247, 248, 250, 252)

Tweede uitgangsvraag: Van 2 artikelen werd de volledige tekst bestudeerd. Tabellen met studiekarakteristieken van de beoordeelde studies zijn te vinden bij de aanverwante producten.(255, 256)
Het artikel van Gulati et al. bleek bij bestudering van de volledige tekst een narratieve opinion paper te zijn en werd dus geëxcludeerd.(256) Derhalve bleef na selectie op basis van de volledige tekst van het artikel alleen de studie van Beaton et al. over voor beantwoording van de uitgangsvraag.(255)

*Kwaliteit van het bewijs*
Een samenvatting van de kwaliteit van bewijs per uitgangsvraag is te vinden bij de aanverwante producten. De kwaliteit van het bewijs was zeer laag, omdat er sprake was van een grote kans op vertekening in de geïncludeerde studies (bijvoorbeeld ten gevolge van selectieve rapportage en beperkte omschrijving van de

methodologie). Ook was er sprake van indirect bewijs omdat verschillende etnische groepen zijn onderzocht, waarbij er twijfel is over de generaliseerbaarheid van de resultaten. Ook werden er grote betrouwbaarheidsintervallen gerapporteerd, hetgeen imprecisie impliceert.

*Inhoudelijk resultaat*

**Leverziekte**

Adams et al. onderzochten of metabool syndroom, hepatische steatose of steatohepatitis geassocieerd zijn met hepatische fibrose bij patiënten met hereditaire hemochromatose. In deze studie werden 86 nieuw gediagnostiseerde patiënten geïncludeerd. Allen ondergingen ook een leverbiopt. In 27% was er sprake van een metabool syndroom. Op basis van het leverbiopt was er in 50% sprake van een steatosis hepatis, in 21% steatohepatitis en in 44% significante fibrose. Er werd geen statistisch significant verband aangetoond tussen het metabool syndroom en fibrose. Er werd een sterke associatie gezien tussen de lever ijzerconcentratie en het optreden van fibrose. De lever ijzerconcentratie was hoger bij patiënten met fibrose.(236)
In het onderzoek van Beaton et al. werden 95 patiënten met hereditaire hemochromatose en cirrose geïncludeerd. De mediane follow-up bedroeg 9,2 jaar (range 0-30 jaar). De auteurs rapporteerden dat 20% van de patiënten met HH en cirrose een hepatocellulair carcinoom kreeg. Als factoren die een statistisch significante relatie hadden met overlijden noemden zij: mannelijk geslacht, hoge ferritineconcentratie, transferrinesaturatie, alanine aminotransferase concentratie, bilirubineconcentratie en creatinineconcentratie. Ook werd een significant verband gezien tussen INR, lever ijzerindex, Child Pugh score en hepatocellulair carcinoom.(255)

**Gewrichtsklachten**

Donnelly et al. vergeleken dragerschap van hemochromatosegenen bij patiënten die een reumatologie- en gewrichtsvervangingskliniek bezochten met een lokale controlepopulatie. In dit onderzoek werden 161 patiënten en 340 controles geïncludeerd. Bij de patiënten waren enkele personen met een verhoogde transferrine saturatie of een verhoogde serumferritine concentratie. Patiënten bleken vaker drager te zijn van een C282Y mutatie.(240)
In het onderzoek van Ross et al. werd de associatie tussen HFE genmutaties en artrose onderzocht. In dit onderzoek werden 176 patiënten met artrose van de hand en 2.138 controlepersonen uit de algemene populatie geïncludeerd. Er bleek geen verschil te zijn tussen patiënten en controles voor wt/wt, H63D/wt, H63D/H63D en C282Y/C282Y. Wel bleek er bij patiënten vaker sprake te zijn van C282Y/wt, vooral bij personen > 65 jaar. Het is niet bekend of de dragers van de genmutaties bekend waren met de diagnose hemochromatose.(248)

**Diabetes mellitus**

Moczulski et al. onderzochten of er een associatie is tussen C282Y en H63D mutaties en diabetische nefropathie bij patiënten met type 2 diabetes. Zij includeerden daarvoor 563 patiënten met type 2 diabetes en vergeleken deze met gezonde controles uit een lokale fabriek. Er bleek verhoogd risico op C282Y mutatie bij patiënten met diabetes. Bij patiënten met een H63D mutatie bleek er juist een associatie met diabetische nefropathie. Het is niet bekend of de patiënten in deze studie reeds bekend waren met de diagnose hereditaire hemochromatose.(245)
Rong et al. publiceerden een systematische review waarin zij het verband tussen mutatie in HFE-genen en het risico op diabetes mellitus onderzochten. In deze review werden 23 studies met in totaal 5.528 patiënten met diabetes mellitus en 6.920 controles geïncludeerd. Er bleek geen relatie te zijn tussen C282Y mutatie en het

optreden van diabetes mellitus. Wel werd er een verband te zijn tussen H63D mutatie en het optreden van diabetes mellitus (OR: 1,20; 95% BI: 1,03-1,41).(247)

**Overig (waaronder cardiaal)**

Asberg et al. vergeleken met gegevens uit een bevolkingsonderzoek de morbiditeit van de 297 personen bij wie middels screening hereditaire hemochromatose (homozygoot C282Y) was ontdekt met die van een controlepopulatie. Er werd gebruik gemaakt van een vragenlijst, lichamelijk onderzoek en bloed onderzoek. Er bleek geen verschil te zijn in algemene gezondheid en mentale aandoeningen. De gescreende patiënten hadden minder vaak angina pectoris, maar vaker artrose, knieklachten, hypothyroïdie en gebruikten vaker thyroxine en antihypertensiva.(237)

In het prospectieve onderzoek van Ellervik et al. werd het risico van hereditaire hemochromatose op symptomatische carotiden atherosclerose, ischemische cerebrovasculaire aandoeningen en ischemische beroerte onderzocht. In dit onderzoek werden 701 patiënten met carotis atherosclerose en 2.777 controlepersonen geïncludeerd, en ook was er een prospectief onderzoek onder 9.178 personen uit de algemene bevolking. Uit dit onderzoek bleek geen significant verband tussen genotype en atherosclerose.(241)

Shizukuda et al. onderzochten of afwijkingen in de linkerventrikelfunctie gevonden kunnen worden bij asymptomatische patiënten met hereditaire hemochromatose. In dit patiënt-controle onderzoek werden onder meer 22 nieuw gediagnostiseerde patiënten met hemochromatose vergeleken met 21 gezonde controles. Voor de meeste onderzochte parameters bleek er geen verschil te zijn tussen de beide groepen. Wel was er bij patiënten een verhoging van de atriumcontractie die mogelijk vroeg herkenbaar zou zijn. (250)

Een meta-analyse van de data was niet mogelijk, vanwege te grote verschillen in opzet van de onderzoeken.

## Zoeken en selecteren

Voor deze uitgangsvraag is in Medline gezocht naar literatuur op 8 november 2016. De literatuur is vervolgens geselecteerd op basis van onderwerp (sluit het artikel aan bij de uitgangsvraag?) en studiekenmerken (ten minste systematisch opgezet onderzoek). De volledige literatuursearch en literatuurselectie zijn weergegeven in de zoekverantwoording.

## Overwegingen

Reeds in de oude richtlijn werd besproken dat de kwaliteit van bewijs laag is. Onderzoeken werden verricht voordat genetisch onderzoek beschikbaar was. Er werd geen eenduidige definitie van HH gehanteerd. Tevens was de methodologische kwaliteit veelal laag. Ook bij de huidige update van de literatuur is de kwaliteit van het bewijs zeer laag. De werkgroep heeft daarom, na het systematische literatuuronderzoek, gebruik gemaakt van ondersteunend bewijs uit de medische literatuur. Deze artikelen zijn niet via systematisch literatuuronderzoek verkregen, en worden ook niet op systematische wijze gerapporteerd, maar geven wel ondersteuning aan de gegeven aanbevelingen. Hieronder volgt derhalve nog extra aandacht voor twee specifieke orgaanschades: leverziekte en artropathie.

**Leverziekte**

Er zijn geen goede cijfers beschikbaar over hoeveel patiënten met hereditaire hemochromatose daadwerkelijk leverziekte en met name levercirrose hebben ontwikkeld. Hereditaire hemochromatose is zelden een indicatie voor levertransplantatie.(257, 258) De kans op levercirrose door HH is klein.(121, 150) Meerdere studies

beschrijven dat de kans op cirrose met name bij een ferritine < 1000 µg/l erg klein is.(150, 181, 182, 193, 259)
Levercirrose is een bekende risicofactor voor hepatocellulair carcinoom. Ook bij levercirrose als gevolg van hereditaire hemochromatose is dit aangetoond.(255, 260)
Leverschade wordt in eerste instantie onderzocht middels bloedonderzoek en echo van de lever. De gouden standaard voor het aantonen van leverfibrose of cirrose is het leverbiopt, met name bij patiënten zonder evidente cirrose op beeldvorming. De fibroscan kan een waardevol en bruikbaar alternatief zijn voor het leverbiopt, maar deze is nog niet voor deze indicatie gevalideerd.

**Gewrichtsklachten**
Gewrichtsklachten komen in de algemene bevolking veel voor. Deze klachten werden in het verleden bij hoge percentages HH patiënten gerapporteerd, tot 95 % toe (EASL).(106) Deze gegevens waren echter afkomstig uit patiëntengroepen die waren geselecteerd op basis van klachten, en veelal nog van vóór de ontdekking van het HFE-gen. Verder geldt voor alle publicaties dat er verschillende definities van de gewrichtsklachten worden gehanteerd: gewrichtspijn – artralgie – artrose - artropathie klinisch, dan wel radiologisch vastgesteld. Tevens zijn er verschillende manieren van dataselectie: zelf rapportering middels vragenlijsten, lichamelijk onderzoek, röntgenonderzoek en gewrichtsvervangende operaties.
Vanaf 1964 zijn er talloze publicaties verschenen over de gewrichtsklachten van patiënten met hereditaire hemochromatose.(36) Veel artsen die deze patiënten behandelen herkennen dit ook. Vaak worden de reeds boven genoemde studies van Beutler en Waalen geciteerd.(42, 261) Zij onderzochten een redelijk grote patiëntengroep en een uitgebreide controlegroep en toonden geen hogere prevalentie van klachten en verschijnselen die vaak met hereditaire hemochromatose in verband worden gebracht. De laatste jaren zijn nog enkele studies verricht, waarbij grote aantallen hereditaire hemochromatose patiënten en controlepersonen betrokken waren. De prevalentie van gewrichtsklachten werd onderzocht in beide groepen.(37-40, 262-266) In enkele publicaties werd gekeken naar het vóórkomen van gewrichtsvervangende operaties als maat voor de gewrichtsklachten.(37, 38, 40) Uit deze onderzoeken komt naar voren dat hereditaire hemochromatose patiënten 2 tot 9 keer meer kans hebben op gewrichtsklachten/-operaties dan controlepersonen. Het valt hierbij op dat bij de HH-patiënten deze klachten op jongere leeftijd optreden, en dat met name de MCP-gewrichten aangedaan zijn. De gewrichtsklachten treden vaak al op 8 – 9 jaar vóór het stellen van de diagnose hereditaire hemochromatose. Er zijn studies die een relatie van de gewrichtsklachten met de overmaat aan ijzer aangeven, maar andere, waarbij de gewrichtsklachten een vroeg optredend symptoom zijn, en de aanleiding vormen tot de diagnose hereditaire hemochromatose.
Gewrichtsklachten worden op geleide van klachten meestal behandeld met pijnstillers zoals paracetamol en NSAID's. Bij persisterende invaliderende klachten en radiologische gewrichtsschade kan verwijzing naar een orthopedisch chirurg overwogen worden voor eventuele gewrichtsvervangende chirurgie.

**Rationale**
Hereditaire hemochromatose is een systeemziekte en hoewel vaak goede data ontbreken, zijn er aanwijzingen dat hereditaire hemochromatose kan leiden tot ernstige orgaanschade, met name levercirrose. Vroege diagnose en behandeling zijn dan ook wenselijk. Derhalve is de commissie van mening dat een clinicus alert moet zijn en de diagnose waar nodig moet overwegen dan wel uitsluiten als verklaring voor orgaanschade. Er lijkt echter een spanningsveld te zijn tussen 'experience' en tegenstrijdige 'evidence' wat betreft symptomatologie. Dat betekent dat wanneer hereditaire hemochromatose wordt gediagnosticeerd, er niet altijd met zekerheid een causaal verband met klachten vastgesteld kan worden.

De commissie adviseert om bij de diagnose hereditaire hemochromatose de patiënt te onderzoeken op orgaanschade in eerste instantie op basis van klinische en niet-invasieve testen. Biochemisch onderzoek aangevuld door een echo van de lever is vaak voldoende als initieel onderzoek naar cirrose. Dit onderzoek kan aangevuld worden middels een leverbiopt om fibrose dan wel een vroeg stadium cirrose te onderkennen. De fibroscan is een veelbelovende techniek voor niet-invasief onderzoek naar fibrose/cirrose. De fibroscan is echter nog niet voldoende onderzocht dan wel gevalideerd voor hereditaire hemochromatose.(267-269) Met name bij nieuw gediagnosticeerde hereditaire hemochromatose patiënten met een ferritine >1000 µg/l, adviseert de commissie de diagnose levercirrose uit te sluiten.(150, 181, 182, 193, 259)
Levercirrose is een belangrijke risicofactor voor hepatocellulair carcinoom. Indien er sprake is van levercirrose op basis van hereditaire hemochromatose is screening op hepatocellulair carcinoom geïndiceerd conform de richtlijnen van de EASL en de AASLD middels halfjaarlijks echo lever.(106, 153) Er is geen plaats meer voor standaard alfafoetoproteïne in het screenen naar hepatocellulair carcinoom.
Er zijn geen data gevonden over hoe om te gaan met orgaanschade nadat de diagnose hereditaire hemochromatose is vastgesteld en adequate behandeling heeft plaatsgevonden. Op basis van de huidige gegevens is er geen indicatie om na diagnose en adequate behandeling van hereditaire hemochromatose te blijven controleren op orgaanschade. Indien er sprake is van orgaanschade zijn er geen aparte aanbevelingen vanuit de commissie. De commissie verwijst hiervoor naar de richtlijnen/protocollen voor elke afzonderlijke ziekte/aandoening.

## Verantwoording

Laatst beoordeeld : 28-10-2018
Laatst geautoriseerd : 28-10-2018

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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