### Criteria Grid

**Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C**

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<tr>
<td><strong>Date of Review:</strong></td>
<td>February 8, 2015</td>
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<tr>
<td><strong>Reviewer(s):</strong></td>
<td>Christine Hu</td>
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#### Part A

<table>
<thead>
<tr>
<th>Category:</th>
<th>Basic Science [ ]  Clinical Science [ ]  Public Health/Epidemiology [ ]  Social Science [ ]  Programmatic Review [x]</th>
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</thead>
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**Best Practice/Intervention:**

- **Focus:**  Hepatitis C [x]  Hepatitis C/HIV [x]  Other: renal diseases, alcohol/drug abuse, hepatitis B etc.
- **Level:**  Group [x]  Individual [ ]  Other: _____________________________________________
- **Target Population:**  HCV patients in Saudi Arabia
- **Setting:**  Health care setting/Clinic [x]  Home [ ]  Other: _____________________________________________
- **Country of Origin:**  Saudi Arabia
- **Language:**  English [x]  French [ ]  Other: _____________________________________________

#### Part B

<table>
<thead>
<tr>
<th>Is the best practice/intervention a meta-analysis or primary research?</th>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
<th>COMMENTS</th>
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<td></td>
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<td></td>
<td>HCV diagnosis and management practice guidelines; Summary of recommendations contained within the guidelines are based on the best available evidence (high quality trials, studies, meta-analysis, systemic reviews or expert opinions) and tailored to HCV patients treated in Saudi Arabia.</td>
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**The best practice/intervention has utilized an evidence-based approach to assess:**

- **Efficacy**  [x]  [ ]  [ ]  Recommendations graded on the basis of evidence (RCTs, meta-analysis, expert...
<table>
<thead>
<tr>
<th>Effectiveness</th>
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<tr>
<td>The best practice/intervention has been evaluated in more than one patient setting to assess:</td>
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<td>Efficacy</td>
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<tr>
<th>The best practice/intervention has been operationalized at a multi-country level:</th>
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<td>There is evidence of capacity building to engage individuals to accept treatment/diagnosis</td>
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<td>There is evidence of outreach models and case studies to improve access and availability</td>
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<td>Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?</td>
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<td>Evidence of manpower requirements is indicated in the best practice/intervention</td>
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<td>Juried journal reports of this treatment, intervention, or diagnostic test have occurred</td>
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<td>Saudi Journal of Gastroenterology</td>
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<td>International guideline or protocol has been established</td>
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<td>Guideline approved only for Saudi Arabia</td>
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<td>The best practice/intervention is easily accessed/available electronically</td>
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<td>Is there evidence of a cost effective analysis? If so, what does the evidence say? Please go to Comments section</td>
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<td>How is the best practice/intervention funded? Please go to Comments section</td>
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<td>The guidelines were approved and endorsed by the Saudi Association for the Study of Liver diseases and Transplantation (SASLT)</td>
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<td>Other relevant information:</td>
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<td>The guidelines need to be updated once additional information regarding direct-acting antiviral therapy is available for the large population of patients with few therapeutic options.</td>
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The Saudi Association for the Study of Liver diseases and Transplantation (SASLT) formed a task force to evaluate the current epidemiology, trends in, and management of the Hepatitis C Virus (HCV) infection in Saudi Arabia. A majority of the members of the committee were hepatologists.

The first step was a broad literature search of published literature on every aspect of the epidemiology, natural history, risk factors, diagnosis and management of HCV. All available literature on the topic was examined critically, and the available evidence was then classified according to its importance. The recommendations contained in it, have been discussed in detail and agreed upon by members of the SASLT task force. The document was also reviewed by a content expert from another country and valuable additional input was incorporated. Subsequently, and after review by the board of directors, the guidelines were approved and endorsed by SASLT.

All recommendations in these guidelines are based on the best available evidence, and tailored to patients treated in Saudi Arabia. They are graded on the basis of evidence.

The purpose of these guidelines is to improve HCV patient care in the Kingdom, and to promote and improve the multidisciplinary care required in the treatment of these patients. They are intended for use by physicians, and offer recommended approaches to the diagnosis, treatment and prevention of HCV. The current document provides a summary list of the recommendations contained within the guidelines.

**GRADING OF RECOMMENDATIONS**

**Grade A**
Recommendation based on at least one high quality randomized controlled trial or at least one high quality meta-analysis of methodologically sound randomized controlled trials.

**Grade B**
Recommendation based on high quality case-control or cohort studies or a high quality systematic review.

**Grade C**
Recommendation based on non-analytic studies (case reports or case series).

**Grade D**
Recommendation based on expert opinion only.

**GOALS OF THESE GUIDELINES**

These are as follows:
1. To provide a concise, evidence-based review of the diagnosis and management of chronic HCV infection in Saudi Arabia.

2. To help initiate plans to prevent HCV infection in the population.
3. To achieve early and accurate diagnosis of patients with HCV infection.
4. To provide an evidence-based approach for the management of HCV-infected patients.
5. To facilitate appropriate and timely referrals between primary, secondary, and tertiary care providers.
6. To identify gaps in the knowledge and understanding of the incidence of HCV in Saudi Arabia that require further research.

EPIDEMIOLOGY

Recommendations
1. HCV testing is recommended for (Grade B).
   a. Individuals with a history of intravenous drug use.
   b. Patients with conditions associated with a high prevalence of HCV infection, including those:
      • With Human Immunodeficiency Virus infection
      • With hemophilia, who received clotting factor concentrates before 1987
      • Who ever underwent hemodialysis
      • With unexplained abnormal aminotransferase levels
   c. Prior recipients of transfusions or organ transplants, including those:
      • Who were notified that they had received blood from a donor who later tested positive for HCV infection
      • Who received a transfusion of blood or blood products before July 1992
      • Who underwent an organ transplant before July 1992
   d. Children born to HCV-infected mothers.
   e. Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood.
   f. Sexual partners of HCV-infected persons.
2. Individuals found to have HCV infection should be counseled regarding prevention of the spread of the virus to others. They should be informed that transmission occurs through contact with their blood, and they should therefore be informed about how to take precautions against the possibility of such exposure (Grade B).

NATURAL HISTORY

Recommendations
1. The Saudi Observatory Liver Disease Registry (SOLID) is a valuable source of data for HCV in Saudi Arabia, and efforts must be made to improve patient registration and the utilization of the registry (Grade D).
2. Large epidemiologic studies are needed to further define the epidemiologic features and natural history of HCV infection in Saudi Arabia (Grade D).
3. Patients with significant fibrosis caused by HCV are at significant risk for disease progression (Grade A).
4. Patients with cirrhosis caused by hepatitis C are at high risk for the development of hepatocellular carcinoma (HCC), and these patients should be regularly screened to detect the onset of early HCC (Grade A).

LABORATORY TESTING

Recommendations
Conditions for these recommendations are:
1. Clinical signs and symptoms of chronic HCV are nonspecific, the liver chemistry and radiographic findings poorly corroborate with the activity and extent of the damage to the liver in early and late stages of the HCV infection. Diagnosis of HCV infection is based on detection of anti-HCV antibodies by enzyme immunoassay and HCV RNA by a sensitive molecular method (lower limit of detection <50 IU/ml), ideally a real-time PCR assay. The diagnosis of chronic hepatitis C is based on the detection of HCV infection (positive anti-HCV antibodies and HCV RNA) in a patient with signs of chronic hepatitis. Rarely, in profoundly immunosuppressed patients, anti-HCV antibodies may not be detected, but HCV RNA is always present.
2. Patients with suspected HCV infection should be tested for anti-HCV by an up-to-date (currently, third generation) ELISA test (Grade B).
3. Immunosuppressed patients may require a test for HCV RNA, if hepatitis is present, but anti-HCV antibodies are undetectable (Grade B).
4. The measurement of HCV RNA concentrations in serum and identifying the HCV genotype are recommended and should be used to determine the duration of treatment (Grade A).
5. Liver fibrosis can be broadly established by means of either biochemical or hematological tests like alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time, platelets, AST-to-platelet ratio index (APRI), those that include specific indirect markers of liver fibrosis, such as a-2-macroglobulin; those that incorporate only direct markers of liver fibrosis (MP3), or combinations of direct and indirect markers (Hepascore, FibroMeter). Sufficient evidence exists to support the view that algorithms perform well in the detection of significant fibrosis (META VIR score F2-F4). Thus, their use in patients with chronic hepatitis C can be recommended for this purpose (Grade A).
6. Liver biopsy is valuable for assessing the status and level of liver inflammation, the potential progression
of fibrosis, and the presence or absence of cirrhosis. It is not mandatory, and should only be considered in patients who are hesitant about HCV treatment, in order to make decisions regarding urgency of treatment. Standard histological scoring systems by a suitably experienced pathologist should be used to encourage uniformity of histological reports. In addition, the risks and benefits of liver biopsies should first be carefully explained to the patient (Grade B).

TREATMENT OF CHRONIC HCV PATIENTS

Indications and contraindications of antiviral therapy
Recommendations
1. Eradication of HCV infection is the primary purpose of antiviral therapy (Grade A).
2. Patients with chronic HCV infection who have had no prior therapy and have compensated liver disease should be evaluated and considered for anti-HCV therapy (Grade B).

Treatment regimen and antiviral side effects
Recommendations
1. In chronic HCV non-genotype 1 infected patients with normal renal function, combination therapy with pegylated IFN-α (peg-IFN) and ribavirin (RBV) is considered the standard of care (Grade A).
2. After initiating combination antiviral therapy, patients should be seen at monthly intervals in the first three months, and then every two to three months until the end of treatment. Patients who have completed the treatment regimen should be seen six months after the end of treatment. Individualized close follow up should be planned, based on the severity of any adverse events (Grade D).

Adverse events associated with pegylated interferon and ribavirin
Recommendations
1. The peg-IFN-α and RBV should be temporarily interrupted if the absolute neutrophil count (ANC) falls below 500/mm³, or hemoglobin falls below 8.5 g/dl respectively (Grade A). The combination of peg-IFN-α and RBV should be stopped if severe hepatitis flare or severe sepsis occur (Grade C).
2. The use growth factors is associated with an increased cost of therapy and a lack of sufficient evidence towards improvement of sustained virologic response (SVR) (Grade B). When deciding to use recombinant erythropoietin (EPO) and G-CSF, an 80% or more of RBV and peg-IFN-α dose should be maintained during the course of therapy so that the benefit of adherence can be achieved (Grade D).

3. Peg-IFN-α-induced neutropenia does not correlate with increased frequency of infection episodes (Grade C). The use of granulocyte colony-stimulating factor (G-CSF) does not reduce the rate of infections (Grade C).

Improving treatment success rates
Recommendations
1. In order to optimize SVR rates, complete adherence to both peg-IFN-α and RBV regimens should be emphasized (Grade B).
2. Pre-treatment weight reduction in obese individuals and good control of diabetes mellitus may increase the chance of SVR (Grade B).

TREATMENT OF CHRONIC HCV NAÏVE PATIENTS

Genotypes 1 and 4 HCV infection
Recommendations
1. Treatment with peginterferon plus ribavirin should be planned for 48 weeks; the dose for peg-IFN-α2a (Pegasys®) is 180 µg subcutaneously per week, and for peg-IFN-α2b (PegIntron®) is 1.5 µg/kg subcutaneously per week together with weight-based (13-15 mg/kg/day) RBV (Grade A).

Genotypes 2 and 3 HCV infection
Recommendations
1. Treatment with peginterferon plus ribavirin should be planned for 24 weeks; the dose for peg-IFN-α2a (Pegasys®) is 180 µg subcutaneously per week, and for peg-IFN-α2b (PegIntron®) is 1.5 µg/kg subcutaneously per week, together with 800 mg RBV (Grade A).
2. Adequate RBV doses at 15 mg/kg should be administrated to patients with genotypes 2 and 3 who have baseline factors that predict low responsiveness to peg-IFN, such as obesity and cirrhosis (Grade D).

Genotype 5 and 6 HCV infection
Recommendations
1. Treatment with peg-IFN plus ribavirin should be planned for 48 weeks; the dose for peg-IFN-α2a (Pegasys®) is 180 µg subcutaneously per week, and for peg-IFN-α2b (PegIntron®) is 1.5 µg/kg subcutaneously per week, together with a weight-based dosage of RBV (Grade C).

Direct-acting antivirals in treatment naïve patients
Recommendations
1. The combination of peg-IFN/RBV is the approved standard of care for chronic hepatitis C, especially non-genotype 1 (Grade A)
2. The most effective regimen for treating HCV genotype 1 is the use of triple therapy, with boceprevir or telaprevir in combination with peg-IFN/RBV (Grade A).
Individualized treatment duration according to on-treatment virologic response

Recommendations
1. A highly sensitive quantitative HCV RNA PCR with a lower limit of detection of 50 IU/ml or less should be used when treating HCV infection (Grade A).
2. Before initiating antiviral therapy, patients must have genotyping performed. Knowledge of the HCV genotype will determine the dose of ribavirin and treatment duration (Grade A).
3. Antiviral therapy must be discontinued if patients fail to achieve more than 2 log reduction in HCV RNA at week 12 of treatment (Null response) (Grade A). Patients who achieve more than 2 Log reduction in HCV RNA at week 12 but remain detectable (≥50 IU/ml) at week 24 should discontinue treatment (partial response) (Grade A).
4. Shortening the duration of antiviral therapy in patients who achieve rapid virologic response (RVR) should also be attempted in patients who lack pretreatment negative predictors (Grade B).
5. Extension of antiviral therapy to 72 weeks should be considered in HCV genotype 1 and 4 patients if delayed virological response is obtained (Grade A). Similarly, patients with genotypes 2 and 3 who have no RVR with pre-treatment negative predictors, may be considered for extension of the treatment to 48 weeks (Grade C).

RE-TREATMENT OF EXPERIENCED CHRONIC HCV PATIENTS

Recommendations
1. HCV patients with non-genotype 1 infection experiencing prior non-response or relapse after non-peg-IFN therapy with or without RBV, or previously treated with peg-IFN monotherapy, may be considered for a second course of therapy with peg-IFN plus RBV (Grade B).
2. HCV patients with non-genotype 1 infection who had previously shown a null or partial response pattern, where an adequate dose of peg-IFN and RBV had been administered during the first course of antiviral therapy, should not be subjected to another course of combination therapy using same or different peg-IFNs (Grade B). These patients should be followed up for progression of liver disease and could wait for new, more effective protease inhibitors (Grade C).
3. Non-responders or relapser patients with genotype 1 HCV infection after treatment with either peg-IFN or non-peg-IFN should be considered for re-treatment with a triple therapy regimen, using direct acting antiviral agents (Grade A).

Role of maintenance antiviral therapy in non-responders

Recommendations
1. Maintenance therapy with peg-IFN is not recommended for patients with bridging fibrosis or cirrhosis who have previously failed a course of peg-IFN and RBV (Grade A).

Direct-acting antivirals in treatment-experienced HCV patients

Recommendations
1. Patients with HCV genotype-1 who have failed prior standard therapy with peg-IFN-α and RBV, can be treated with triple therapy with boceprevir or telaprevir, together with peg-IFN-α and weight-based RBV (Grade A).

TREATMENT OF ACUTE HEPATITIS C

Recommendations
1. There is no clear evidence on the optimum timing for the start of acute HCV therapy, but treatment can be delayed up to 12 weeks after acute onset of hepatitis to allow for spontaneous resolution (Grade B).
2. Treatment with either standard IFN or peg-IFN-α monotherapy for 24 weeks is recommended, however, pegINF-α is preferable because of its convenience in administration (Grade B)

TREATING SPECIAL POPULATIONS

Treatment of patients with severe liver disease

Recommendations
1. Compensated cirrhotics should be treated to prevent future complications (Grade A).
2. Treatment should be started carefully, with close monitoring for side-effects, and lower dosages might be used once the patient has been placed on a liver transplant list, aiming for HCV clearance prior to transplantation. However, this approach is applicable in only around 50% of patients, and tolerance is poor, particularly in patients with decompensated cirrhosis (Grade C).
3. Cirrhotics should undergo regular surveillance for HCC, irrespective of SVR (Grade B).

Post-liver transplantation recurrence

Recommendations
1. Once chronic hepatitis C recurrence has been documented histologically after liver transplantation, cautious treatment by an experienced physician should be started (Grade A).
2. Urgent treatment should be initiated in patients with
significant fibrosis one year after transplantation since it predicts rapid disease progression and graft loss (Grade B).

3. Liver biopsy while on treatment is indicated, if liver enzymes worsen, to rule out graft rejection, although it is rare (Grade C).

**HIV co-infection**

**Recommendations**

1. Treatment regimen is the same in HIV co-infected and non-HIV infected patients but the dose of RBV should always be weight-based (Grade B).
2. Treating HCV in co-HIV infected patients may require longer treatment duration (72 weeks for genotype 1 and 48 weeks for genotypes 2 and 3) (Grade B).
3. Before using RBV, the physician should make sure that patients are not on AZT, or ddI (Grade C).

**HBV co-infection**

**Recommendations**

1. Treatment regimen is the same as for mono-infected patients (Grade B).
2. Concurrent HBV nucleoside/nucleotide analogue therapy is indicated if there is a significant HBV replication at any stage, pre-, peri- and post-HCV clearance (Grade C).

**Treatment of patients with renal disease**

**Recommendations**

1. Liver biopsy should be individualized if the decision is made to treat HCV in a chronic renal disease patient (Grade C).
2. The same standard combination antiviral therapy can be used to treat persons with chronic HCV infection and mild renal disease (GFR >60 mL/minute) (Grade C).
3. Non-hemodialysis patients with severe renal disease can be treated cautiously with reduced doses of both peg-IFN (alpha-2a, 135 µg/week; alpha-2b, 1 µg/kg/week) and RBV (200-800 mg/day) (Grade C).
4. Patients on hemodialysis can safely be treated with peg-IFN-monotherapy (Grade A).
5. Combination treatment with individualized doses of RBV can be considered in selected patients (Grade C).
6. Patients on a renal transplant list should be treated prior to transplantation to avoid the risk of treatment-induced acute graft rejection post-transplantation (Grade B).
7. Treatment is recommended post-renal transplant only in selected patients, and those with fibrosing cholestatic hepatitis (Grade C).
8. Patients with cryoglobulinemia and mild to moderate proteinuria or slowly progressive renal disease can be treated with either standard IFN or reduced doses of peg-IFN-α and RBV (Grade C).
9. Patients with cryoglobulinemia and marked proteinuria with evidence of progressive renal disease or an acute flare of cryoglobulinemia can be treated with rituximab, cyclophosphamide plus methylprednisolone, or plasma exchange, followed by interferon-based treatment once the acute process has subsided (Grade C).

**Alcohol and drug abuse**

**Recommendations**

1. Alcohol consumption should be strongly discouraged (Grade A).
2. Patients on stable maintenance substitution can be treated for HCV in an interdisciplinary team who need to also consider their slightly reduced SVR-rates when compared to conventional HCV patients, as the treatment should be individualized (Grade B).
3. Illicit drug users should continue receiving support and counseling parallel to HCV treatment (Grade C).

**Treatment of persons with psychiatric illnesses**

**Recommendations**

1. Patients with HCV infection and concomitant mental and psychiatric disorders can be considered for treatment using the currently approved regimens (Grade C).
2. Treatment of hepatitis C infection in patients with psychiatric disorders should be undertaken only with the support of a multi-disciplinary team that should include psychiatric counseling services prior to therapy (Grade C).

**Hemoglobinopathies**

**Recommendations**

1. Patients with hemoglobinopathies can be treated with combination therapy, but need careful monitoring for hematologic side effects (Grade C).

**CONCLUSIONS**

SASLT Guidelines for HCV provided a concise, updated, evidence-based review of the diagnosis and management of chronic hepatitis C virus infection in Saudi Arabia. This may help to initiate plans to prevent HCV infection in the population, to bring about early and accurate diagnosis of patients with HCV infection, to facilitate appropriate and timely referrals between primary, secondary, and tertiary care providers and to identify gaps in the knowledge and understanding of the incidence of HCV in Saudi Arabia that require further research. As noted above there is a large population of patients with few therapeutic options, and direct-acting antiviral therapy has become the focus of investigations and once additional information is available, this guideline needs to be updated.
DISCLOSURES

Dr. Sanai is a consultant for, advises, is on the speakers’ bureau of, and received grants from Bristol-Myers Squibb. He has been a consultant for, and advised Scherring-Plough and Merck Sharp and Dohme, is on the speakers’ bureau of, and received grants from Roche and Glaxo-SmithKline. Dr. Altraif is a consultant and advises Scherring-Plough, Merck Sharp and Dohme and Roche, and has received grant support from Roche. Dr Alghamdi is on the speakers’ bureau of Bristol-Myers Squibb, Roche and Merck Sharp and Dohme. Dr. Alswat advises and is on the speakers’ bureau of Merck Sharp and Dohme. Dr. Alfaleh has been a consultant for Schering Plough and has received grant support from Schering Plough.

Source of Support: Nil, Conflict of Interest: None declared.

Author Help: Online submission of the manuscripts

Articles can be submitted online from http://www.journalonweb.com. For online submission, the articles should be prepared in two files (first page file and article file). Images should be submitted separately.

1) **First Page File:**
Prepare the title page, covering letter, acknowledgement etc. using a word processor program. All information related to your identity should be included here. Use text/rtf/doc/pdf files. Do not zip the files.

2) **Article File:**
The main text of the article, beginning with the Abstract to References (including tables) should be in this file. Do not include any information (such as acknowledgement, your names in page headers etc.) in this file. Use text/rtf/doc/pdf files. Do not zip the files. Limit the file size to 1 MB. Do not incorporate images in the file. If file size is large, graphs can be submitted separately as images, without their being incorporated in the article file. This will reduce the size of the file.

3) **Images:**
Submit good quality color images. Each image should be less than 4 MB in size. The size of the image can be reduced by decreasing the actual height and width of the images (keep up to about 6 inches and up to about 1200 pixels) or by reducing the quality of image. JPEG is the most suitable file format. The image quality should be good enough to judge the scientific value of the image. For the purpose of printing, always retain a good quality, high resolution image. This high resolution image should be sent to the editorial office at the time of sending a revised article.

4) **Legends:**
Legends for the figures/images should be included at the end of the article file.