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CLINICAL ARTICLE

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How to define failure of intradetrusor injections of botulinum toxin A for neurogenic detrusor overactivity

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Abstract

Introduction: Neurogenic detrusor overactivity (NDO) has a major impact on patients' quality of life and can lead to upper urinary tract complications. Intradetrusor botulinum toxin type A injections are administered as second-line treatment to these patients following the failure of anticholinergic agents. The aim of the DETOX 2 study is to propose a consensus definition of the failure of intradetrusor botulinum toxin injections for NDO in patients presenting spinal cord injury, spina bifida, or multiple sclerosis (MS) with self-catheterization.

Abbreviations: ACH, anticholinergic agents; BDO, bladder detrusor overactivity; HAS, French National Authority for Health; MS, multiple sclerosis; TB-A, botulinum toxin type A.

Method: This study followed the method adopted by the French National Authority for Health for recommendations by consensus. Based on a review of the literature and a preliminary survey, a steering committee compiled a questionnaire and selected a rating group comprising 16 experts from the Neuro-Urology Committee of the French Urology Association (cnuAFU) and Genulf. The experts were asked to complete the online questionnaire. At the end of the first round, all participants came together to discuss any disagreements and a second-round online questionnaire was completed to reach a consensus.

Results: Thirteen of the 16 experts approached completed both rounds of questionnaires. A strong consensus was reached for two proposals (median score = 9/10) which were therefore included in the definition from the first round: at least one repeat injection of the same botulinum toxin at the same dose must be given to rule out failure on technical grounds and a duration of efficacy <3 months must be considered a failure. At the end of round 2, a relative consensus was reached regarding the clinical criterion defining failure (median score = 7/10) and the urodynamic criterion of failure (median score = 8/10). An additional proposal was selected during this second round on the need for a voiding diary (median score = 8/10).

Conclusion: The first consensus definition of failure of an intradetrusor injection of TB-A for NDO has been achieved with this study: persistence of detrusor overactivity with maximum detrusor pressures >40 cm H_2O and/or a compliance issue and/or persistence of urinary incontinence and/or urgency and/or a number of daily self-catheterizations >8/day and/or efficacy <3 months. This study will help to standardize research on the failure of the intradetrusor botulinum toxin for NDO in clinical practice and clinical research.

KEYWORDS

botulinum toxin, failure, intradetrusor injections of botulinum toxin, neurological detrusor overactivity

1 | INTRODUCTION

Lower urinary tract dysfunction is a major problem for neurological patients with spinal cord injuries, spina bifida, or multiple sclerosis (MS).[1] It impacts the quality of life and life expectancy of these patients.[2] Neurogenic detrusor overactivity (NDO) is the primary pathophysiological determinant of urinary incontinence and lower urinary tract symptoms in these patients and can cause uronephrological damage potentially culminating in end-stage renal failure. Currently, anticholinergic (ACH) agents are still the first-line treatment for NDO.[3,4] However, they are often poorly tolerated due to side effects such as dry mouth and constipation.

Since the 2000s, botulinum toxin A has been the second-line treatment for NDO in neurological patients proving refractory to anticholinergic drugs.[5] This is an effective, well-tolerated treatment[6] requiring repeat injections every 6–9 months.[7] However, the failure rate varies from 6% to 32% depending on the studies, and increases over time.[8] This considerable variability in reported results is linked to the lack of consensus thus far on the definition of the failure of an intradetrusor injection of botulinum toxin A (TB-A).

A survey (DETOX 1) has provided an initial overview of the potential definition of the failure of intradetrusor injections of botulinum toxin. It indicated that the latter should be both clinical and urodynamic.[9]

This survey was followed by a formalized expert consensus study—DETOX 2—in a bid to obtain a validated, consensus definition. The aim was therefore to propose a consensus definition of the failure of intradetrusor TB-A for NDO in patients with spinal cord injury, spina bifida, or MS with self-catheterization.

2 | PATIENTS AND METHODS

2.1 | General methodology

This study followed the method adopted by the French National Authority for Health (HAS) for recommendations by consensus RAND/UCLA.[10] Based on a review of the literature and a preliminary survey, a steering committee comprising two neuro-urology experts (B. P. and X. G.) compiled a questionnaire. The steering committee (B. P., X. G., M. D. S., and A. E.) then appointed a rating group comprising 16 experts from the Neuro-Urology Committee of the Association Française d'Urologie (French Urological Association) and GENULF (Groupe d'Etude de Neuro-Urologie de la Langue Française - French-speaking Neuro-Urology Study Group) who were asked to complete the online questionnaire (Table 1).

The questionnaire was sent by email using the SurveyMonkey app®.

The questionnaire was submitted once. At the end of this first round, the participants came together to discuss any disagreements and remove the proposals for which no consensus had been reached. According to HAS, a median value greater than 7 is required in order for a consensus to be reached. Ratings from 7 to 9 denote a strong consensus. Ratings from 5 to 9 denote a relative consensus. No consensus was reached for a given item if the median number of votes in the first round was less than 4 (Table 2). A questionnaire modified at the end of the meeting was submitted to the expert committee for a second round of scoring. A consensus was then reached.

2.2 | Questionnaire

The questionnaire was drawn up on the basis of published data and the results of the DETOX 1 survey.[9] It focused on patients doing self-catheterization with urodynamically confirmed NDO treated with intradetrusor injections of TB-A in patients presenting spinal cord injury, spina bifida, or MS. This concept was clearly explained to the participants before they completed the questionnaire. A 20–30 injections trigone sparing template was considered a standard for the purpose of that study. Forty questions were asked in total. The experts had to rate each proposal from 1 to 9 (Supporting Information: Annexe 1).

A score of 1 was given to a totally inappropriate or unacceptable proposal whereas a score of 9 indicated that the proposal in question was both acceptable and adequate in the expert's opinion. A score of 5 indicated indecision whilst scores ranging from 2 to 8 reflected potential interim situations.

2.3 | Statistical analysis

For each question, the median was calculated using the JMP v.12.0 software (SAS Institute Inc.).

TABLE 1 Lists of experts.

First name Name	Position
Alain RUFFION	Urologist
Alexia EVEN (AE)	Physical Medicine and Rehabilitation
Andrea MANUNTA	Urologist
Benjamin BERNUZ	Physical Medicine and Rehabilitation
Benoit PEYRONNET (BP)	Urologist
Christian SAUSSINE	Urologist
Emmanuel CHARTIER-KASTLER	Urologist
Evelyne CASTEL-LACANAL	Physical Medicine and Rehabilitation
Frédérique LE BRETON	Physical Medicine and Rehabilitation
Gérard AMARENCO	Physical Medicine and Rehabilitation
Gilles KARSENTY	Urologist
Jacques KERDRAON	Physical Medicine and Rehabilitation
Loic LE NORMAND	Urologist
Maire-Aimée PERROUIN-VERBE	Urologist
Marianne DE SEZE (MDS)	Physical Medicine and Rehabilitation
Pierre DENYS	Physical Medicine and Rehabilitation
Véronique PHÉ	Urologist
Xavier GAMÉ (XG)	Urologist

TABLE 2 Conditions for reaching a consensus between experts and the judgment adopted, based on the median value and the distribution of scores taken into consideration.

Proposal deemed	Degree of group consensus	Conditions for reaching a consensus	
		Median values	Score distribution within the range
Appropriate	Strong consensus	≥7	[7–9]
	Relative consensus	≥7	[5–9]
Inappropriate	Strong consensus	≤3	[1–3]
	Relative consensus	≤3.5	[1–5]
Uncertain	Undecided	4 ≤ median ≤ 6.5	[1–9]
	No consensus	All other situations	

TABLE 3 Definition of failure of intradetrusor botulinum toxin A for detrusor overactivity after 2 rounds.

Proposal	Type of consensus	Round in which consensus has been reached	Median score/10
Urodynamic failure criterion: Presence of detrusor overactivity with maximum detrusor pressures >40 cm H_20 and/or compliance issue (<20 mL/cm H_20)	Relative	2nd round	7
Clinical failure criterion: Persistent urinary incontinence (excluding stress incontinence) and/or urgency and/or a number of daily self-catheterizations >8/day (with diuresis <40 mL/kg/day)	Relative	2nd round	8
A duration of efficacy <3 months should be considered a failure.	Strong	1st round	9
To eliminate technical grounds for failure, at least one reinjection of the same toxin at the same dose must have been given.	Strong	1st round	9
The clinical criteria for failure must be based on a voiding diary	Relative	2nd round	8

3 | RESULTS

Thirteen of the 16 experts contacted completed both rounds of the questionnaire, that is, a response rate of 68%.

At the end of round 1, strong consensus was reached regarding two proposals, which were then included in the definition. The following items were included: "at least one repeat injection of the same TB-A at the same dose must be given to rule out failure on technical grounds" and "a duration of efficacy <3 months must be considered a failure."

At the end of round 2, a relative consensus was reached regarding the clinical criterion defining failure (median score = 7/10): "persistent urinary incontinence (excluding stress urinary incontinence) and/or a daily number of self-catheterizations exceeding 8 per day" and the urodynamic criterion of failure (median score = 8/10): "presence of detrusor overactivity with maximum detrusor pressures exceeding 40 cm H_2O and/or a compliance issue (<20 mL/cm H_2O)."

An additional proposal was selected in the second round. This concerned the failure of the toxin and the need to implement a voiding diary (median score = 8/10) (Table 3).

No consensus was reached regarding the clinical criteria, toxin intolerance, a duration of efficacy of less than 6 months for the injection, items discussing the number of episodes of urinary incontinence, weekly efficacy reduced by 50% or greater than or equal to one per day or per week and the use of a Likert scale to assess patient satisfaction (Table 4).

With regard to urodynamic criteria, the persistence of low bladder capacity <250 mL measured using cystomanometry was not selected by the experts and was therefore eliminated after the two rounds.

TABLE 4 List of the various proposals rejected at the end of two rounds.

Clinical criteria	Urodynamic criteria
Intolerance to intradetrusor injection of botulinum toxin (generalized weakness) should be considered a failure.	Persistent low bladder capacity <250 mL measured by cystomanometry
Duration of efficacy of less than 6 months should be considered a failure.	
In the event of partial urodynamic clinical improvement, the patient's request to change treatment should be considered as a failure.	
Reduction in the number of weekly episodes of urinary incontinence, but less than 50%.	
Number of episodes of urinary incontinence greater than or equal to 1 per day	
Number of episodes of urinary incontinence greater than or equal to 1 per week	
Number of episodes of urgency greater than or equal to 1 per week	

4 | DISCUSSION

Since the 2000s, botulinum toxin injections have become standard treatment for NDO proving refractory to anticholinergic agents in patients with spinal cord injury or MS. Intradetrusor botulinum toxin A failure rates as high as 32% have been recorded.[6] A definition for botulinum toxin A failure in NDO proving refractory to anticholinergic agents was agreed in our study. This definition is based on clinical and urodynamic criteria: persistence of detrusor overactivity with maximum detrusor pressures >40 cm H_20 and/or poor compliance and persistence of urinary incontinence (excluding stress UI) and/or urgency and/or number of daily self-catheterizations >8/day and/or duration of efficacy <3 months. To our knowledge, this study is the first to define TB-A failure by expert consensus. This could lead to clinical trials involving this patient cohort, for which no robust published data are available. Furthermore, practices could be standardized in the event of failure of intradetrusor TB-A for NDO, particularly with regard to potential indications for urine diversion such as augmentation cystoplasty[11] or cystectomy with a noncontinent trans-ileal diversion.

The expert consensus is based on data akin to current neuro-urology practice: a clinical evaluation criterion reflecting patients' quality of life (persistence of UI, urgency, number of self-catheterizations >8 per day) and a urodynamic criterion (presence of a compliance issue <20 mL/cm H_20 or maximum detrusor pressure >40 cm of H_20) reflecting the other key objective of neuro-urological management, namely the prevention of organic complications.[3]

The committee validated the use of a voiding diary to authenticate failure. It is particularly useful for detecting poor intermittent catheterization performance with excessive catheterization volumes, which can lead to incontinence despite good control of the intravesical pressure schedule, or indeed a large number of catheterizations which may reflect poor control of the pressure schedule as well as a precautionary approach on occasion.

Persistence of urinary tract infections or an increase in the number of infections was not considered, despite the fact that they may be responsible for the discontinuation of treatment in current practice and that a link has been proven between TB-A efficacy and a reduction in the number of urinary tract infections.[12] The multifactorial nature of urinary tract infections in neurological patients and the absence of uniformly validated diagnostic criteria certainly impacted the participants' decision not to include this criterion in the definition of failure.

Similarly, cystomanometric capacity of less than 250 mL was not selected by the experts despite the fact that it may indirectly reflect toxin efficacy. Bladder capacity increases with TB-A injections and is, therefore, an indirect marker of toxin efficacy.[13,14] This criterion could be used to devise a new screening grid for patients at risk of a poor response to intradetrusor TB-A injections.

Several studies have shown that in patients who are refractory to one botulinum toxin A, a reinjecting higher dose of the same botulinum toxin A or switching to another botulinum toxn A can yield good results.[15,16] This proposal was mentioned in the DETOX 1[9] study and was not integrated due to a lack of consensus among the participating experts.

In practice, injections of abobotulinum toxin-A (ABO), Dysport(®) are often offered before considering a more invasive treatment such as a cystectomy. One may assume that clinical failure of an injection of an alternate toxin may be considered as a failure. However, this criterion was not included in the present survey.

This is a definition based on the French National Authority for Health (HAS) method for recommendations by consensus and is deemed to be an "expert opinion." This study has a low level of proof, namely grade C,[17] based on proof and rating levels set out in HAS good practice recommendations. Nevertheless, this method seemed an obvious choice as it is apparently very difficult to validate the diagnostic performance of such a definition given the heterogeneity of the neurological population with neurodegenerative conditions that can lead to earlier withdrawal, particularly in patients with MS.[14]

This article has a number of limitations that should be acknowledged. The choice of experts is open to discussion. They all belong to learned neuro-urology societies such as the AFU or neuro-urology research groups such as GENULF. The centers chosen are French neuro-urology centers. No international expert neuro-urology center was approached. The urodynamic and clinical criteria used are international criteria validated in numerous studies on neurogenic overactive bladder.[7,18]

The questionnaire used was not validated before this study which may be regarded as a limitation. Another limitation worth highlighting is the number of participating experts, which remains relatively low. Only relative consensus could be reached regarding the clinical and urodynamic failure criteria. Finally, the methodology used (proposed by HAS) is not, to our knowledge, used internationally, which could limit its scope. However, we hope that the definition of the failure of intradetrusor TB-A proposed in this study will help to standardize clinical practices and research projects on this topic.

5 | CONCLUSION

The first consensus definition for failure of an intradetrusor TB-A injection for NDO has been proposed in this study: persistence of detrusor overactivity with maximum detrusor pressures >40 cm H_2O and/or a compliance issue and persistence of urinary incontinence and/or urgency and/or a number of daily self-catheterizations >8/day and/or efficacy <3 months. At least one repeat injection of the same toxin at the same dose is required to establish failure of intradetrusor TB-A. This study could help to standardize research into the failure of intradetrusor TB-A for NDO in clinical practice and clinical research.

AUTHOR CONTRIBUTIONS

Camille Mailho performed the analysis and wrote the paper. Benoit Peyronnet conceived and designed the analysis, collected the data, performed the analysis, wrote the paper. Marianne De Seze conceived and designed the analysis and reviewed the paper. Alexia Even conceived and designed the analysis and reviewed the paper. Maire-Aimée Perrouin-Verbe conceived and designed the analysis and reviewed the paper. Gérard Amarenco conceived and designed the analysis and reviewed the paper. Emmanuel Chartier-Kastler conceived and designed the analysis and reviewed the paper. LoicLe Normand conceived and designed the analysis and reviewed the paper. Andrea Manunta conceived and designed the analysis and reviewed the paper. Gilles Karsenty conceived and designed the analysis and reviewed the paper. Jacques Kerdraon conceived and designed the analysis and reviewed the paper. Alain Ruffion conceived and designed the analysis and reviewed the paper. Christian Saussine conceived and designed the analysis and reviewed the paper. Frédérique Le Breton conceived and designed the analysis and reviewed the paper. Benjamin Bernuz conceived and designed the analysis and reviewed the paper. Evelyne Castel-Lacanal conceived and designed the analysis and reviewed the paper. Pierre Denys conceived and designed the analysis and reviewed the paper. Véronique Phé conceived and designed the analysis and reviewed the paper. Xavier Gamé conceived and designed the analysis, collected the data, performed the analysis, wrote the paper.

CONFLICT OF INTEREST STATEMENT

The conflicts of interest have been attached.

DATA AVAILABILITY STATEMENT

All data are available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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