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Guidelines

Kidney function monitoring in inflammatory bowel disease: The MONITORED consensus

Lucas Guillo[a,*], Pierre Delanaye[b,c], Martin Flamant[d], Lucile Figueres[e], Sabine Karam[f], Sandrine Lemoine[g], Alban Benezech[h], Anne-Laure Pelletier[i], Aurélien Amiot[j], Bénédicte Caron[k], Carmen Stefanescu[l], Gilles Boschetti[m], Guillaume Bouguen[n], Jean-François Rahier[o], Jean-Marc Gornet[p], Jean-Pierre Hugot[q], Joëlle Bonnet[p], Lucine Vuitton[r], Maria Nachury[s], Mathias Vidon[t], Mathieu Uzzan[l], Mélanie Serrero[a], Nina Dib[u,v], Philippe Seksik[w], Xavier Hebuterne[x], Jean-Philippe Bertocchio[y], Christophe Mariat[z], Laurent Peyrin-Biroulet[k]

[a] Department of Gastroenterology, University Hospital of Marseille Nord, University of Aix-Marseille, Marseille, France
[b] Department of Nephrology-Dialysis-Transplantation, University of Liège (ULiege), CHU Sart Tilman, Liège, Belgium
[c] Department of Nephrology-Dialysis-Apheresis, Hôpital Universitaire Carémeau, Nîmes, France
[d] Physiologie-Explorations Fonctionnelles, FHU APOLLO, Assistance Publique Hôpitaux de Paris, Hôpital Bichat-Claude Bernard, Université de Paris, CRI, INSERM F-75018, Paris, France
[e] Université de Nantes, Institut de Transplantation Urologie Néphrologie (ITUN), CHU Nantes, Service de néphrologie-immunologie clinique, CHU de Nantes, France
[f] Division of Nephrology and Hypertension, Saint-George Hospital University Medical Center, Beirut, Lebanon
[g] Service de Néphrologie, dialyse, hypertension et exploration fonctionnelle rénale, Hôpital Edouard Herriot, Lyon, France
[h] Departement of Gastroenterology, Henri Duffaut Hospital, Avignon, France
[i] Departement of Gastroenterology, Bichat Hospital, APHP, Paris, France
[j] Department of Gastroenterology, Groupe Hospitalier Henri Mondor-Albert Chennevier, APHP, EC2M3-EA7375, University of Paris Est Créteil, Créteil, France
[k] Department of Gastroenterology and Inserm NGERE U1256, University Hospital of Nancy, University of Lorraine, Vandoeuvre-lès-Nancy, France
[l] Department of Gastroenterology, IBD unit, Beaujon Hospital, APHP, Clichy, France
[m] Department of Gastroenterology, Hospices Civils de Lyon, Lyon-Sud Hospital, Pierre Bénite, and INSERM U1111 - CIRI, Lyon, France
[n] Department of Gastroenterology, Centre Hospitalier Universitaire Pontchaillou, Rennes, France
[o] Department of Gastroenterology, CHU UCL Namur, Yvoir, Belgium
[p] Department of Gastroenterology, Saint-Louis Hospital, APHP, Paris, France
[q] Department of Pediatric Gastroenterology, Hôpital Universitaire Robert Debré, Assistance Publique Hôpitaux de Paris, Université de Paris, Paris, France
[r] Department of Gastroenterology, Besancon University Hospital, Besancon, France
[s] Univ, Lille, Inserm, CHU Lille, U1286 - INFINITE - Institute for Translational Research in Inflammation, F-59000 Lille, France
[t] Department of gastroenterology, CHI Créteil, Créteil, France
[u] Hepato-Gastroenterology Department, Angers University Hospital, Angers, France
[v] HIFIH Laboratory, UPRES 3859, SFR 4208, Angers University, Angers, France
[w] Department of Gastroenterology, Centre de recherche Saint-Antoine, Sorbonne Université, APHP, Hôpital Saint-Antoine, Paris, France
[x] Gastroenterology and Clinical Nutrition, CHU of Nice, University Côte d'Azur, Nice, France
[y] Nephrology Department, Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France
[z] Service de Néphrologie, Dialyse, Transplantation Rénale, Hôpital Nord, CHU de Saint-Etienne, EA 3065, Université Jean MONNET, Saint-Etienne, France

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ABSTRACT

Background and aims: Patients with inflammatory bowel diseases (IBD) are exposed to drug-related nephrotoxicity and kidney-related extra-intestinal manifestations (EIMs). Patients should be monitored but guidance is lacking in current international recommendations. The objective of the Kidney Function Monitoring in Inflammatory Bowel Disease (MONITORED) initiative was to achieve an expert consensus about monitoring kidney function in IBD.

Methods: A literature review was first conducted. Then, an expert consensus meeting, involving 28 attendees representing French-speaking gastroenterologists and nephrologists, was held as part of an academic

* Corresponding author at: Department of Gastroenterology, University Hospital of Marseille Nord, University of Aix-Marseille, Chemin des Bourrely, 13015 Marseille, France.

E-mail address: lucas.guillo690@gmail.com (L. Guillo).

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initiative on May 28, 2021. An anonymous Delphi process was used to discuss and vote on statements. Agreement was defined as at least 75% of participants voting for any one statement.
Results: Experts reached consensus on 11 criteria for referral to the nephrologist. Concerning kidney function monitoring, participants unanimously validated the use of serum creatinine with estimation of the glomerular filtration rate via the MDRD or CKD-EPI equations. A blood ionogram and a urine sample with measurement of a protein-to-creatinine ratio were also broadly agreed validated. Experts recommended performing this monitoring at IBD diagnosis, prior introducing a new treatment, and annually for EIMs screening and evaluation of treatment tolerance. An evaluation 3 months after starting mesalamine and then every 6 months was felt necessary, while for biologics an annually monitoring was deemed sufficient.
Conclusion: The MONITORED consensus proposed guidelines on how to monitor kidney function in IBD. These recommendations should be considered in clinical practice to preserve kidney function and ensure the best approach to our patients.

1. Introduction

Inflammatory bowel disease (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), are chronic debilitating diseases with a relapsing and remitting course [1,2]. Currently, based on latest recommendations, Mesalamine (or 5-aminosalicylic acid, 5-ASA) remains the backbone therapy for mild to moderate UC [3,4]. Despite an overall safety profile similar to placebo, many cases of nephrotoxicity have been reported with 5-ASA [5–8]. Mesalamine-related nephrotoxicity can be a serious complication and delays in diagnosis and treatment discontinuation can lead to end-stage renal disease [6,9,10]. Moreover, nephrotoxicity has also been reported with anti-tumor necrosis factors agents (anti-TNF) and with vedolizumab [11–14]. Finally, kidney-related extra-intestinal manifestations (EIMs) (e.g., nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis or amyloidosis) can also occur along IBD course independently to the associated treatments [15–17]. Depending on definition, the prevalence of these EIMs ranges from 4% to 23% in patients with IBD [15,17].

In clinical practice, it remains difficult for gastroenterologists to decide when to refer to the nephrologist when patients encountered drug-related nephrotoxicity or kidney EIMs. In addition, international recommendations lack guidance on how to monitor kidney function in patients with IBD [18–26], leading to a poor follow-up and delayed management of kidney events. The objective of the Kidney Function Monitoring in Inflammatory Bowel Disease (MONITORED) initiative was to achieve an expert consensus to provide clear recommendations to the gastroenterologists for standardizing in daily practice the assessment of kidney function and when to refer to the nephrologist.

2. Methods

2.1. Steps prior the consensus meeting

The MONITORED academic initiative comprised two steps. A literature review was first conducted between July to August 2020 to identify how and when kidney function should be assessed and monitored in patients with IBD [27]. Two authors (LG and FD) searched PubMed, Embase, and Web of Science databases for relevant studies on this topic. The following Medical Subject Heading (MeSH) terms alone or matched with the Boolean operators "AND" or "OR" were used: "mesalamine", "5-ASA", "nephrotoxicity", "kidney diseases", "inflammatory bowel disease, "Crohn disease", "ulcerative colitis", "renal insufficiency", "kidney failure", "drug monitoring", "guideline". Then, they independently screened titles and abstracts. All editorials, notes, comments, or letters were excluded. Articles were selected on the basis of their clinical relevance and full-text manuscripts were analyzed for inclusion. Any disagreements between investigators were resolved through collegial discussion. Finally, they accurately checked the reference lists of the included studies for any additional relevant work.

2.2. Conduct of the consensus meeting

A virtual consensus meeting in the form of a webinar took place on May 28, 2021. The purpose of the meeting was to define: (i) when to refer to the nephrologist; (ii) the adequate blood and urine tools for monitoring kidney function; and (iii) its adequate timing of the kidney function monitoring. Based on the literature review [27] and on the international Kidney Disease: Improving Global Outcomes (KDIGO) recommendations [28,29], proposed statements were prepared prior to the consensus meeting by LG LF, PD, MF, CM and LPB, who formed the scientific committee. French-speaking experts from the GETAID (Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif) and from the SFNDT (Société Francophone de Néphrologie Dialyse et Transplantation) were invited to join the meeting. Overall, 28 attendees participated to the meeting, including 7 expert nephrologists and 21 expert gastroenterologists. Results of the literature review were presented to the members of the panel to ensure attendees were exposed to the most up to date literature. Following this introduction, individual statements were presented and modified following the Delphi process Final voting was carried out in an anonymous manner using the webinar software. Votes were carried out using the webinar software (Zoom) with a pop-up voting window for each participant. Voting time was limited to 1 minute. Agreement was defined as at least 75% of participants voting for one proposed statement. If a 75% agreement was not achieved, further discussion ensued which may have included amendment of voting statements where required, followed by a second round of voting if controversial. If agreement could not be reached after two rounds of voting, then the statement was definitively "excluded".

3. Results

As previously published [27], the review highlighted that many monitoring schemes are available and current international recommendations propose conflicting monitoring strategies due to a lack of medical evidence. To date, the best monitoring strategy remains unknown and clear guidelines to standardize timing and tests to be performed are still lacking, demonstrating the need for a consensus to homogenize practices.

The aim of the recommendations that are presented here is to provide simple and clear guidelines to assist gastroenterologists in their clinical practice and are largely based on expert opinion. The nephrologists were invited to introduce specifics of kidney function

Table 1
Criteria for referring to the nephrologist.

Proposed statements	Voting results	
	Number of ballots	Votes at last ballot (n/N)
Significant change in kidney function		
Serum creatinine concentration at baseline	1	90% (19/21)
30% increase in serum creatinine concentration from baseline	1	90% (19/21)
When to refer to the nephrologist		
In case of significant change (30%) in serum creatinine	1	89% (16/18)
eGFR < 75ml/min/1.73m^2 in patients < 45 years	1	94% (17/18)
eGFR < 60ml/min/1.73m^2 in patients 45 to 65 years	1	100% (18/18)
eGFR < 45ml/min/1.73m^2 in patients > 65 years	1	100% (18/18)
Presence or onset of albuminuria (> 30mg/g)	1	78% (14/18)
Presence or onset of proteinuria (> 150mg/g)	1	83% (15/18)
Suspected drug nephrotoxicity	1	100% (19/19)
Suspected kidney EIM	1	84% (16/19)
Persistent hypo- or hyperkalemia	1	89% (17/19)
First episode of nephrolithiasis	1	84% (16/19)
Onset of microscopic hematuria	1	84% (16/19)

EIM, extra-intestinal manifestation; eGFR, estimated glomerular filtration rate.

Table 2
Tools for monitoring kidney function.

Proposed statements	Voting results	
	Number of ballots	Votes at last ballot (n/N)
Blood tools		
Serum creatinine concentration	1	100% (19/19)
Ionogram (sodium and potassium concentrations)	1	84% (16/19)
Estimation of GFR via an equation from serum creatinine concentration: MDRD or CKD-EPI	1	89% (17/19)
Urinary tools		
On urine sample (to be checked within 3 months if positive)	2	95% (20/21)
Protein-to-creatinine ratio (PCR)	2	81% (17/21)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Table 3
Timing for monitoring kidney function.

Proposed statements	Voting results	
	Number of ballots	Votes at last ballot (n/N)
For all IBD patients		
At the IBD diagnosis	1	95% (19/20)
Annually, for EIMs screening and evaluation of treatment tolerance	1	100% (20/20)
Prior introducing a new IBD treatment	1	75% (15/20)
For patients treated with 5-ASA		
3 months after initiating the treatment, then every 6 months	1	84% (16/19)
For patients treated with biologics		
Annually	1	94% (16/17)

EIM, extra-intestinal manifestation; IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylic acid.

monitoring, and to guide the discussion and votes. Before starting the meeting, experts warned about the tolerance of the proposed monitoring and the need for easy-to-use tools in daily clinical practice to ensure the best adherence by our patients. Participants also felt that the age of patients should be taken into account in the interpretation of kidney function [30]. Statements with agreement among the participants are listed in *Tables 1 to 3* according to different chapters of the consensus (criteria for referral to the nephrologist, tools for the kidney function monitoring, and timing of the kidney function monitoring). Statements that required amendment before agreement or that were excluded are shown in *Supplementary Table 1*.

3.1. Criteria for referring to the nephrologist (Table 1)

In a practical way, the panel discussed the definitions of acute kidney injury (AKI) and chronic kidney disease (CKD) as established by KDIGO and whether they could be used in the setting of IBD patients. Regarding AKI, the KDIGO provides definitions with specific cut-offs. However, these cut-offs are based on epidemiologic studies and are validated for intensive care patients. Patients with IBD are mainly followed on an outpatient basis. Experts stated that for outpatients, significant change in kidney function is a better approach to define an acute event that may reflect kidney injury and suggests referring to the nephrologist. They further validated that serum creatinine is the most affordable and easiest marker in this setting. Statements were therefore amended prior to the vote. The panel validated the requirement of baseline serum creatinine at baseline (90%) and a 30% increase in serum creatinine from baseline (90%) as the definition of a significant change in kidney function. Regarding CKD, experts agreed with definitions published in the KDIGO recommendations, which are presented in Fig. 1.

Compared to KDIGO recommendations, some criteria to refer to the nephrologist were discussed and adjusted to a clinical outpatient practice. In accordance with previous discussions, participants

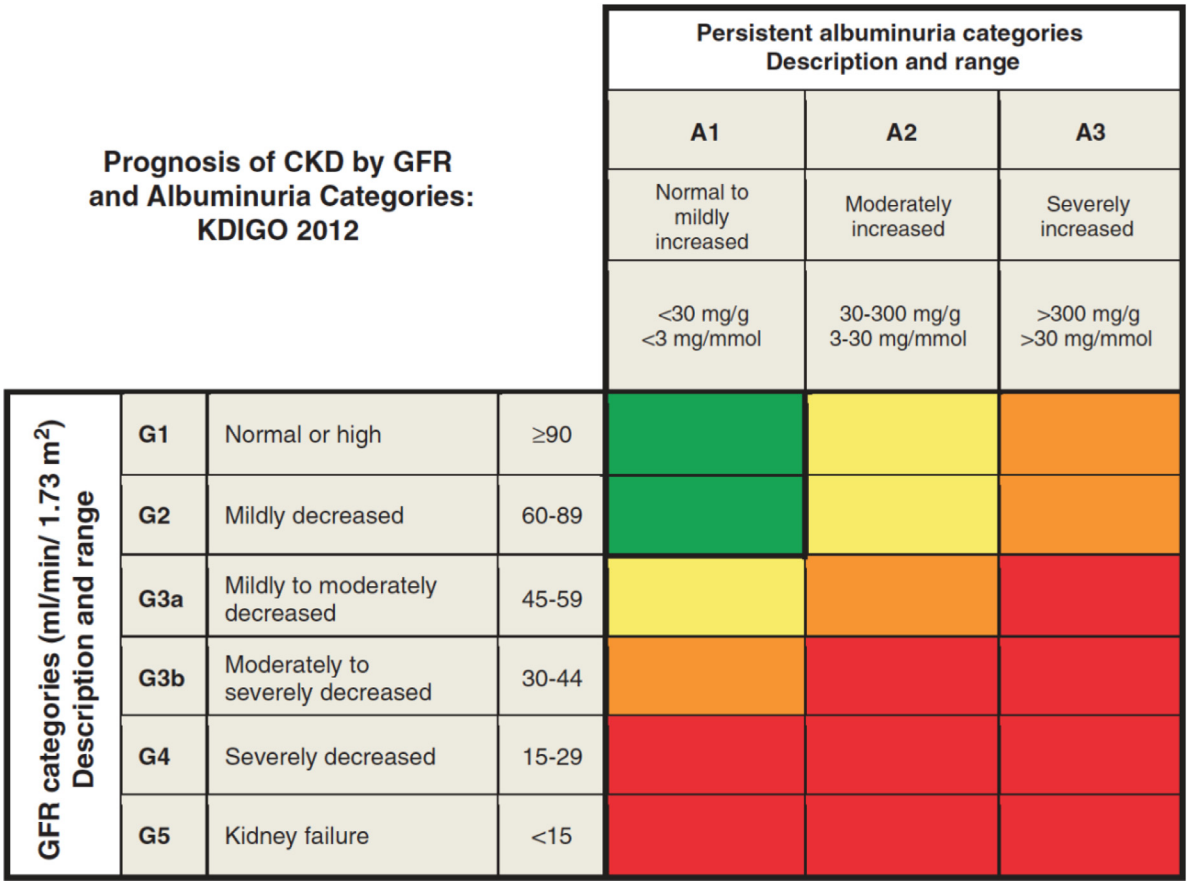

Fig. 1. Classification and prognosis of chronic kidney disease from the KDIGO.
CKD, chronic kidney disease; GFR, glomerular filtration rate;
Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
Reproduced from *Kidney Disease: Improving Global, Outcomes (KDIGO) CKD Work Group. Kidney inter Suppl. 2013; 3: 1–150.*

accepted to refer to a nephrologist in case of significant change (30%) in serum creatinine (89%). Experts felt that considering age along with estimated glomerular filtration rate (eGFR) is critical to properly refer patients. Hence, the experts panel have proposed age-specific thresholds of eGFR for which it is necessary to refer [30]. The panel unanimously accepted to refer patients with an eGFR < 60ml/min/1.73m^2 in patients aged 45 to 65 years (100%) and an eGFR < 45ml/min/1.73m^2 in patients older than 65 year-old (100%), and almost unanimously for patients with an eGFR < 75ml/min/1.73m^2 in patients younger than 45 year-old (94%). The presence or onset of albuminuria (> 30mg/g) or proteinuria (> 150mg/g) were also validated (78% and 83%, respectively) as criteria requiring nephrological expertise. Participants unanimously accepted to refer patients to the nephrologist for a suspected drug nephrotoxicity (100%). Experts agreed with the following criteria (84%): a suspected kidney-related EIM, a first episode of nephrolithiasis and an onset of microscopic hematuria. Finally, the presence of a persistent hypo- or hyperkalemia was also a criterion widely validated (89%) to refer patients to the nephrologist.

3.2. Tools for monitoring kidney function (Table 2)

First, blood testing tools were discussed by the panel. Experts unanimously agreed to use serum creatinine concentration (100%). They also highlighted that the measurement method (enzymatic or Jaffe) and the machine must be the same during follow-up of patients to avoid bias. Participants also broadly validated GFR estimation via calculation from serum creatinine among MDRD (Modification of Diet in Renal Disease) or CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) (89%). These two equations present advantages and limits, but no data are available on the optimal approach in the field of IBD. In addition, experts considered that physicians should always use the same equation during the follow-up of a specific patient. Of note, in general population, the CKD-EPI equation is recommended by the KDIGO [29]. A blood ionogram including natremia and kalemia was also validated (84%) by attendees.

Second, urinary tools were debated. Regarding collection methods, participants almost unanimously adjudicated (95%) that a urine sample (to be checked within 3 months if positive) is the best approach for patients screening. A 24-hour urine collection and a urine dipstick did not reach consensus (0% each). Indeed, adherence to a 24-hour collection is poor in clinical practice, especially if it needs to be repeated. Urine dipstick is an easy tool, but it mainly detects albuminuria and need to be completed by protein-to-creatinine ratio (PCR). Experts validated to perform a PCR on the urine sample (81%), while the albumin-to-creatinine ratio (ACR) did not reach consensus (67%). ACR is currently recommended by the KDIGO guidelines [29], but kidney injury in IBD are predominantly tubulo-interstitial and not glomerular, therefore ACR is less relevant in this context. For PCR, experts nephrologists recommended to use the cut-offs values of KDIGO guidelines[29]: normal to mildly increased < 150 mg/g; moderately increased 150-500 mg/g; severely increased > 500 mg/g. Albuminuria and creatininuria performed alone were not validated by the panel (14% and 0%, respectively).

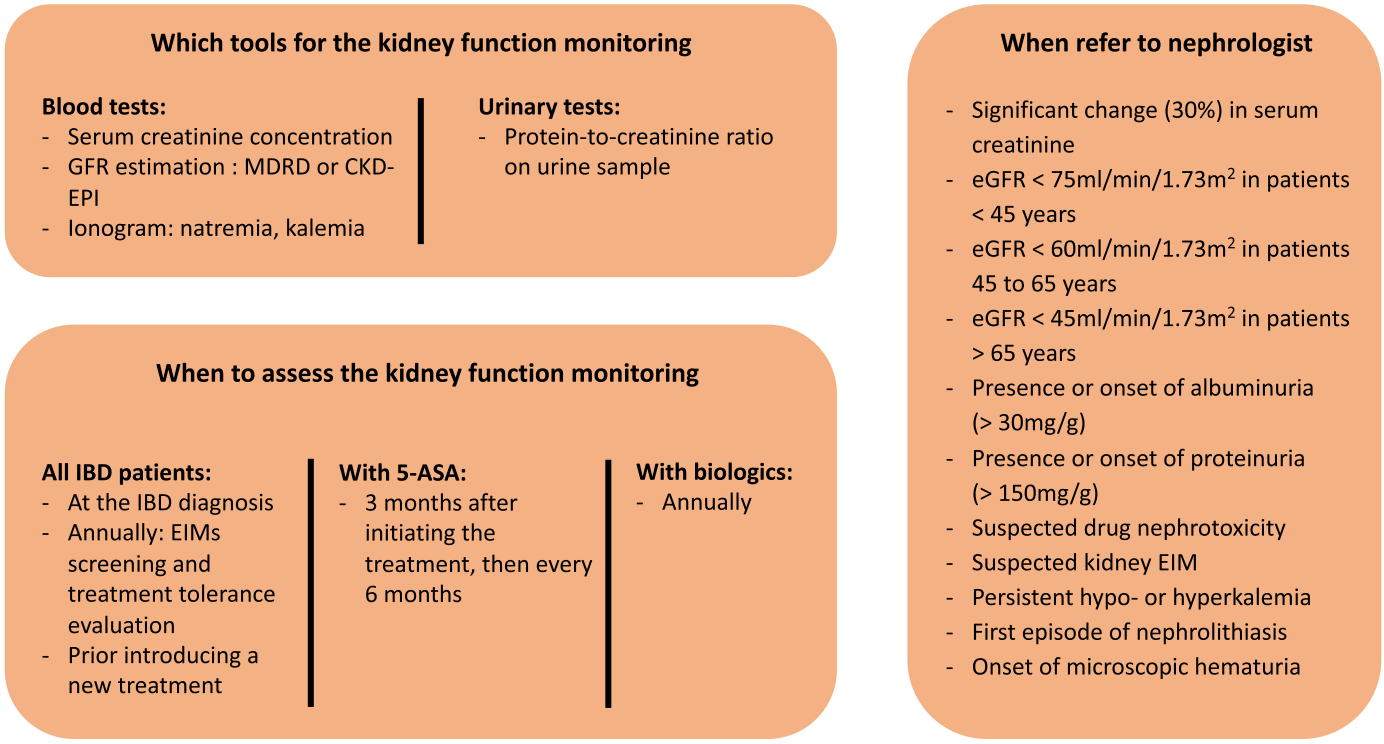

Fig. 2. Recommendations for monitoring kidney function in IBD patients.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EIMs, extra-intestinal manifestations, IBD, inflammatory bowel diseases; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

3.3. Timing for monitoring kidney function (Table 3)

First, attendees debated the timing for all IBD patients, without considering ongoing treatment. Experts almost unanimously agreed with an evaluation at the IBD diagnosis (95%). They unanimously validated an annual evaluation for EIM screening and evaluation of treatment tolerance (100%). Indeed, the proposed tools for monitoring are accessible and non-invasive for patients. The panel did not reach consensus on a biannual evaluation in case of factors associated with CKD progression (20%), or an evaluation based on CKD prognosis (40%). Indeed, the feeling was that a biannual evaluation may induce non necessary screening in many patients. Participants validated an evaluation prior to any introduction of a new IBD treatment (75%).

Second, the monitoring for patients treated with 5-ASA was approached. According to the literature data [27], experts felt that an evaluation 3 months after the introduction of 5-ASA should be performed. Considering the potential severity of tubulointerstitial nephritis and to avoid delays in diagnosis, participants agreed with the recommendations of the Food and Drug Administration handbook of mesalamine [31,32]. Hence, the panel reached consensus on an evaluation 3 months after starting of treatment, then every 6 months (84%). The other statements did not reach consensus (*Supplementary Table 1*).

Finally, the monitoring for patients treated with biologics was discussed. Although the safety profile appears reassuring with these molecules, some case reports of nephrotoxicity are available in the literature, mainly with anti-TNF agents [11–13,33–36]. Experts highlighted there is currently no recommendation for monitoring kidney function with biologics therapies. The panel felt that an annual evaluation should be necessary, as previously validated by the panel in the general case. Attendees almost unanimously reached consensus on annually monitoring the kidney function (94%). The other statements did not reach consensus (*Supplementary Table 1*).

4. Discussion

Approach to kidney function monitoring is an important part of the management of IBD patients considering the potential severe drug-related damage and the onset of EIMs [6,7,27]. Current international guidelines lack guidance for gastroenterologists in this field [27]. The MONITORED initiative is the first consensus addressing kidney function monitoring in the IBD setting. Overall, 23 recommendations were established to guide about when to assess for kidney function and guidance to refer patients to the nephrologist, which are summarized in Fig. 2. These guidelines were based on a literature review [27], international recommendations [28,29] and on French-speaking experts opinion guided through a Delphi process. Statements were mainly prepared based on the KDIGO recommendations [28,29], which are international guidelines from experts nephrologists to physicians. Since it was a French-speaking academic initiative with gastroenterologists and nephrologists, agreement incorporated diverse practice settings on the topics considered. Statements were discussed to be simple and applicable for the daily clinical practice. While statements were created based on literature evidence [27] and published guidelines [18–26,28,29], they also largely depict the opinion of expert IBD physicians. Therefore, 7 expert nephrologists, including one Belgian expert (PD) and one Lebanese expert (SK), were invited to the consensus to guide discussions and ensure that proposed recommendations are). Although it is a French-speaking consensus, there is no reason not to extrapolate the statements, as they are simple and adapted to the practice and the tools easily accessible.

For monitoring kidney function, participants proposed to use serum creatinine concentration with an estimation of the GFR via MDRD or CKD-EPI equations, a blood ionogram and a protein-to-creatinine ratio on a urine sample. These exams are easy and non-invasive. The panel felt that this monitoring should be performed at the time of IBD diagnosis, prior starting a new treatment and then annually. For patients treated with 5-ASA, an evaluation at

3 months and then every 6 months was proposed, while for biologics an annual assessment was decided. The nephrotoxicity with 5-ASA is rare and idiosyncratic, without dose or drug relationship. If most cases are diagnosed within the first 12 months, but it can be delayed [27]. An international multicentric study analyzing 151 cases of confirmed 5-ASA-induced nephrotoxicity reported that the median time of kidney injury was 3 years after starting treatment [8]. Conversely, in a recent retrospective cohort study based on a United Kingdom's primary care database and including 355,601 patients with IBD, no significant association was detected between 5-ASA users and non-users [37]. However, this study had some limitations: authors looked for "chronic kidney disease" and not acute kidney disease; data came from medical records about prescriptions issued rather than dispensed; all confounding factors were not taken into account [37]. A sporadic or weak nephrotoxic effect of 5-ASA could not be excluded with this study. On the other hand, it has been shown that 5-ASA-induced nephrotoxicity can lead to end-stage kidney disease, especially in cases of delayed diagnosis and even after treatment withdrawal [6,7]. Recommendations of these patients' follow-up was discussed according to this risk. Accordingly, kidney function of IBD patients should be closely monitored. Data on biologics-related nephrotoxicity are scarcer, but cases of tubulointerstitial nephritis, glomerulonephritis or nephrotic syndrome in patients with IBD have been reported [11–14,34,35], justifying a monitoring. The MONITORED consensus did not provide an exhaustive treatise on when referring IBD patients with kidney injury. The panel relied mainly on KDIGO recommendations [28,29]. However, according to suggestions of expert nephrologists, some statements were excluded or modified to be consistent with the current nephrologic clinical practice. Thus, the panel identified 11 patient referral situations to the nephrologist (Fig. 2).

In conclusion, the MONITORED initiative provides a framework for properly monitoring kidney function of patients with IBD and referring them in appropriate situations. Collaboration with nephrologists is critical to prevent and limit kidney complications along the course of IBD. Adherence to the presented recommendations should guide gastroenterologists in their clinical practice. Further work is needed to evaluate whether the compliance with these guidelines impact kidney prognosis in IBD.

Conflict of interest

L Guillo declares consulting fees for Abbvie. A Amiot declares counseling, boards, lecture, transports or fees from Abbvie, Hospira, Takeda, Gilead, Biocodex, Janssen, Ferring and MSD. B Caron has received lecture and/or consulting fees from Abbvie, Amgen, Celltrion, Janssen, Takeda. G Boschetti has served as a speaker and advisory board member for Abbvie, Janssen, Ferring, Norgine, Tillotts, Pfizer, Celltrion, Takeda, Amgen, Sandoz. G Bouguen has received lecture fees from Abbvie, Ferring, MSD, Takeda, Otsuka, Amgen, Biogen, Celtrion, Janssen, Tillots and Pfizer and consultant fees from Takeda, Janssen, Mylan, Vifor Pharma and Gilead. JM Gornet has received personal fees from Amgen, Janssen Cilag, Sanofi, Takeda, Roche and Tillots Pharma. J Bonnet has received consulting fees for Amgen. L Vuitton has received lecture fees from Abbvie, MSD, Takeda, Ferring, Janssen and Pfizer, and research grants from MSD, Takeda and Pfizer. M Nachury received board membership, consultancy, or lecture fees from Abbvie, Adacyte, Amgen, Arena, CTMA, Celltrion, Ferring, Fresenius-Kabi, Janssen, Mayoli-Spindler, MSD, Pfizer, Takeda. M Uzzan has served as a speaker for Janssen and Abbvie. M Serrero declares lecture and consulting fees for Abbvie, Celltrion, Ferring, Janssen, MSD, Takeda and Tillotts. L Peyrin-Biroulet has served as a speaker, consultant and advisory board member for Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillotts, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC- Pharma, Index Pharmaceuticals, Amgen, Sandoz, For- ward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, Theravance.

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Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

Authors' Contributions

LG and LPB participated in the study concept and design, acquisition of data, analysis and interpretation of data, along with drafting of the manuscript. All authors participated in the consensus meeting on 28 May 2021, critically reviewed the manuscript for important intellectual content and approved the final version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.11.008.

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