Guidelines from an expert panel for the management of diabetic macular edema in the Malaysian population

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Abstract

- **Aim:** To derive a Malaysia guideline and consensus as part of the Malaysia Retina Group’s efforts for diagnosis, treatment, and best practices of diabetic macular edema (DME). The experts’ panel suggests that the treatment algorithm to be divided into groups according to involvement of the central macula. The purpose of DME therapy is to improve edema and achieve the best visual results with the least amount of treatment load.

- **METHODS:** On two different occasions, a panel of 14 retinal specialists from Malaysia, together with an external expert, responded to a questionnaire on management of DME. A consensus was sought by voting after compiling, analyzing, and discussion on first-phase replies on the round table discussion. A recommendation was deemed to have attained consensus when 12 out of the 14 panellists (85%) agreed with it.

- **RESULTS:** The terms target response, adequate response, nonresponse, and inadequate response were developed when the DME patients’ treatment responses were first characterized. The panelists reached agreement on a number of DME treatment-related issues, including the need to classify patients prior to treatment, first-line treatment options, the right time to switch between treatment modalities, and side effects associated with steroids. From this agreement, recommendations were derived and a treatment algorithm was created.

- **CONCLUSION:** A detail and comprehensive treatment algorithm by Malaysia Retina Group for the Malaysian population provides guidance for treatment allocation of patients with DME.

- **KEYWORDS:** diabetic macular edema; guidelines; consensus; diabetic retinopathy; Malaysia

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INTRODUCTION

**Diabetic Macular Edema and Vision Loss** Diabetic macular edema (DME) is a retinal thickening...
involve the central fovea to macula which is one of the most prevalent causes of visual loss worldwide. It is characterized by a buildup of fluid in the central region of the retina because of fail blood-retinal barrier. In the healthy people, the central retinal thickness (CRT) varies between 212±19 and 289±16 μm while in DME patients, the CRT can vary from 225 to >450 μm. Localized edema is caused by leakage from clusters of microaneurysms, whereas diffuse edema is caused by broad capillary leakage. DME can manifest as the appearance of hard exudates which produce blurring and distortion of central vision, and can be measured by a reduction in best-corrected visual acuity (BCVA). Diabetic retinopathy (DR) is the presence of microvascular abnormalities in the fundus of diabetic patients which can be seen during clinical examination or color fundus photography. The earliest and least serious form of DR is the dot-like microaneurysms, which are discrete saccular outpouchings of the capillary wall that have sharp edges and look like a small red dot. DR is a one of the ocular diabetic complication caused by long-term diabetes. Prolong or uncontrolled diabetic can cause damage to the blood vessels in the eyes, which may lead to vision loss. Globally, 34.6% of diabetic patients have DR, while in Malaysia, 10.4% of ageing diabetic have it, which results in blindness. Active screening and early diagnosis of DR are crucial to preventing vision loss since it, which results in blindness. The ophthalmologist has several treatment options which consist of various procedures with different outcomes measure, including laser photocoagulation, anti-vascular endothelial growth factor (VEGF), steroids, and surgical therapy. These strategies have heralded the beginning of a new era in DME therapy. When laser treatment and anti-VEGF fail to give an adequate impact in DME patients, the pars plana vitrectomy operation is done. Pars plana vitrectomy reduces the macula’s thickness and improves visual acuity (VA) by mechanically removing vitreous fluid.

**How to Detect Diabetic Macular Edema**

**Optical coherence tomography** OCT scan is the industry-recognized gold standard for DME diagnosis. It may be used to recognize different types of DME, detect macula traction, and locate edema to specific retina layers. Diverse retinal thickening, cystoid macula edema, serous retinal detachment without posterior hyaloidal traction, and posterior hyaloidal traction with tractional retinal detachment are morphologic manifestations of DME on OCT. Subretinal fluid and/or small intraretinal cystoid fluid and/or external limiting membrane and inner segment/outer segment integrity and vitreomacular adhesion are a good baseline predictor for good treatment response with high vision gains and/or good final VA which is a prognostic marker from OCT for DME. Contrarily, baseline abnormalities of the retinal inner layers, disruption of the inner and outer photoreceptor segments, and/or the external limiting membrane, which may result in irreversible photoreceptor destruction and loss, as well as baseline subfoveal choroid thinness, are predictors of poor visual outcomes post-treatment.

After dexamethasone implants in eyes with DME, biomarkers such as subretinal fluid, inner segment/outer segment continuity, the lack of hyperreflective foci, and an attached vitreoretinal interface indicated improved visual results. Anti-VEGF (ranibizumab) biomarkers such as ellipsoid zone disruption and the lack of epiretinal membrane have been linked to superior therapy outcomes. A potential predictive biomarker for the visual consequences of DME is the organization of the retinal inner layers. Disorganization of the inner layer of retinal has been connected to both disruption of the outer retina and an increase in the severity of DR. Cystoid macular edema, serous retinal detachment of subretinal fluid and retinal enlargement or thickening were all seen on OCT in individuals with DME. Hyperreflective foci is another prognostic sign for DME, which forms plexiform layer’s outer confluent plaques and is found within the walls of intraretinal microaneurysms. The foci may be an early sign of DME barrier failure since they are believed to be extravasated proteins and/or lipoproteins. In DME patients, higher baseline hyperreflective foci levels indicate therapy response as measured by VA improvement and CRT decrease after three months.

**Fluorescein Angiography** When OCT angiography is not available, fluorescein angiography plays important role in identifying treatment failure or inadequate response, identifying the foveal avascular zone, guiding supplemental laser therapy and diagnosing of co-existing peripheral DR. In order to evaluate the central and peripheral retina, fluorescein angiography may be employed.

**SUBJECTS AND METHODS**

**Ethical Approval** This study used all the published data. Ethical approval is not required. This study was registered with National Medical Research Register (NMRR) with registration number NMRR ID-22-01045-RUP.

In early 2021, a team of experts from Malaysia comprising 14 ophthalmologist who were medical retina specialist with an external reviewer convened together to discuss recent research and developed a consensus guideline for the treatment of DME and how they relate to international trends and practices.
Consensus Development  The Malaysia Retina Group’s efforts to establish local treatment guidelines and consensus for the management of DME and to get recommendations based on the best-updated practice resulted in the present current consensus. Prior to the conference, 11 recommended statements and one management algorithm were created using existing guideline recommendations, regional health care reimbursement policies, and treatment trends. A thorough discussion of each statement was followed by a secret vote. When ≥85% of experts voted, it was considered that consensus had been reached. Discussions were repeated, statements were changed, and voting continued until an agreement was reached.

RESULTS

Recommendation  The DME patients were characterized according to their therapy response patterns to provide the recommendations. Table 1 is a summary of the consensus guidelines for DME management.

Treatment Goal  Although available treatments can retain and improve vision for the great majority of patients, it can be associated with significant expenses and visit burdens; hence, identifying the best treatment regimen is crucial. In significant pilot investigations of DME treatment agents, it is decided that BCVA will be the main endpoint. Various studies using ranibizumab injection in patients with clinically significant macular edema with center involvement linked to DME in RISE (registered on ClinicalTrials.gov as NCT00473330)/RISE (NCT00473382) and randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with DME [MAED (NCT00168337 and NCT00168389)] where the proportion of patients acquiring >15 letters in BCVA from baseline was identified as the primary objective. However, DME resolution occurs when ranibizumab is used alone or in combination with laser treatment when the primary outcome was the mean change in BCVA from baseline [RESTORE (NCT01609374)] [20], VIVID (NCT01363440)/VISTA (NCT01331681) [23], Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I [24] and DRCR.net Protocol T studies. From the clinical setting, improvement of VA may not be achieved, due to the Snellen is the commonest tool we use for VA testing instead of Early Treatment Diabetic Retinopathy Study chart. In other cases, VA improvement is achieved after the disappearance of macular edema. Therefore, these factors led to the development of this set of guidelines, which determine the most effective treatments for the disease and inform ophthalmologists about the most recent advancements in clinical practice and the necessity of prompt suggestion to retina specialist for additional management when required.

Diabetic Macular Edema Treatment Options  The consensus’s recommendations were simplified into an algorithm (Figure 1)}
Injections. Depending on financial resources, early intensive therapy will be advised. Early intensive therapy with minimum five to six first monthly dosages, with a maximum of eight to nine injection in the first year, may provide positive outcomes and enable for lessen burden of therapy in upcoming years. The VA can be significantly improved with monthly injection of anti-VEGF drugs with every reactivation of the disease protocol (PRN protocol) or treat-and-extend injectable treatment. DRCR.net Protocol I study using ranibizumab with a treat-and-extend strategy may be used. DME: Diabetic macular edema.

**Table 2 The overview for management of DME**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central involved DME with vision impairment (6/9 or worse)</td>
<td>In the ideal situation, authorized anti-VEGF with proven efficacy and safety is used. Steroid implant. Focused/grid laser is the next step if anti-VEGF or steroids are not an option.</td>
</tr>
<tr>
<td>DME with central involvement and excellent vision (VA greater than 6/9), (three alternatives currently, with community consensus on the best management)</td>
<td>If DME continues, observation until visual deterioration, followed by either focal/grid laser or anti-VEGF treatment. Focal/grid laser up to a loss of vision, followed by anti-VEGF treatment if DME continues.</td>
</tr>
<tr>
<td>Non-central involved DME</td>
<td>Observation until central-involved DME, then check the Focal/grid laser in selected cases where observation is judged to be inferior, such as in pregnancy or rapidly worsening cataract, or when macula edema rapidly extending towards the center of the macula</td>
</tr>
</tbody>
</table>

DME: Diabetic macular edema; VA: Visual acuity; VEGF: Vascular endothelial growth factor.
maintaining good visual outcomes\textsuperscript{[27]}. VA is considered stable when there is no change after two successive injections and there is a change of under 10% in the central macular thickness on the OCT. Therefore, when DME is stable during follow up, it will be advisable to consider treating and extending the regime. However, steroid (dexamethasone) injection can be considered if there is no response after five to six injections, especially in pseudo phakic patients.

All anti-VEGF agents are equally effective and any of them can be used as a first-line treatment. However, Protocol T results indicate that aflibercept can be started in patients a worse VA (20/50 or less) who had baseline fluorescein angiography readings of 20/32 to 20/40. Treatment with anti-VEGF agents reportedly improved patients’ vision by one to two lines at two years with no significant differences among agents\textsuperscript{[25]}. The intravitreal use of VEGF inhibitors may increase the incidence of arterial thromboembolic events. Nonfatal myocardial infarction, nonfatal stroke, and vascular death are all considered to be arterial thromboembolic events. A Meta-analysis of anti-VEGF drugs for patients with DME who received intensive monthly anti-VEGF for two years suggests that the risk may be related to cumulative medication exposure. The analysis revealed a possible increased risk of fatalities and cerebrovascular accidents\textsuperscript{[20]}. Ranibizumab with doses of 0.5 mg and 0.3 mg was found to have hazard ratios of 1.05 and 0.78 for arterial thromboembolic events, 0.84 and 0.94 for myocardial infarction 0.94 and 0.53 for stroke or transient ischemic attack, 1.63 and 0.59 for stroke (excluding transient ischemic attack), and 2.17 and 2.51 for vascular death when compared to sham\textsuperscript{[26]}. Study on off label bevacizumab showed that the overall systematic side effect of intravitreal injections range from 0 to 39.3%. The majority of these occurrences are minor, unmanaged and retrospective\textsuperscript{[28]}. Steroid implant Before beginning treatment, steroid implants should be given to patients with high-risk cardiovascular disease. Potential candidates for treatment include patients with a history of vitrectomy, severe edema (greater than 500 μm), pseudophakic patients (steroid implant is contraindicated in patients with anterior chamber intraocular lens, patients who are scheduled for cataract surgery, and patients with low compliance.

After six weeks of the injection, regular intraocular pressure (IOP) should be measured in patients with no other ocular comorbidities and followed-up at months two to three after therapy. Retreatment may be recommended every four to six monthly, depending on the results. If the reaction is positive, it may be possible to consider additional evaluation and therapy at 4- to 6-monthly intervals while keeping an eye on side effects and contraindications. If the reaction is insufficient or no reaction is given, switch to another anti-VEGF drug.

According to MEAD study, patients receiving 0.7 dexamethasone exhibited IOP increases of at least 10 mm Hg in 27.7% of cases and >35 mm Hg in 6.6% of cases, and with 41.5% requiring IOP-lowering medications. Only one patient required surgical intervention\textsuperscript{[32]}. In the majority of clinical trials, 20% of patients/eye had IOP increase of interest. IOP-lowering agents and anti-glaucoma mediation were not necessary in the majority of IOP increase cases\textsuperscript{[31]}. Retinal/vitreous/subconjunctival hemorrhage was another minor problem that occurred in 1%-2% of patients\textsuperscript{[31]}. Problems relating to cataracts were observed in nearly half of phakic patients in several studies\textsuperscript{[31]}. The dose of 0.7 g Ozurdex arm of the MEAD trial gave an unfavorable event relating to cataracts occur at an incidence of 67.9% mostly in phakic patients. Following cataract surgery, the patient’s eyesight improved from baseline\textsuperscript{[22]}.

**Focal/grid laser** For non-centre involving DME (defined as edema outside 100 μm radius of the foveal centre and/or meeting the Early Treatment Diabetic Retinopathy Study-Clinically Significant Macular Edema definitions\textsuperscript{[32]} and rescue laser for DME involving the centre is indicated after at least six months of anti-VEGF treatment. Other indications include DME affected eyes with a CRT <300 μm\textsuperscript{[10]}. Both Protocol I from the DRCR.net and Protocol T suggested postponing focal/grid laser therapy for at least 24wk. The visual outcomes of Protocol I were better to those of rapid laser with ranibizumab\textsuperscript{[27]}. Ideally, focal laser should be used in conjunction with grid laser to treat diffuse macular leakage, leaky microvascular abnormalities, and non-perfusion in thicker retinas\textsuperscript{[10]}. Every three to four months, the focal/grid laser should be redone. If edema continues or does not improve despite receiving anti-VEGF therapy (if available, if it is thought that using more laser could be beneficial).

There are several potential side effects of laser treatment, including the growth of laser scars (atrophic creep), secondary choroidal neovascularization central scotoma, deterioration of colour vision, night vision, and contrast sensitivity, as well as subretinal fibrosis and visual-field sensitivity deterioration\textsuperscript{[1]}. **Pars plana vitrectomy + membrane peeling** In situations with tractional macular edema, therapy is indicated with or without additional intravitreal steroid treatment\textsuperscript{[33]}.

**Special Conditions** Blood sugar control patient, cataract surgery, pregnant DME patients, vitrectomized eyes, stable pre-existing glaucoma and endophthalmitis should all be considered while managing DME.

**Blood sugar control** Poor glycemic control is linked to DME degeneration\textsuperscript{[34]}. Glycemic management prevents diabetes from developing and slows down its course\textsuperscript{[35]}. Education on the importance of managing diabetes is crucial for DME patients.
Cataract surgery  Prior to cataract surgery DME should preferably be treated and stabilized. Cataract surgery might provide the highest BCVA.[30] The potential development of cataracts should be discussed with patients using steroids for DME. Steroid therapy causes cataracts to worsen in those who already have them, requiring cataract surgery to attain the maximum BCVA. In DME patients who undergoing peri- operatively, anti-VEGF treatment can be given prior to cataract surgery or steroid treatment may be taken into consideration during cataract surgery.[36].

Treatment in pregnant DME patients  Diabetic pregnant women are more prone to develop retinopathy and disease progression.[37] Despite substantial improvement in DME management, the recommended therapy for DME during pregnancy has remained the same throughout the years. One of the therapies options is laser therapy. Other options include subthreshold laser and intravitreal corticosteroids. Due to concerns about fetal safety, anti-VEGF therapy should be avoided.[38] Intravitreal steroids are regarded as a pregnancy-safe treatment option for DME resistant to laser therapy.[14]. Intravitreal dexamethasone implantation is effective treatment option for pregnant women with DME.[39].

Vitrectomized eyes  The effectiveness of anti-VEGF in vitrectomized eyes is inconclusive.[36] There are no significant changes in BCVA and central macular thickness between vitrectomized and non-vitrectomized eyes after anti-VEGF injections in some studies, whilst others imply decreased intravitreal efficacy because of increased molecular clearance. In both vitrectomized and non-vitreoretinalized eyes, intravitreal dexamethasone implants are beneficial in treating chronic DME.[40].

Stable pre-existing glaucoma  Presently there is no definition of “stable glaucoma”. However, the patient’s clinician will consider glaucoma as ‘stable’ when the IOP remains below the target IOP which will be determined by the patient’s clinician or when patients is on less than three medications and requiring no medication changes over a 48-month period during which no further visual field loss monitored.[41]. Anti-glaucoma treatment should be continued throughout the course of steroid treatment in DME patients with stable pre-existing glaucoma. If IOP is not controlled, treatment should be stopped, and the patient should be sent to a glaucoma specialist.[36].

Endophthalmitis According to large scale meta-analyses, the incidence of endophthalmitis following intravitreal injections range from between 0.035% to 0.065%.[42]. Out of 2928 injections of dexamethasone for DME, only two occurrences of acute endophthalmitis were recorded after treatment in the MEAD research[32]. Retrospective studies conducted in the United States found that the incidences of endophthalmitis following the use of aflibercept, bevacizumab, and ranibizumab were 0.100%, 0.056% and 0.046% respectively.[43]. If patients did not react to intravitreal antibiotics, there are anecdotal situations where the implants were removed following vitrectomy in the lack of recommendations.[44].

DISCUSSION
Appropriate treatment is required to prevent vision loss in DME. Prior to creating an individualized treatment plan for DME, it is crucial to consider risk factors such as the disease’s severity, risk of cataracts, presence of exudates, history of vitrectomy, use of anti-VEGF and steroids, and patient compliance. DME can be treated with intravitreal corticosteroids, vitreoretinal surgery when required, anti-VEGF medications, and retinal laser photocoagulation. Several circulating proinflammatory cytokines such as hyperreflective retinal spots and subfoveal neuroretinal detachment have recently been explored as serum biomarkers for response in individuals with refractory DME, and their possible link with the DR and DME development.[45-46]. DR severity is correlated to cytokine levels but not VEGF levels. The effectiveness of anti-VEGF in vitrectomized eyes is uncertain. According to several research, that higher clearance of the molecule reduces intravitreal effectiveness,[47], while in another research, patients with DME with vitrectomized and non vitrectomized eyes did not significantly vary in BCVA or central macular thickness following anti-VEGF injection.[48]. Triamcinolone acetonide also show similar outcomes.[49]. In both vitrectomized and non-vitrectomized eyes, intravitreal dexamethasone implants are beneficial in treating chronic DME.[40]. However, vitrectomy has no impact on the effectiveness or safety profile of dexamethasone implants for DME.[50]. Spectral domain-OCT offers potential criteria for predicting dexamethasone implants response; nevertheless, more research is needed. When macular thickening cannot be detected clinically but can be measured by OCT, the disease is known as the subclinical DME. Lobo et al[51] found patients with evidence of subclinical DME have relatively small percentage to develop clinically severe DME with continuous monitoring, glycemic control, and comprehensive treatment for other risk factors such as hypertension and hyperlipidemia. The current gold standard of treatment is anti-VEGF therapy however, the use in different type of patients may result in interindividual differences[52].

The pathogenesis of DME is usually complicated by inflammation. In DME patients whose pathophysiology includes inflammation as a major factor, steroids may result in more favorable treatment results. A number of DME inflammatory pathways are also targeted by corticosteroids, particularly intravitreal dexamethasone, beside to VEGF. This involves retinal leukostasis, and synthesis of proinflammatory mediators (interleukin 6, monocyte chemoattractant protein-1),
A study conducted by Sudhalkar et al. to determine the relationship between the position of dexamethasone intravitreal implants in the vitreous cavity and ocular hypertension, found that the treatment satisfaction of DME patients who received dexamethasone intravitreal implants had a statistically significant improvement. However, a study conducted in Sweden with anti-VEGF injections and additional; treatment such as laser and dexamethasone implants showed no change at four years when compared with baseline.

Proliferative DR and DME have different retinal microvascular patterns that indicate small-vessel disease. When DME is present in proliferative DR, patients on oral anti hyperglycemic medications may be at an increase chance of developing cardiovascular disease.

Pan-retinal photocoagulation should be used to treat naive proliferative DR. Patients with non-proliferative DR have two clinical options: the exudate may be used to treat naive proliferative DR. Patients with non-proliferative DR have two clinical options: the exudate may be used to treat naive proliferative DR. Patients on oral anti hyperglycemic medications may be at an increase chance of developing cardiovascular disease. Pan-retinal photocoagulation should be used to treat naive proliferative DR. Patients with non-proliferative DR have two clinical options: the exudate may be used to treat naive proliferative DR. Patients on oral anti hyperglycemic medications may be at an increase chance of developing cardiovascular disease.

The first-line therapy is anti-VEGF injection in conjunction with pan-retinal photocoagulation in patients with severe non-proliferative DR who have progressed to the proliferative stage of DR. In the past several years, DME management has changed as a result of advancements in imaging technology and the introduction of new drugs. Therefore, in the future, in light of new research, our recommendations may need to be changed. In conclusion, laser coagulation is the first line treatment for individuals without central macular disease. Patients with central macular involvement who have not recent experienced cardiovascular disease should be advised to start using anti-VEGF drugs. Steroids or changing to different anti-VEGF medication should be thought about in the event of non-responders. The safety measures that should be taken during steroid/intravitreal dexamethasone treatment owing to its potential side effects, including IOP spike, glaucoma, and cataract development, are well covered by the consensus recommendation.

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