

Mark, P. , Dekkers, I., Blankestijn, P., Leiner, T. and Roditi, G. (2018) Letter on 'European dermatology forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin, Part 2: Scleromyxedema, scleredema and nephrogenic systemic fibrosis'. *Journal of the European Academy of Dermatology and Venereology*, 32(2), e84-e85. (doi:[10.1111/jdv.14774](https://doi.org/10.1111/jdv.14774))

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

This is the peer-reviewed version of the following article: Mark, P. , Dekkers, I., Blankestijn, P., Leiner, T. and Roditi, G. (2018) Letter on 'European dermatology forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin, Part 2: Scleromyxedema, scleredema and nephrogenic systemic fibrosis'. *Journal of the European Academy of Dermatology and Venereology*, 32(2), e84-e85, which has been published in final form at [10.1111/jdv.14774](https://doi.org/10.1111/jdv.14774). This article may be used for non-commercial purposes in accordance with [Wiley Terms and Conditions for Self-Archiving](#).

<http://eprints.gla.ac.uk/154356/>

Deposited on 03 January 2018

Dear Prof. Dr. med. Dr. phil. Johannes Ring

We read with interest the guidelines recently published on sclerosing diseases of the skin (Part 2: Scleromyxedema, scleredema and nephrogenic systemic fibrosis)[1, 2]. However, we are concerned that the guideline recommendations proposed for prevention of nephrogenic systemic fibrosis (NSF) are potentially dangerous. Although we recognise the challenges in constructing comprehensive guidelines, we are concerned that this may be because the guidelines have not involved a multidisciplinary team.

If the guideline development process followed by a rigorous literature search and critical evaluation of evidence as in a GRADEing approach (<http://www.gradeworkinggroup.org/>) then the guideline may have focused on diagnosis and treatment rather than speculating on methods to prevent NSF (we note that the authors do not suggest how to prevent scleromyxedema or scleredema).

It is striking the list of authors and affiliations contains neither radiologists nor any renal physicians - all authors are either dermatologists or rheumatologists. Rheumatologists have become heavy users of imaging, however, usually less where gadolinium based contrast agent (GBCA) enhancement is vital, while dermatologists request little imaging. These groups may not fully understand the value of GBCA enhanced radiological investigations and appreciate the risks versus benefits. Most cases of NSF have been detected by nephrologists, as the patients attend for regular haemo- or peritoneal dialysis.

The guideline document makes the simplistic assumption that administration of GBCAs in renal failure patients will almost certainly lead to NSF. Clearly this is not the case, since even in a large cohort of end stage renal failure patients on dialysis in whom double and triple doses of gadodiamide (Omniscan, GE Healthcare – now considered a ‘high risk’ agent) were administered, only 3% developed clinically manifest NSF. Thus, the vast majority of approximately 97% did not develop NSF[3]. Hence there must be other risk factors for NSF that have yet to be ascertained. For the cyclic chelate GBCAs (Dotarem, Gadovist & ProHance) there are virtually no unconfounded cases of NSF reported (and those published are controversial) while for gadobenate dimeglumine (MultiHance) there are none recorded[3, 4]. Furthermore, NSF itself is highly variable clinically, ranging from a rapidly progressive highly morbid systemic disease to isolated patches of skin thickening with little clinical import.

Our main concern is that the guideline recommends the use of haemodialysis (HD) after GBCA exposure to prevent NSF. The evidence for this is based on opinion rather than evidence. This is particularly true for the GBCAs used in Europe following the Committee for Medicinal Products for Human Use (CHMP) decision restricting use of linear gadolinium chelates. Indeed, there are risks in initiating HD in patients with no other indication for HD, such as those associated with central venous cannulation (haemorrhage, pneumothorax, infection) as well as the risk of HD itself. This decision would be hard to defend given the lack of evidence, dubious postulated benefits (especially if 'high-risk' agents are not used) and associated risks of initiating HD[5].

NSF is thankfully now, as far as we can tell, no longer a clinical concern. The last published case in which this diagnosis was a patient who manifested skin thickening 5.5 years following an exposure that occurred prior to the 2007 FDA warning (exposed to high dose Omniscan, now barred by the CHMP decision in Europe)[6, 7]. However, if a clinician suspects a new diagnosis of NSF, we suggest collaboration with a recognised expert in this field such as via the NSF registry (<http://www.icnfd.org>).

In summary, we are concerned that this document could influence inappropriate and potentially dangerous practice regarding avoidance of NSF and would urge the authors to urgently revisit these guidelines involving a multidisciplinary team including radiologists, nephrologists and dermatopathologists.

Dr Patrick Mark
Clinical Reader in Nephrology (Institute of Cardiovascular and Medical Sciences)
University of Glasgow
Glasgow, Scotland, United Kingdom

Dr Ilona Dekkers
Radiologist
Leiden University Medical Center, Leiden, The Netherlands

Prof Peter Blankenstijn
Professor of Nephrology
Department of Nephrology, University Medical Center, Utrecht, The Netherlands

Prof Tim Leiner
Professor of Radiology, Chair of Cardiovascular Imaging

Department of Radiology, Utrecht University Medical Center, Utrecht, The Netherlands

Dr Giles Roditi
Consultant Cardiovascular Radiologist,
NHS Greater Glasgow & Clyde
Honorary Clinical Associate Professor, Glasgow University
President British Society of Cardiovascular Imaging / British Society of
Cardiovascular CT (www.bsci.org.uk)
Glasgow, Scotland, United Kingdom

References & Links –

- [1] Knobler R, Moinzadeh P, Hunzelmann N, Kreuter A, Cozzio A, Mouthon L, et al. European Dermatology Forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin, Part 1: localized scleroderma, systemic sclerosis and overlap syndromes. *J Eur Acad Dermatol Venereol*. 2017.
- [2] Knobler R, Moinzadeh P, Hunzelmann N, Kreuter A, Cozzio A, Mouthon L, et al. European dermatology forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin, Part 2: Scleromyxedema, scleredema and nephrogenic systemic fibrosis. *J Eur Acad Dermatol Venereol*. 2017.
- [3] Collidge TA, Thomson PC, Mark PB, Traynor JP, Jardine AG, Morris ST, et al. Gadolinium-enhanced MR imaging and nephrogenic systemic fibrosis: retrospective study of a renal replacement therapy cohort. *Radiology*. 2007;245; 168-175 [PubMed](#) .
- [4] Collidge T, Thomson P, Mark P, Willinek W, Roditi G. Is this really a true case of NSF following Gadovist exposure alone? *Nephrol Dial Transplant*. 2010;25; 1352-1353; author reply 1353-1354.
- [5] Ramalho M, Ramalho J, Burke LM, Semelka RC. Gadolinium Retention and Toxicity-An Update. *Adv Chronic Kidney Dis*. 2017;24; 138-146.
- [6] Thomson LK, Thomson PC, Kingsmore DB, Blessing K, Daly CD, Cowper SE, et al. Diagnosing nephrogenic systemic fibrosis in the post-FDA restriction era. *J Magn Reson Imaging*. 2015;41; 1268-1271.
- [7] Agency EM. EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans. 2017.