# Disputes & Debates: Editors' Choice



## Editors' Note: Clinical Subgroups and Factors Associated With Progression in Patients With Inclusion Body Myositis

Dr. Michelle and investigators from the Johns Hopkins Myositis Center retrospectively analyzed clinical and pathologic data from 335 patients with inclusion body myositis (IBM) to identify unique phenotypes of the condition. The distinct clinical and pathologic characteristics of each demographic subgroup may be useful in clinical trial design and prognostication. Among the key findings, patients meeting criteria for IBM were diagnosed after a mean delay of 5 years, with fewer than half of patients (43%) with muscle biopsies demonstrating all 3 pathologic hallmarks (endomysial inflammation, rimmed vacuoles, and mononuclear invasion). Based on the limited sensitivity of muscle biopsy, Dr. Stenzel and colleagues agree with the authors that one should emphasize the clinical examination in making a diagnosis of IBM and supplement these observations with more advanced diagnostic testing and sequencing of mitochondrial DNA in muscle biopsy samples. Dr. Michelle et al. note that immunohistochemical testing and mitochondrial testing are not available in most US laboratories and their specificity in differentiating IBM from polymyositis may be limited. They stress the value of the 2011 European Neuromuscular Centre consensus diagnostic criteria, which combine clinical and pathologic features to establish the diagnosis. An update to these 2011 criteria is anticipated shortly.

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*Neurology*® 2023;101:499. doi:10.1212/WNL.0000000000207782

## Reader Response: Clinical Subgroups and Factors Associated With Progression in Patients With Inclusion Body Myositis

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*Neurology*® 2023;101:499–500. doi:10.1212/WNL.0000000000207783

We read with interest the article by Michelle et al.[1] about clinical subgroups and factors associated with progression in patients with inclusion body myositis (IBM). The authors used Griggs criteria,[2] European Neuromuscular Centre 2011 criteria, and Lloyd Greenberg data-derived criteria,[3] including endomysial inflammation, invasion of non-necrotic fibers, and rimmed vacuoles.

This triad was only seen in 43% of biopsies and rimmed vacuoles were present in only 66%, which are low percentages. The authors argued that incomplete histopathologic patterns—apart from clinical misdiagnosis—may be a reason for misclassification as polymyositis (PM). They proposed less invasive diagnostic criteria and putting more value on clinical examination, such as quadriceps and finger-flexor weakness.

It has been shown that a diagnosis of PM has to be re-evaluated with modern approaches[4] and that many of the PM-mito cases are actually patients with early IBM, which cannot be identified on clinical grounds only because many patients have, in fact, mild nonspecific clinical signs.[5]

We recommend more precise and complete diagnostic procedures,[4] including major histocompatibility complex class I and II, p62, TAR DNA-binding protein 43, complement patterns,

Author disclosures are available upon request (journal@neurology.org).

T-cell characterization,[6] and mitochondrial abnormalities,[7] to determine whether a biopsy specimen corresponds to IBM.


1. Michelle EH, Pinal-Fernandez I, Casal-Dominguez M, et al. Clinical subgroups and factors associated with progression in patients with inclusion body myositis. *Neurology*. 2023;100(13):e1406-e1417. doi:10.1212/WNL.0000000000206777
2. Griggs RC, Askanas V, DiMauro S, et al. Inclusion body myositis and myopathies. *Ann Neurol*. 1995;38(5):705-713. doi:10.1002/ana.410380504
3. Lloyd TE, Mammen AL, Amato AA, Weiss MD, Needham M, Greenberg SA. Evaluation and construction of diagnostic criteria for inclusion body myositis. *Neurology*. 2014;83(5):426-433. doi:10.1212/WNL.0000000000000642
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5. Kleefeld F, Uruha A, Schänzer A, et al. Morphologic and molecular patterns of polymyositis with mitochondrial pathology and inclusion body myositis. *Neurology*. 2022;99(20):e2212-e2222. doi:10.1212/WNL.0000000000201103
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## Author Response: Clinical Subgroups and Factors Associated With Progression in Patients With Inclusion Body Myositis

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*Neurology*® 2023;101:500. doi:10.1212/WNL.0000000000207784

We thank Stenzel et al. for their comment on our article[1] and agree that muscle biopsy analysis should ideally use more "modern" pathologic analysis to help distinguish polymyositis (PM) from inclusion body myositis (IBM). We have recently shown that transcriptomics[2,3] or reverse transcription PCR detection of mis-splicing events from muscle biopsies because of TAR DNA-binding protein 43 loss of function is sensitive and specific for a diagnosis of IBM.[4] This finding confirms a recent report that detection of mis-splicing predicts clinical development of IBM among patients diagnosed pathologically with "PM-Mito."[5]

In clinical practice, however, many clinical pathology laboratories in the United States do not routinely perform extensive immunohistochemical studies to help distinguish PM from IBM. Furthermore, the specificity of some pathologic features reported in IBM, for example, the presence of p62-positive aggregates,[5] have been questioned and require further validation. For these reasons, the 2011 European Neuromuscular Centre (ENMC) consensus diagnostic criteria use a combination of clinical and pathologic features to help establish the diagnosis.[6] Recent and ongoing international IBM clinical trials use the 2011 ENMC criteria, although an ENMC meeting is planned this year to update the diagnostic criteria.[7]

Hopefully, development of more precise pathologic criteria can be widely agreed upon and used to diagnose IBM more accurately in the future.


1. Michelle EH, Pinal-Fernandez I, Casal-Dominguez M, et al. Clinical subgroups and factors associated with progression in patients with inclusion body myositis. *Neurology*. 2023;100(13):e1406-e1417. doi:10.1212/WNL.0000000000206777
2. Ikenaga C, Date H, Kanagawa M, et al. Muscle transcriptomics shows overexpression of cadherin 1 in inclusion body myositis. *Ann Neurol*. 2022;91(3):317-328. doi:10.1002/ana.26304
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Author disclosures are available upon request (journal@neurology.org).

CORRECTION

# Randomized Double-Blind Placebo-Controlled Trial of the Corticosteroid-Sparing Effects of Immunoglobulin in Myasthenia Gravis

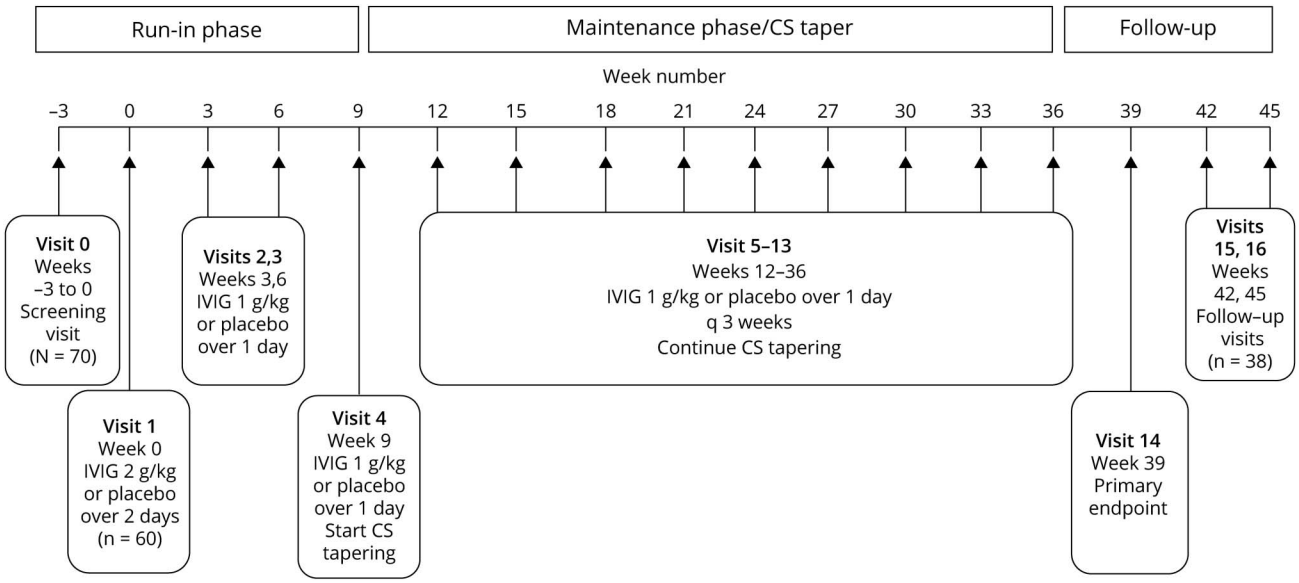
*Neurology*® 2023;101:501. doi:10.1212/WNL.0000000000207433

In the Research Article "Randomized Double-Blind Placebo-Controlled Trial of the Corticosteroid-Sparing Effects of Immunoglobulin in Myasthenia Gravis" by Bril et al.,[1] the maintenance dose in Figure 1 should be "1g/kg." Dosing is correctly reported in the abstract and body of the article. The corrected Figure 1 is below. The authors regret the error.

## Reference

1. Bril V, Szczudlik A, Vaitkus A, et al. Randomized double-blind placebo-controlled trial of the corticosteroid-sparing effects of immunoglobulin in myasthenia gravis. *Neurology*. 2023;100(7)e671-e682.

**Figure 1** Timeline for Evaluation of Potential Steroid-Sparing Effects of IV Immunoglobulin (IGIV-C) in Myasthenia Gravis




Additional information on patient disposition throughout the study is included in Figure 2. CS = corticosteroid.