Protocole National de Diagnostic et de Soins (PNDS)
Déficits du Cycle de l'Urée

Argumentaire

Filière de Santé Maladies Rares G2M

Mai 2021

Cet argumentaire a été élaboré par le centre de référence des Maladies Héréditaires du Métabolisme CHU Jeanne de Flandre Lille. Il a servi de base à l'élaboration du PNDS du Cycle de l'Urée.
Le PNDS est téléchargeable sur le site de la filière G2M
http://www.filiere-g2m.fr/

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Liste des abréviations

AAH : allocation aux adultes handicapés
ACS : aide à la complémentaire santé
AEEH : allocation d'éducation de l'enfant handicapé
AESH : accompagnant d'élève en situation de handicap (anciennement AVS)
AJPP : allocations journalières de présence parentale
ALD : affection de longue durée
AMM : acidémie méthylmalonique
ANC : apports nutritionnels conseillés
ANSM : agence nationale de sécurité du médicament et des produits de santé
AP : acidémie propionique
ARG1D : déficit en arginase 1
ASLD : déficit en argininosuccinate lyase/argininosuccinylurie
ASSD : déficit en argininosuccinate synthétase/citrullinémie de type I
ATU : autorisation temporaire d'utilisation
AVS : auxiliaire de vie scolaire
CAVAD : déficit en anhydrase carbonique Va
CCMR : centre de compétence maladies rares
CDAPH : commission des droits et de l'autonomie des personnes handicapées
CEAM : carte européenne d'assurance maladie
CNAMTS : caisse nationale d'assurance maladie des travailleurs salariés
CPDPN : centre pluridisciplinaire de diagnostic prénatal
CPS1D : déficit en carbamyl phosphate synthétase 1
CRMR : centre de référence maladies rares
CVVHDF : hémodiafiltration continue veino-veineuse
DADFMS : denrées alimentaires destinées à des fins médicales spéciales
DCI : dénomination commune internationale
DGP : diagnostic prénatal
ESAT : établissement et service d'aide par le travail
ETP : éducation thérapeutique du patient
FAM : foyer d'accueil médicalisé
HD : hémodialyse
i.m : intra-musculaire
i.v : intra-veineux
IRM : imagerie par résonance magnétique
KTC : cathéter central
MAS : maison d'accueil spécialisée
MDPH : maison départementale des personnes handicapées
MPR : médecine physique et de réadaptation
NAA : N-acétyl aspartate
NAGSD : déficit en N-acétylglutamate synthase
NE : nutrition entérale
NEDC : nutrition entérale à débit continu
NGS : « next-generation sequencing », le séquençage haut débit
ORNT1 : antiport ornithine-citrulline mitochondrial
OTCD : déficit en ornithine transcarbamylase

PAI : projet d’accueil individualisé
PCH : prestation de compensation du handicap
PEAtc : potentiels évoqués auditifs du tronc cérébral
PEV : potentiels évoqués visuels
PIRES : protocole inter régimes d'examens spéciaux
PNDS : protocole national de diagnostic et de soins
PPS : projet personnalisé de scolarisation
RNP : références nutritionnelles pour la population
RQTH : reconnaissance de la qualité de travailleur handicapé
SESSAD : service d’éducation spéciale et de soins à domicile
SMR : spectroscopie par résonance magnétique
SNG : sonde naso-gastrique
Syndrome triple H : syndrome d’hyperornithinémie-hyperammoniémie-homocitrullinurie
UCD : « Urea Cycle Disorders », Déficits du Cycle de l’Urée
VMO : vitamines, minéraux et oligo-éléments

Préambule

Le présent protocole national de diagnostic et de soins (PNDS) a pour objectif de présenter aux professionnels de santé la prise en charge optimale et le parcours de soins d'un patient atteint d'un déficit du cycle de l'urée. Il vise à leur donner les outils qui permettent d'évoquer et de confirmer le diagnostic, de prévenir les séquelles neurologiques, de poser les indications thérapeutiques, de définir les modalités et l'organisation du suivi.
Il s'agit d'un outil pragmatique auquel le médecin peut se référer pour la prise en charge de cette maladie, notamment au moment d'établir le protocole de soins avec le médecin conseil et le patient dans le cadre de l'admission en affection longue durée (ALD) n°17, relative aux maladies héréditaires du métabolisme.
Le PNDS ne peut cependant pas envisager tous les cas spécifiques, toutes les comorbidités, toutes les particularités thérapeutiques et tous les protocoles de soins hospitaliers, ni se substituer à la responsabilité individuelle du médecin vis-à-vis de son patient.

Le PNDS sur les déficits du cycle de l'urée a été élaboré selon la « méthode d'élaboration d'un protocole national de diagnostic et de soins pour les maladies rares » publiée par la Haute Autorité de Santé en 2012 (guide méthodologique disponible sur le site de la HAS : www.has-sante.fr). Le présent argumentaire comporte l'ensemble des données bibliographiques analysées pour la rédaction du PNDS.

Le projet de ce PNDS a été porté par le CRMR Maladies Héréditaires du Métabolisme (MHM) de l'Hôpital Jeanne de Flandre, CHU de Lille, sous l'égide de la filière G2M.

Le groupe de rédaction est composé de médecins pédiatre et adulte spécialisés, biochimistes, psychologues ainsi que des diététicien(ne)s expert(e)s dans la prise en charge de cette maladie. Chacun est issu d'un centre de référence ou de compétence en maladies héréditaires du métabolisme, et afilié à la filière G2M et à la Société Française des Erreurs Innées du Métabolisme (SFEIM).

Après analyse et synthèse de la littérature médicale et scientifique pertinente, les rédacteurs ont établi le plan et rédigé les chapitres d'une version préliminaire du PNDS. L'intégralité de cette version préliminaire a été relue et commentée entre rédacteurs lors de vioconférences afin d'aboutir à une version 1 du PNDS.

Cette version 1 a alors été soumise à un groupe de lecture multidisciplinaire et multiprofessionnel. Les déficits du cycle de l'urée étant des maladies rares, à prise en charge essentiellement hospitalière et nécessitant l'intervention de nombreux professionnels médicaux et paramédicaux, la composition du groupe de lecture a cherché à regrouper :

- des professionnels de santé de filières maladies rares G2M assurant le diagnostic et le suivi de ces pathologies dans leur pratique hospitalière, issus de régions différentes, de spécialités pédiatriques et adultes.

- des professionnels de santé de spécialités différentes intervenant dans la prise en charge du patient (réanimateur, biochimistes, pharmacien).

- un représentant de la médecine de ville.

- un représentant d'une association de patients.

Les relecteurs ont été réunis lors de 2 sessions de visioconférences et ont donné leur avis sur le fond et la forme du document, en particulier sur la justesse, la lisibilité et l'applicabilité du PNDS. Les

commentaires du groupe de lecture ont ensuite été analysés et discutés entre relecteurs et rédacteurs, afin d'intégrer les corrrections collégialement acceptées dans la version finale du PNDS.

Argumentaire

1 Stratégie de recherche bibliographique

Les déficits du cycle de l'urée ont fait l'objet de recommandations européennes en 2012 (méthodologie SIGN, Scottish Intercollegiate Guideline Network) par Häberle *et al* avec révisions en 2019 (méthodologie GRADE, Grading of Recommendations, Assessment, Development and Evaluation).
L'argumentaire du PNDS repose sur les recommandations révisées de 2019 :

Häberle J, Burlina A, chakrapani A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders : first revision. J Inherit Metab Dis. 2019;42:1192–1230

Ces recommandations s'appuyaient sur la bibliographie existante jusqu'en 2018. Une mise à jour de la littérature a donc été effectuée avec recueil des quelques articles publiés entre 2018 et mai 2020, notamment sur la base de données PUBMED, à partir des mots clés.

2 Synthèse bibliographique

2.1 Recommendations de bonnes pratiques

Tableau 1. Recommandations de bonne pratique

Auteur, année, référence, pays	Objectif	Stratégie de recherche bibliographique renseignée (oui/non)*	Recueil de l'avis des professionnels (oui, non, lesquels)	Recueil de l'avis des patients (oui, non)	Populations et techniques (ou produits) étudiées	Résultats (avec grade des recommandations si disponible)
Häberle J et al, 2019	Réévaluer les recommandations existantes, les mettre à jour et proposer de nouvelles recommandations pour le diagnostic et la prise en charge des patients atteint d'un déficit du cycle de l'urée	Oui Revue systématique de la littérature entre 2011 et 2018 Bases de données MEDLINE, Embase, bibliothèque Cochrane, Medlink et Orphanet ainsi que les sites internet des sociétés nationales et internationales pour les maladies métaboliques congénitales Méthodologies SIGN (*Scottish Intercollegiate Guideline Network*) et GRADE (*Grading of Recommendations, Assessment, Development and Evaluation*)	Oui Réunion d'un groupe d'établissement des recommandations (GER) : 17 experts internationaux en médecine métabolique, biochimie clinique, nutrition, néphrologie, et psychologie	Oui	Patients atteints d'un déficit du cycle de l'urée	**R1 (modérée)** : considérer un déficit du cycle de l'urée (à tout âge) en cas de détresse neurologique, de symptômes psychiatriques, d'insuffisance hépatique, de suspicion d'intoxication et en cas de DD (diagnostic différentiel ? abréviation à ajouter au début) d'une septicémie néonatale **R2 (forte)** : Toujours doser l'ammoniémie (attention aux recommandations pré-analytiques) en cas des conditions définies en R1 **R3 (modérée)** : En cas d'hyperammoniémie, doser AAS (abréviation à ajouter au début) et faire un profil des acylcarnitines et commencer le traitement d'emblée sans attendre les résultats **R4 (modérée)** : DD sepsis néonatal ! **R5 (modérée)** : Confirmation d'un déficit du cycle de l'urée par biologie moléculaire **R6 (forte)** : Diagnostic prénatal de préférence par analyse génétique moléculaire **R7 (modérée)** : Dépistage néonatal pose problème **R8 (modérée)** : Arrêter le catabolisme protidique et mise en route immédiate du traitement de détoxification de l'ammoniac **R9 (modérée)** : Préparation d'emblée d'une éventuelle épuration extracorporelle **R10 (faible)** : Chez l'adulte, considérer l'épuration extracorporelle en première ligne **R11 (forte)** : Hémodiafiltration à prioriser, transfusion déconseillée

						R12 (modérée) : Perfusion de serum glucosé polyionique à forte dose avec lipides (après avoir éliminé un trouble de la B-oxidation des acides gras). Limitation de la durée de l'arrêt d'apport en protéines (24-48h maximum ?) **R13 (modérée)** : Maintien essentiel d'un équilibre métabolique nutritionnel **R14 (modérée)** : Mélange des acides aminés essentiels est indispensable surtout en cas de tolérance protidique basse et prise de phénylbutyrate **R15 (modérée)** : ETP indispensable devant le traitement diététique au long court **R16 (faible)** : L'utilisation d'une nutrition entérale par sonde doit être évaluée **R17 (faible-modérée)** : Documents écrits sur le traitement destinés au personnel soignant **R18 (modérée)** : Chélateurs d'azote recommandés et prescrits au cas par cas **R19 (faible)** : En cas de grossesse, le benzoate de sodium est recommandé **R20 (modérée)** : Supplémentation en L-arginine et/ou L-citrullinine fortement recommandée. La L-arginine est contre-indiquée en cas de ARG1D **R21 (forte)** : L'utilisation de N-Carbamyl-L-glutamate est recommandée comme traitement de première ligne en cas de NAGSD **R22 (faible)** : La vaccination selon le schéma national est recommandée **R23 (opinion expert)** : Une chirurgie élective est programmée dans un CR MHM (avec fiche d'urgence) **R24 (modérée)** :

						Greffe hépatique à considérer en cas de mauvaise réponse/compliance thérapeutique, qualité de vie médiocre, sans atteinte neurologique **R25 (modérée/forte)** : La greffe hépatique doit se faire avant l'instauration d'une éventuelle atteinte neurologique (idéalement entre 3 et 12 mois de vie). Greffe hépatique recommandée devant une atteinte hépatique progressive et/ou décompensations récurrentes malgré TTT (abréviation à définir au début) médical optimal standard **R26 (opinion expert)** : Un monitoring clinique, biochimique et nutritionnel est essentiel **R27 (forte)** : Seuils recommandés : ammoniac <80 µmol/L, glutamine <1000 µmol/L, Arginine, EAA et BCAA (abréviations à définir au début) dans la fourchette des normes **R28 (modérée)** : IRM cérébrale (de préférence avec spectroscopie) recommandée **R29 (modérée)** : Evaluation du QI (abréviation à définir au début) et testing neuropsychologique recommandés **R30 (forte)** : Suivi psychologique et encadrement des familles fortement recommandés **R32 (forte)** : Traitement par carbamylglutamate exclusif en cas de NAGSD **R33 (forte)** : Pour l'OTCD, recours à la biologie moléculaire en première intention. Si non contributif, les essais enzymatiques sur plasma, foie ou intestin sont recommandés **R34 (forte)** :

						En cas de citrullinémie de type 1, la biologie moléculaire est fortement recommandée à but thérapeutique et prénatal **R35 (forte)** : En cas de ASLD, la recherche de l'ASA (abréviation à définir au début) est recommandée, Puis la biologie moléculaire pour le conseil génétique et à but prénatal **R36 (modérée)** : L'utilisation de la L-arginine à forte dose est déconseillée en cas de ASLD à risque des complications neurologiques et hépatiques **R37 (modérée)** : En cas de ARG1D, le traitement de routine (comme pour tout autre UCD) est recommandé, SANS utiliser d'arginine **R38 (modérée)** : En cas de syndrome de HHH, un régime hypoprotidique et une supplémentation par citrulline ou arginine sont recommandés
Summar M et al, 2008	Registre international	registre	oui		260 patients (1982-2003)	2/3 late onset UCDs

Häberle J, Burlina A, Chakrapani A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis. 2019;42:1192-1230.

Summar ML, Dobbelaere D, Brusilow S, Lee B. Diagnosis, symptoms, frequency and mortality of 260 patients with urea cycle disorders from a 21-year, multicentre study of acute hyperammonaemic episodes. Acta Paediatr. 2008;97(10):1420-1425.

2.2 Revues systématiques de la littérature

Tableau 2. Revues systématiques de la littérature

Auteur, année, référence, pays	Objectif	Stratégie de recherche renseignée (oui/non)*	Critères de sélection des études	Populations et techniques (ou produits) étudiées	Critères d'évaluation	Résultats et signification
Maillot F et al, 2016	Revue Française			Population UCD adulte	Etude rétrospective	Revue de la Prise en charge adulte en France
McKiernan PJ, 2021	1. moment d'indication de greffe 2. outcome 3. facteurs de prédiction de survie	Revue de l'expérience américaine de la greffe hépatique dans les maladies métaboliques	Etude américaine	5996 patients	Etude rétrospective (1987-2017)	Enfants : greffe x 6 Adulte : statut quo
Stepien KM, 2019	Revue internationale			Population UCD adulte	Etude rétropective	Approche d'un management systématique
Moreau C, 2019	Revue Langue Française			Femmes UCDs enceintes	Etude rétrospective	Suivi multidisciplinaire recommandée

∗ date de début et fin de la recherche, bases de données, mots clés renseignés

Maillot F, Blasco H, Lioger B, Bigot A, Douillard C. Diagnosis and treatment of urea cycle disorders in adult patients. Rev Med Interne. 2016;37:680-684.

Patrick J McKiernan, Armando Ganoza, James E. Squires et al. Evolving trends in liver transplant for metabolic liver disease in the United States. Liver Transpl 2019 Jun;25(6):911-921. doi: 10.1002/lt.25433

Stepien KM, Geberhiwot T, Hendriksz CJ, Treacy EP. Challenges in diagnosing and managing adult patients with urea cycle disorders. J Inherit Metab Dis. 2019 Nov;42(6):1136-1146. doi: 10.1002/jimd.12096. Epub 2019 May 8. PMID: 30932189.

Moreau C, Joueidi Y, Peoc'h K, Bardou-Jacquet E, Le Lous M, Bendavid C, Lavoué V, Damaj L, Dessein AF. Grossesse en cas de maladies métaboliques à expression hépatique : quels risques pour la mère et l'enfant ? Ann Biol Clin 2019 ; 77(6) : 605-18

2.3 Etudes cliniques

Tableau 3. Etudes cliniques						
Auteur, année, référence, pays	**Objectif**	**Méthodologie, niveau de preuve**	**Population**	**Intervention**	**Critères de jugement**	**Résultats et signification**
Husson MC et al, 2016	Etude rétrospective		61 patients UCD (2000-2010)			Benzoate de sodium est sûr et efficace
Boneh A, 2014	Etude rétrospective	Relecture des régimes alimentaires	28 patients			Recommandations sur des apports et compositions alimentaires

Husson MC, Schiff M, Fouilhoux A, Cano A, Dobbelaere D, Brassier A, Mention K, Arnoux JB, Feillet F, Chabrol B, Guffon N, Elie C, de Lonlay P. Efficacy and safety of i.v. sodium benzoate in urea cycle disorders: a multicentre retrospective study. Orphanet J Rare Dis. 2016 Sep 23;11(1):127.

Boneh A. Dietary protein in urea cycle defects: How much? Which? How? Mol Genet Metab. 2014 Sep-Oct;113(1-2):109-12. doi: 10.1016/j.ymgme.2014.04.009. Epub 2014 May 10. PMID: 24857408.

Annexe 1. Recherche documentaire et sélection des articles

Recherche documentaire

Sources consultées	Bases de données : Medline, Embase, the Cochrane Library, Medlink, Pubmed Sites internet : Orphanet
Période de recherche	2008-2020
Langues retenues	Anglais, Français
Mots clés utilisés	Troubles du cycle de l'urée, UCD, ammoniac, N-acétylglutamate synthase, carbamyl phosphates synthétase, ornithine carbamyl transférase, argininosuccinate synthétase, argininosuccinate lyase, arginase-1, syndrome d'hyperornithinémie-hyperammoniémie-homocitrullinurie (syndrome triple H)
Nombre d'études recensées	345
Nombre d'études retenues	8

Critères de sélection des articles

Les déficits du cycle de l'urée ayant fait l'objet de recommandations Européennes révisées en 2019 (Haberle et al, 2019), les articles les plus récents et les plus pertinents ont été retenus à partir de 2018.

Annexe 2. Liste des participants

Ce travail a été coordonné par le **Dr. Dries DOBBELAERE**, coordonnateur du Centre de Référence des Maladies Héréditaires du Métabolisme, CHU Lille, Hôpital Jeanne de Flandre, Lille

Ont participé à l'élaboration du PNDS :

Rédacteurs (ordre alphabétique)

- **Mme Valérie Barbier, psychologue, Paris.** Centre de Référence constitutif, Maladies Héréditaires du Métabolisme, CHU Necker-Enfants Malades
- **Mme Claire Belloche, diététicienne, Paris.** Centre de Référence constitutif, Maladies Héréditaires du Métabolisme, CHU Necker-Enfants Malades
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- **Pr Pascale de Lonlay, pédiatre métabolicien, Paris**. Centre de Référence constitutif, Maladies Héréditaires du Métabolisme, CHU Necker-Enfants Malades, AP-HP. Coordonnatrice de la filière maladies rares G2M.
- **Dr Dries Dobbelaere, pédiatre métabolicien, Lille**. Centre de référence constitutif, Maladies Héréditaires du Métabolisme, CHU Lille
- **Mr Laurent François, diététicen, Paris.** Centre de Référence constitutif, Maladies Héréditaires du Métabolisme, CHU Necker-Enfants Malades
- **Dr Apolline Imbard, biochimiste, Paris.** Laboratoire de Biochimie métabolomique, Centre de Référence constitutif, Maladies Héréditaires du Métabolisme, CHU Necker-Enfants Malades
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- **Dr Esther Noel,** Centre de Compétence Maladies Héréditaires du Métabolisme, CHU de Strasbourg
- **Mr William Perret, dieteticien, Bordeaux,** Centre de Compétence Maladies Héréditaires du Métabolisme, CHU Bordeaux
- **Dr Samia Pichard, pédiatre métabolicien, Paris.** Centre de Référence Maladies Héréditaires du Métabolisme, CHU Necker-Enfants Malades, AP-HP, 75015 PARIS.
- **Dr. Gustavo SOTO ARES, neuroradiologue, Lille**. CHU Lille

Groupe de travail multidisciplinaire de relecture.

- **Association les Enfants du Jardin**
- **Dr Jean-Baptiste Arnoux, pédiatre métabolicien, Paris.** Centre de Référence Maladies Héréditaires du Métabolisme, CHU Necker-Enfants Malades, AP-HP, 75015 PARIS.
- **Dr Juliette Bouchereau, pédiatre métabolicien, Paris.** Centre de Référence Maladies Héréditaires du Métabolisme, CHU Necker-Enfants Malades, AP-HP, 75015 PARIS.
- **Mme Anne Debrabander, dieteticienne.** Centre de référence constitutif, Maladies Héréditaires du Métabolisme, CHU Lille
- **Dr Roselyne Garnotel, Biochimiste, Reims.** Centre de Compétence constitutif, Maladies Héréditaires du Métabolisme, CHU Reims
- **Dr Marie Joncquel, biochimiste, Lille.** Centre de Référence constitutif, Maladies Héréditaires du Métabolisme, CHU Lille
- **Dr Benoit Leroy, medecin généraliste, Saint-Omer.**

Gestion des intérêts déclarés
Tous les participants à l'élaboration du PNDS sur les Déficits du Cycle de l'Urée ont rempli une déclaration d'intérêt disponible sur le le site internet http///www.filiere-g2m.fr/

Les déclarations d'intérêt ont été analysées et prises en compte, en vue d'éviter les conflits d'intérêts, conformément au guide HAS « Guide des déclarations d'intérêts et de gestion des conflits d'intérêts » (HAS, 2010).

Modalités de concertation du groupe de travail multidisciplinaire
Télé/visioconférences :
04/09/2020
25/11/2020
23/02/2021
02/03/2021
08/03/2021

Annexe 3. Références bibliographiques

1. Häberle J, Boddaert N, Burlina A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis. 2012;7:32.
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