Inclusion body myositis: advancements in diagnosis, pathomechanisms, and treatment

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Purpose of review
To review new advances in inclusion body myositis (IBM) and discuss them in light of current knowledge on diagnosis, pathomechanisms, and treatment perspectives.

Recent findings
IBM is a treatment refractory inflammatory myopathy in middle-aged patients that leads to a slow, relentlessly progressive muscle weakness, and atrophy. Recent data collections suggest that mortality in IBM patients is somewhat elevated compared with the general population. One major risk factor for death is severe dysphagia, which can now be determined by a novel real-time MRI technique. Recently, proposed diagnostic criteria with a combination of clinical and histopathological features have improved sensitivity and specificity. cytosolic 5′-nucleotidase 1A antibodies have been characterized in IBM patients and their pathophysiologic role has recently been studied. New inflammatory pathomechanisms have been identified in IBM muscle and may help to design novel treatment strategies. A broad spectrum of immunosuppressive and immunomodulatory trials have been conducted, but – so far– no effective treatment is available. Current therapeutic attempts aim to block the myostatin pathway or restore the protein homeostasis.

Summary
The expanding knowledge of the complex disease, the refinement of diagnostic criteria, and developments in diagnostic procedures are expected to foster the much needed design of new treatment approaches for future clinical trials.

Keywords
cN1A autoantibodies, diagnostic criteria, dysphagia, immunoglobulin G, inclusion body myositis

INTRODUCTION

Inclusion body myositis (IBM) belongs to the group of inflammatory myopathies, which also includes dermatomyositis (DM), polymyositis (PM), necrotizing myopathy, and overlap myositis. IBM patients are mostly beyond 50 years of age at initial presentation. IBM can be distinguished from the other inflammatory myopathies by its unique clinical presentation with asymmetrical muscular weakness and atrophy, predominantly affecting long finger flexors and the quadriceps muscles. The histopathological hallmarks of the disease include a T-cell-dominated immune infiltration and myodegenerative features like multiple protein aggregates inside muscle fibers. IBM usually does not respond to standard immunosuppression such as by glucocorticosteroids, methotrexate, or azathioprin.

EPIDEMIOLOGY AND LIFE EXPECTANCY

The prevalence of IBM is highest in Whites in Northern Europe, North America, and Australia, ranging from 4.9 to 33 per million and even 51.3 per million people for the group of patients above 50 years of age [1–3]. In a recently published meta-analysis of nine publications, the metaprevalence was 24.8 per million in total [4▪]. It is thought that the prevalence of IBM is underestimated, for example, because of a wrong diagnosis as PM. In recent studies, there is an increase in prevalence, which could be explained with growing disease awareness and improved diagnostic tools. Men are about two-fold more often affected than women [5,6].

The disease course is typically slowly progressive over decades and leads to increasing impairment of

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Curr Opin Rheumatol 2017, 29:000–000
DOI:10.1097/BOR.0000000000000436

KEY POINTS

- The diagnosis depends on clinical, histological, and serological parameters.
- Dysphagia is a common, relevant, and sometimes initial symptom that often requires special attention.
- Standard immunosuppression is usually not justified and IVIG may be suitable for selected patients, particularly in case of severe dysphagia.
- Novel effective treatment strategies will depend on a better understanding of the pathomechanisms.

daily activities, particularly those involving hand and finger muscles such as writing, using knife and fork, getting dressed, and so on. Mobility is increasingly limited, leading to walking sticks or walker dependence after 5–10 years. The rate of yearly progression in weakness is about 5% [5,6]. The mortality has recently been shown to be somewhat increased as reflected by an international questionnaire of 'IBM experts' [3,7▪]. There is no evidence of increased risk of malignancy in IBM patients [8].

CLINICAL SYMPTOMS

Patients with IBM usually display a typical pattern of involved muscles. In general, the quadriceps femoris and the long finger flexors are mainly affected. Other muscle groups that are commonly affected include the biceps and the foot dorsiflexors. With progression of the disease, all affected muscle become atrophic. An affection of paraspinal muscles can cause camptocormia or a dropped head syndrome in IBM patients [9].

An important symptom of the disease is dysphagia which is noted in 40–80% of IBM patients [10▪,11,12]. Patients typically report that food gets stuck in their throat and that they need to swallow repeatedly for clearance. In some cases, dysphagia is the initial, presenting symptom [13,14]. Assessment of swallowing is usually performed by videofluoroscopy [11]. A recent study demonstrates that real-time MRI is comparably reliable for detection of an impaired food passage in patients with dysphagia because of IBM [10▪]. Compared with videofluoroscopy, this novel tool has the advantage that it does not rely on X-rays and it can visualize soft tissue such as muscle. Thus, real-time MRI may be an ideal tool for assessing and monitoring dysphagia as part of clinical care as well as in clinical studies of IBM. Patients with only a mild swallowing impairment usually do not report this as part of the history [12]. Therefore, the use of formal swallowing questionnaires appears to be advisable not to overlook a relevant dysphagia in IBM patients: Such questionnaires include the swallowing-related quality of life questionnaire as well as the Sydney swallowing questionnaire [15]. The swallowing scales correlated well with the flexible endoscopic evaluation of swallowing and real-time MRI. Both questionnaires have been used in detecting swallowing problems in different neurological and nonneurological diseases such as Parkinson's disease or amyotrophic lateral sclerosis [16–18].

DIAGNOSTIC CRITERIA

Diagnosis of IBM is often delayed by an average of 5 years from symptom onset and is usually made by a combination of clinical, electrodiagnostic, and pathological assessment [9]. There have been different diagnostic criteria used for research and daily practice issues. Griggs *et al.* [19] defined in 1995 the diagnostic criteria for IBM: they are much focused on histopathological features so that the diagnosis of a definite IBM can only be made if all pathological features are present, that is, mononuclear cell invasion of nonnecrotic fibers, vacuolated muscle fibers, and evidence of protein accumulation. It has been shown that an overweight of histopathological changes vs. clinical symptoms will likely lead to an underdiagnosis of IBM and overdiagnosis of PM [20]. The inherent problems of overemphasizing histopathological diagnosis of definite IBM is the fact that one or more of the required features will often be absent. In a retrospective study, enhanced specificity and sensitivity could be found when tissue sections were examined looking for rimmed vacuoles in combination with the respective distribution of p62 and inflammatory changes [21]. In tissue sections lacking rimmed vacuoles, the estimation of inflammatory changes appearing simultaneously with mitochondrial malformation resulted in higher sensitivity and good specificity. The European Neuromuscular Centre (ENMC) criteria for IBM took into account the typical clinical phenotype and performed more inclusive compared with Griggs' criteria [1]. In 2013, revised ENMC criteria for IBM were published and used an approach of combining clinical, laboratory, and pathological observations [22]: a distinction between clinico-pathologically defined IBM, clinically defined IBM, and probable IBM was suggested (Table 1). A recent study evaluated different sets of diagnostic criteria from various previous publications and most of them – including the revised ENMC criteria – showed poor sensitivity: Using machine learning techniques in an approach

Table 1. ENMC diagnostic criteria of inclusion body myositis

	Clinico-pathologically defined IBM	Clinically defined IBM	Probable IBM
Clincal and laboratory criteria	Duration >12 months Age at onset >45 years sCK no greater than 15 ULN Knee extension weakness at least hip flexion weakness and/or Finger flexion weakness more than shoulder abduction weakness	Duration >12 months Age at onset >45 years sCK no greater than 15 ULN Knee extension weakness at least hip flexion weakness and Finger flexion weakness more than shoulder abduction weakness	Duration >12 months Age at onset >45 years sCK no greater than 15 ULN Knee extension weakness at least hip flexion weakness or Finger flexion weakness more than shoulder abduction weakness
Pathologic criteria	All of the following: Endomysial inflammatory infiltrate Rimmed vacuoles Protein accumulation[a] or 15–18-nm filaments	One or more of: Endomysial inflammatory infiltrate Up-regulation of MHC class I Rimmed vacuoles Protein accumulation[a] or 15–18-nm filaments	One or more of: Endomysial inflammatory infiltrate Up-regulation of MHC class I Rimmed vacuoles Protein accumulation[a] or 15–18-nm filaments

The table provides clinical, laboratory, and pathological criteria for diagnosis of clinico-pathologically defined, clinically defined, and probable IBM as proposed by the ENMC workshop 2011.
ENMC, european neuromuscular center; IBM, inclusion body myositis; MHC, major histocompatibility complex; sCK, serum creatine kinase; TDP, transactive response dna binding protein; ULN, upper limit of normal.
[a]Demonstration of amyloid or other protein accumulation by established methods (e.g., congo red, crystal violet, thioflavin T/S, or immunostaining for p62, SMI-31, and TDP-43).
Adapted with permission [22].

including 371 patients, best specificity and sensitivity was identified by combining finger flexor or quadriceps weakness with endomysial inflammation and either invasion of nonnecrotic fibers or rimmed vacuoles [23]. The international standard of care in IBM has been discussed at an ENMC workshop in 2011 [22] and an IBM guideline development group has been formally established. This group has assessed the best practice for diagnosis and treatment of IBM [24] by a Delphi method and a live meeting for all participants of the group Publication of the results is expected soon.

CN1A ANTIBODIES

The reliability of the diagnosis is hampered by the fact that the clinical presentation as well as the histological picture can be very variable and until today no precise biomarker is available. In 2011, a circulating antibody against a 43 kDa muscle protein was described in blood samples from IBM patients [25]. This antibody was later characterized being reactive against the cytosolic 5'nucleotidase 1A [26,27]. However, despite initial enthusiasm about this antibody as a potential new biomarker for IBM, recent data demonstrate that IBM patients are positive in a range of not more than 33–61% [28▪–31▪]. Moreover, other autoimmune disorders such as PM (5%), DM (15%), systemic lupus erythematodes (14–20%), and especially Sjögren's syndrome (23–36%) show a high rate of cytosolic 5'-nucleotidase 1A (cN1A) antibodies [28▪,29▪].

So far, it is unclear if the autoantibody status is useful to distinguish different IBM subtypes, for example, a more severe phenotype. Some authors describe a higher adjusted mortality risk in patients with cN1A antibody positivity [30▪], whereas others did not identify a relevant difference between these two groups of IBM patients [28▪,31▪]. The response rate to immunosuppressive treatment did also not differ significantly between antibody-positive and negative patients [31▪].

Histopathologically, antibody-positive patients tend to have increased cyclooxygenase-deficient muscle fibers [30▪] and a lower frequency of rimmed vacuoles [28▪]. In-vitro and in-vivo exposure to immunoglobulin G from cN1A-positive patients led to p62-aggregates in rhabdomyosarcoma cells and in muscle fibers of injected mice [31▪].

Testing for antibody status in suspected IBM can be of diagnostic value, as demonstrated in suggested diagnostic algorithms [32]. Despite some implication for diagnosis, the pathogenic relevance of cN1A antibodies in IBM remains open and is currently studied by several groups.

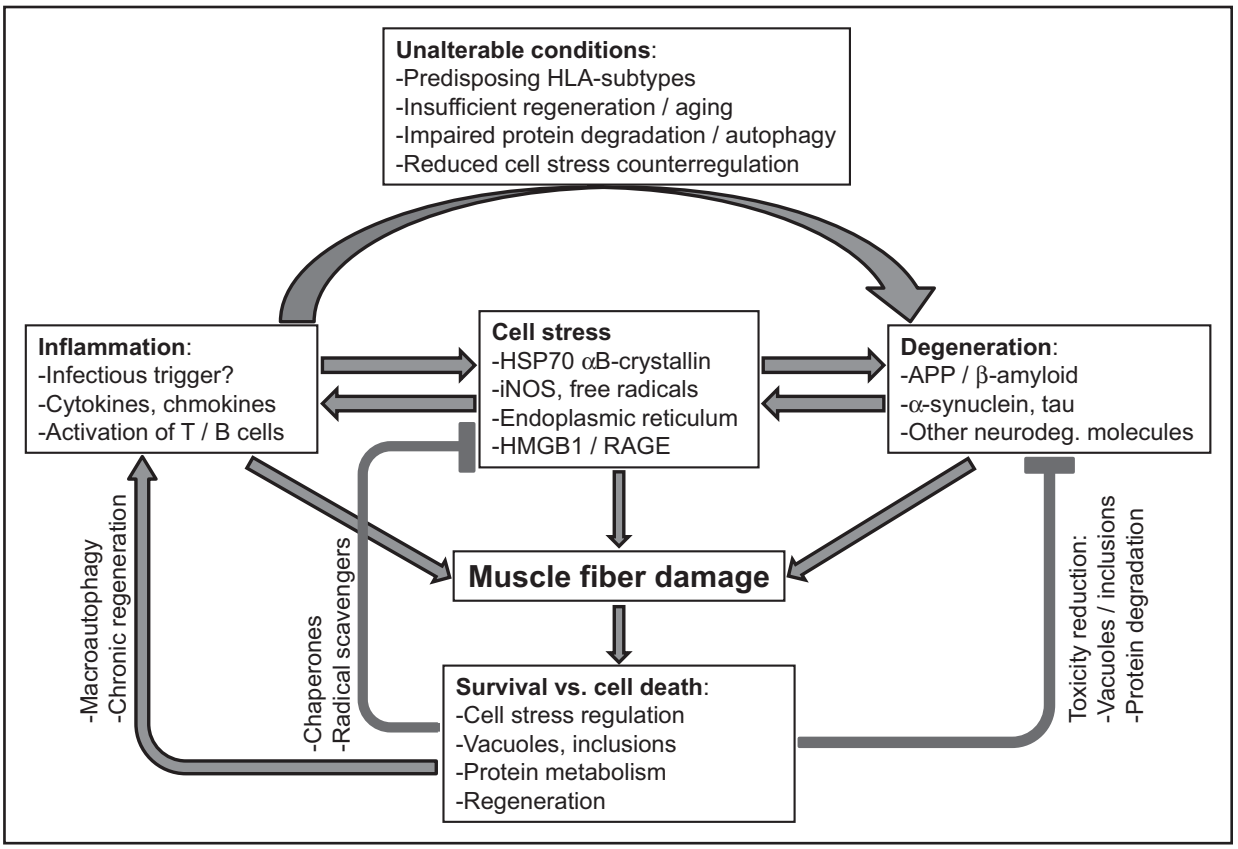

FIGURE 1. Model of IBM pathogenesis, initial damage to the muscle because of a potential infection or other inflammatory stimulus may, in case of a distinct genetic predisposition, cause chronic inflammation and subsequent protein dyshomeostasis in the skeletal muscle. Protein accumulation and inflammation are interlinked by cell stress mechanisms, which can fuel a vicious cycle with an ultimately irreversible degeneration of the muscle. Endogenous regulators of chaperons or formation of vacuoles may alleviate the cell stress. By contrast, upon autophagic processing, endogenous antigens presented via MHC class II may augment the inflammatory cell stress. Adapted with permission [39]. APP, amyloid precursor protein; HMGB, high mobility group box; HSP, heat shock protein; MHC, major histocompatibility complex; RAGE, receptor for advanced glycation end products.

PATHOMECHANISMS

The coexistence of two very different hallmarks, inflammation and myodegeneration, explains the complexity of the pathogenesis of IBM. Inflammation with autoaggressive T cells attacking nonnecrotic fibers, upregulation of major histocompatibility complex (MHC) class I antigens, and an upregulation of inflammatory mediators is accompanied by a myodegenerative disease with protein accumulation, vacuolization, and mitochondrial changes [33–35,36▪▪]. There are several links between inflammatory and degenerative pathomechanisms, such as intracellular nitric oxide or impaired autophagy [37,38] (Fig. 1). However, the precise interplay of degenerative and inflammatory mechanisms has so far remained elusive.

Since the initial description of virus-like inclusions in IBM four decades ago, it has been speculated that viruses might play a role in the pathogenesis of IBM. In general, it is conceivable that antiviral response mechanisms will affect self-tolerance, autoantigen recognition, and/or chronic stimulation of low affinity, autoaggressive effector cells such as cluster of differentiation (CD)8^+ T cells. Despite manifold efforts, no study so far provides sufficient evidence of a direct attack in IBM affected muscle fibers [40]. However, an increased incidence of IBM in Hepatitis C virus-infected patients was recently described [41]. Presence of human leukocyte antigen (HLA)-A* 0201-HIV-gag-positive endomysial T cells has been demonstrated in IBM muscle samples [42]; However, the HIV gag antigen was found only in macrophages, but not in muscle fibers. A recent study on HIV-positive patients with myositis demonstrated typical features of IBM-like rimmed vacuoles and finger flexor weakness [43]. Interestingly, the cN1A autoantibody was present in 64% of the HIV patients with myositis. Taken together, a pathogenic role of a putative viral trigger of autoimmunity in IBM cannot be ruled out, but more conclusive data are warranted.

The autophagic machinery in skeletal muscle is capable of removing misfolded proteins. In IBM, it could be demonstrated that accumulated amyloid precursor protein (APP) and Aβ are targeted for lysosomal degradation via macroautophagy [44]. Furthermore, the proinflammatory cytokines tumor necrosis factor-α, and interleukin-β in combination with interferon (IFN)-γ have been shown to cause an upregulation of the autophagic activity in cultured myoblasts [38,45]. Antigen presentation via MHC II has been shown to be regulated by the autophagic machinery, serving as an interesting link between inflammation and degeneration in IBM disease [46]. In a recent study, proteomic analysis revealed accumulation of FYVE and coiled-coil protein (FYCO)1 in rimmed vacuoles [47]. Further analysis showed overexpression of rare missense variants of FYCO1 in IBM patients, leading to an impaired autophagic function. In another approach to identify genetic risk factors for IBM, missense pathogenic variants of the valosin containing protein and p62/SQSTM1 have been found by whole-exome sequencing in 181 IBM patients [48]. Both molecules are involved in autophagosome maturation and degradation. These genetic data support the hypothesis of an underlying defect of autophagosome function in IBM, which could be a crucial prerequisite in IBM pathogenesis in that an inflammatory stimulus can trigger a chronic cell stress response which drives a vicious cycle with upregulation and overloading of the autophagic machinery. Such predisposing factors could act together with HLA alleles such as DRB1∗0301, which has been demonstrated to be associated with a more severe disease course of IBM [32].

TREATMENT

Despite the pronounced inflammatory features on muscle biopsy, immunosuppressive or immunomodulatory drugs such as glucocorticosteroids, azathioprin, methotrexate, or IFN-β are not effective in IBM and studies with etanercept and anakinra failed to demonstrate an improvement [5,49–54]. Alemtuzumab, a lymphocyte-depleting antibody against CD52, led to a transient improvement in some patients in an unblined proof of concept study [55]. In a subsequent post hoc analysis, a downregulation of inflammatory markers was noted without an effect on degenerative molecules, which could possibly explain the insufficient long-term effect of this drug [56]. In view of the small sample size and open-label design of this study, the results need to be interpreted with care. Comparable results were obtained in a post hoc analysis of biopsies from a placebo-controlled trial with intravenous immunoglobulin G (IVIG) and prednisolone, which down-modulated inflammatory mediators, but failed to block nitric oxide stress in the muscle and in a corresponding in-vitro model [57]. As immunosuppression generally fails in IBM, treatment with glucocorticosteroids or other immunosuppressants is not recommended, particularly in view of the potential side-effects. Treatment with immunoglobulin G – either intravenously or subcutaneously – can be associated with a stabilization or even transient, mild improvement of muscle strength and particularly an improved dysphagia in several IBM patients [58,59] and own observations (unpublished data). Therefore, particularly in patients with relevant dysphagia, a probatory treatment with IVIG can be justifiable in selected patients [60] (see below for details).

Aside from immunosuppressive or immunomodulatory strategies, drugs with alternate mechanisms of actions have failed in small clinical studies including oxandrolone, an anabolic steroid [61], and simvastatin, a cholesterol lowering agent [62]. Lithium as a drug that reduces phosphorylation of APP, increases proteasome activity and inhibits glycogen synthase kinase 3β in APP – overexpressing cultured human muscle fibers is currently tested in a clinical trial. Arimoclomol, a drug already tested in amyotrophic lateral sclerosis [63], ameliorated the disease course and improved muscle strength in mutant valosin-containing protein mice, which develop an inclusion body myopathy [64▪]. Within the same report, the drug appeared to be well tolerated in a clinical concept study in IBM patients. A large placebo-controlled study is currently underway. For the future, it may be of interest to design studies that target inflammation and degeneration at the same time [60,65,66]. For this reason, it is imminent to better understand the unique interplay between inflammation, cell stress pathways, and accumulation of aberrant proteins in the disorder (see above).

Targeting the impaired regeneration potential in IBM has been put into focus by blocking the binding of myostatin to its receptor activin RII. Activation of this pathway leads to inhibition of muscle growth with phosphorylation and activation of downstream effectors of the activin RII receptor [67]. In a proof of concept trial with 14 IBM patients, an increased thigh muscle volume on MRI and improvement in the 6-min walking test was observed [68]. However, the subsequent double blind placebo-controlled trial did not meet its primary endpoint (data not published yet).

Another potent inhibitor of myostatin is follistatin, delivered by an adenovirus-mediated gene therapy. In a proof of concept trial with six IBM patients, this vector was directly injected into the

quadriceps muscle. All of the treated patients improved in 6-min walking test compared with an untreated control group [69▪]. A placebo-controlled trial would be required to determine the efficacy.

TREATMENT OF DYSPHAGIA

Dysphagia in IBM is thought to be caused by an upper esophageal sphincter dysfunction due to an impairment of suprahyaloidual muscles [10▪,12]. Treatment with cricopharyngeal myotomy or pharyngoesophageal balloon dilatation showed a reasonable benefit in a small group of patients [70,71]. A more recently published study revealed that most of the patients have an abnormal hyolaryngeal excursion and would, therefore, not benefit from this procedure [72]. In several case series, local injection of botulinum toxin into the upper esophageal sphincter was effective in improving dysphagia [70,73]. IVIG led to a relevant improvement of dysphagia in clinical trial settings [50,74]. Based upon our own observations, selected patients may respond surprisingly well and may display an improvement of dysphagia for several months to years. Treatment approaches for dysphagia in muscle disorders have recently been evaluated in a Cochrane review [75].

CONCLUSION

In recent years, a range of new aspects have been addressed in the field of IBM with respect to epidemiology, diagnostic criteria, pathomechanisms, and novel treatment approaches. So far, no effective pharmacological therapy has been identified. A better understanding of the complex disease and possible predisposing genetic factors will be crucial to develop successful treatment strategies. The development and evaluation of reliable diagnostic criteria will help to identify suitable patients for future clinical trials.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

J.S. has received honoraria, research grants, or reimbursements for travel from Bayer, Biogen, BioMarin, Biotest, CSL Behring, Grifols, Hormosan, Novartis, Octapharma, Ultragenyx, and VitalAire.
K.S. has received reimbursements for travel from Biotest, CSL Behring, and Grifols.

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