Role of TNF alpha in schistosoma mansoni infection and cirrhotic liver

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Abstract: Hepatitis C is a wide spread viral disease that is the most common cause of cirrhotic liver. Schistosomiasis has been the most important public health problem in Egypt. Periportal fibrosis (PPF) of liver is due to deposition of collagen and is called pipetem. Cirrhosis is a diffuse process of fibrosis. TNF α is a proinflammatory cytokine tumour has emerged as a key factor in various aspects of liver disease. The goal of this study to assess the levels of serum TNF alpha in patients with schistosomiasis mansoni and patients with hepatic cirrhosis due to virus C infection and their role in the process of liver fibrosis and cirrhosis. A cross-sectional descriptive study carried out in outpatient clinic, Ahmed Maher Teaching hospital, Hepatology Department, Egypt. This study was performed on 30 subjects: 10 schistosomal and 10 cirrhotic, compared to 10 control subjects; apparently healthy, parasite-free. The following laboratory investigations were done: parasitological investigations include stool analysis by simple sedimentation method and kato-katz technique, routine liver enzymes and serum TNF-α by an enzyme linked immunosorbent assay (ELISA). Detection of hepatic virus C +ve patients was confirmed via +ve anti HCV antibodies (Abs) (ELISA), and negative hepatitis B surface antigen (HBs Ag). Abdominal sonar was done to diagnose liver cirrhosis and detect degree of PPF. In schistosomiasis mansoni and cirrhotic group, serum levels of TNF-α were significantly higher than those of control group (P<0.05) and significantly increase the risk of developing advanced Periportal Fibrosis (95% CI 1.01 to 2.54, P = 0.048). These results suggest that TNF alpha may be considered as a marker for morbidity in Hepatitis +ve virus C infection, whereas in schistosomal patients, considered as a marker for degree of periportal fibrosis.

Keywords: Schistosomiasis mansoni, PPF (Periportal Fibrosis), Cirrhosis, Tumour Necrosis Factor Alpha (TNF-α).

1. INTRODUCTION

Schistosomiasis is caused by infection with parasitic trematodes of the genus Schistosoma. Adult Schistosoma mansoni worms live in the mesenteric blood vessels around the gut, and the hepatoplenic form of the disease is thought to be associated with the host’s immune response to parasite eggs lodged in the presinusoidal capillary beds of the liver [1]. Most infected individuals living in schistosomiasis endemic areas do not suffer severe liver damage, but a minority go on to develop hepatoplenic morbidity characterized by hepatosplenomegaly, hepatic periportal fibrosis, and portal hypertension, which may lead to the formation of esophageal varices and hematemesis. The prevalence of hepatoplenic schistosomiasis varies significantly between different endemic areas[2]–[4]. Although the risk of developing severe hepatoplenic disease is higher in individuals who experience higher intensities of infection.[5]

In Schistosoma mansoni infection, periportal fibrosis of the liver is a consequence of excessive deposition of collagen along the branches of the portal tract.[6] Liver fibrosis is the net result of the imbalance between the collagen fiber synthesis and decomposition. The amount of collagen increases and also the ratio of fibro-connective tissue versus liver cellular tissue increases.[7] The classic, pipetem fibrosis is due to fibrotic bands originating from the granulomas, and the disturbance of the hepatic architecture is not sufficient to justify the term "cirrhosis".[8],[9]. Cirrhosis is a diffuse process of fibrosis following hepatocellular necrosis with nodule formation.[10] In the liver, necrosis is associated with portal inflammation, interface hepatitis,[11] collapse of hepatic lobules, formation of diffuse fibrous septa and nodular regrowth of liver cells.[12] Septal fibrosis appears as periportal, portal-portal and portal central septa. With ongoing necrosis, inflammation associated with progressive fibrosis and parenchymal regeneration, eventually leads to cirrhosis. [13] Tumour necrosis factor-α (TNF-α) is a cytokine produced mainly by activated macrophages and in smaller amounts by several other cell types. TNF-α functions as a two-edged sword in the liver. TNF-α plays a key role in the proliferative response during liver regeneration. It functions both as a comitogen and as an inducer to the transcription factor kB, which has antiapoptotic effects. On the other hand, TNF-α is an important pathogenic mediator in patients with viral hepatitis by inducing hepatocyte apoptosis.[14]

1.2. RESEARCH QUESTION

The research question for the purpose of this study is: ‘Is the serum levels of TNFα related to the degree of liver fibrosis in cirrhotic patients and patients with schistosomiasis mansoni?’
1.3 OBJECTIVE
The objective of the study is to measure the levels of serum TNF alpha in patients with schistosomiasis and patients with hepatic cirrhosis due to virus C infection and their role in the process of liver fibrosis and cirrhosis in hepatic patients attending hepatology outpatient clinic, Ahmed Maher Teaching hospital.

2. MATERIALS AND METHODS

2.1 RESEARCH AND DESIGN
This is a cross sectional study conducted in (Ahmed Maher Teachung hospital, Egypt in the period between July 2012 – and –July 2013.

2.2 STUDY SAMPLE:
The study participants included thirty attending outpatient hepatology clinic. The sampling method was convenient and the sample size was thirty ($n = 30$) participants in outpatient consented to participate in the study.
The study participants were divided into three equal groups:

- **Group I**: 10 apparently healthy, parasite free, individuals with matched age and sex were enrolled as control.
- **Group II**: 10 patients with established Schistosoma mansoni infection. Diagnosis of schistosomiasis was done by detection of living S.mansoni ova (simple sedimentation and kato-katz technique for egg counting).
- **Group III**: 10 adult patients with cirrhotic liver of pure viral C origin with +ve anti HCV antibodies (Abs), and negative hepatitis B surface antigen (HBs Ag). Proven by sonar also.

The inclusion criteria for this study were individuals from endemic areas who have at least one positive parasitological exam for S. mansoni.

The eligibility criteria are as follow: 1, they had a diagnosis of schistosomiasis and/or hepatitis C +ve at least one year ago; 2, they had hepatic fibrosis diagnosed by ultrasonographic imaging, they were at least 25 year old. A cross sectional study differs from a longitudinal study in that it uses observation representing a single point in time.

2.3 EXCLUSION CRITERIA
We include individuals between twenty five and 60 years old. We did not include alcoholic individuals and those with positive serology for HIV, HTLV-1, or hepatitis virus types B, all of which are conditions that could interfere with the immunological response. Cognitive impairment or language barriers were not included in the sample.

2.4 SAMPLE SIZE:
In order to correct any losses and provide a better breakdown of the independent variables, the sample size was adjusted by a proportional factor of 1.25. Thus, the sample size for this study was established at 30 patients. The number of patients needed to assess the internal consistency was considerably lower, being obtained by Non-Parametric Approach to calculate sample size based on scales in Healthcare Area, which estimates the sample size by the number of items and categories of the data collection instrument.

2.5 CLINICAL EVALUATION

2.5.a Schistosomiasis patients:
Patients with +ve schistosoma mansoni were selected randomly from people who live in poor sanitary conditions and agriculture is the predominant occupation, where unsanitary water is used for bathing, washing clothes and utensils, and leisure, exposing the residents to high risk of Schistosoma infection. Diagnosis of schistosomiasis was done by detection of living S.mansoni ova in stool samples after a cross-sectional parasitological surveys using Kato-Katz [15] and sedimentation techniques were conducted in three different stool samples collected on different days.

2.5.b Hepatitis C positive patients (HCV+ve patients):
Patients with cirrhotic liver of pure viral C origin were diagnosed with +ve anti HCV antibodies (Abs), and negative hepatitis B surface antigen (HBs Ag). Abdominal sonogram was done to confirm the diagnosis.

2.6. ULTRASOUND EXAMINATION
Abdominal ultrasound (USG) were performed using the Quantum 2000 Siemens and Elegra Siemens ultrasound with a convex transducer of 3.5–5.0Mhz. Liver span was measured in the midclavicular line and midline. The liver was also examined for smoothness of surface, echogenicity and posterior attenuation of the sound bean, and portal vein diameter outside the liver midway between its entrance into the portal hepatic and its first bifurcation in the liver. Periportal fibrosis was observed as multiple diffuse echogenic areas.

Grading of periportal fibrosis was determined by the mean total thickness of four portal tracts after the first division from the right and left branches of portal vein (PT1) as follow: degree 0, mean thickness < 3 mm; degree I, mean thickness 3 to 5 mm; degree II, mean thickness > 5 to 7 mm; and degree III mean thickness > 7mm (16–18).

The scores of periportal fibrosis were grouped according to the severity, being degree 0 without periportal fibrosis. Incipient periportal fibrosis was considered to individuals with degree I and moderate to severe periportal fibrosis to those with degrees II and III [19].

2.7. BLOOD SAMPLING
Venous blood was withdrawn from each individual after an overnight fast. Blood was left to clot and was then centrifuged. Serum was removed and routine laboratory tests were performed on the same day. Serum samples for assay of HCV Abs, HBs Ag and TNF- $\alpha$ were stored at -20 °C until time of assay.

2.8. LIVER ENZYMES
Aspartate and Alanine aminotransferases (AST) and (ALT) using the Autoanalyzer Konelab 30i.

2.9. SERUM TNF- $\alpha$
Serum TNF- $\alpha$ was determined by an enzyme linked immunosorbent assay. This assay employs the quantitative non-competitive sandwich enzyme immunoassay technique using one polyclonal antibody and another monoclonal antibody specific for TNF- $\alpha$ (Bender Med System Vienna Austria).
2.10 STATISTICAL ANALYSIS

Data analysis was performed using SPSS software, release 12. Statistical analyzes involved: descriptive analyzes the significance test to check the normality of continuous variables, chi-square and correlation test to compare between different groups using the Kruskal-Wallis test to find relationship between different groups as regards of the TNF-α, sonographic findings and other independent variables, and binary logistic regression. Chi square analysis was used to test for statistical significance. (P < 0.05 = statistical significance).

2.11 ETHICAL ASPECTS

The protocol for the study was approved by the Ethical and Research Committee of the Hospital. Data were collected only after the informed consent had been signed by all patients.

3. RESULTS

Table (1): Some liver enzyme assay of the studied groups:

<table>
<thead>
<tr>
<th></th>
<th>Controls (group I)</th>
<th>Schistosomiasis (group II)</th>
<th>Cirrhosis (group III)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(AST) unit/l</td>
<td>24.2±7.3</td>
<td>21.6±7</td>
<td>33.3±25</td>
<td>0.0001*</td>
</tr>
<tr>
<td>(ALT) unit/l</td>
<td>11.8±5.5</td>
<td>7.3±2.8</td>
<td>31±15.5</td>
<td>0.0001*</td>
</tr>
</tbody>
</table>

Data are presented as mean ± S D and were analyzed using Kruskal-Wallis test. (P < 0.05 = statistical significance).

Liver enzymes tests results were significantly different in the three studied groups.

Table (2): Serum TNF-α levels in the three studied groups:

<table>
<thead>
<tr>
<th></th>
<th>Controls (group I)</th>
<th>Schistosomiasis (group II)</th>
<th>Cirrhosis (group III)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α (pg/ml)</td>
<td>158.3±10</td>
<td>184.2±38</td>
<td>18.4±38</td>
<td>0.0001*(I,II) 0.0001*(I,III) 0.027*(II,III)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD and were analyzed using Mann Whitney-test. (P< 0.05 = statistical significance).

(I, II) controls versus schistosomiasis.

(I, III) controls versus cirrhosis.

(II, III) schistosomiasis versus cirrhosis.

Tabe (2) shows that serum TNF-α levels in the schistosomal group were significantly higher than the values of the controls. Also in the cirrhotic group the values were significantly higher when compared with those of the controls...mean value was significantly higher in cirrhotic group compared to schistosomal patients (group II), P =0.027.

Table (3): Crude and Adjusted Odds Ratios for Levels of TNF and Periportal Fibrosis

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>1.51</td>
<td>0.94, 2.41</td>
<td>0.089</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.55</td>
<td>0.97, 2.51</td>
<td>0.066</td>
</tr>
</tbody>
</table>

In this study all cases of schistosomiasis were moderate to severe degree of PPF (grade II and III).

Table (3) shows that elevated levels of TNF-α to Sh. mansoni at baseline significantly increased the risk (OR = 1.63) of moderate to severe periportal fibrosis in a model adjusted for age and sex only(95% CI 1.01 to 2.54, P = 0.048).

4. DISCUSSION

The development of periportal fibrosis can occur as a result of chronic schistosomiasis infection and accounts for the severe forms of the disease. [20] This fact characterizes schistosomiasis as a serious public health problem. In the present study, results of the routine laboratory liver enzymes tests show significant difference concerning the AST and ALT between the three studied groups (Table 1) which agrees with results of other studies.[21] Environmental factors could influence both the prevalence of the hepatosplenic manifestation of schistosomiasis and immune responses. Such influences could be important cofactors involved in a causal linking of elevated TNF with disease, or merely confounding factors, having an independent effect on the occurrence of hepatosplenic involvement. [22]

The majority of individuals who had the most severe degree of periportal fibrosis were over 40 years of age, and there was no influence of gender on periportal fibrosis development. This is in agreement with other authors who have demonstrated that most individuals who develop periportal fibrosis are over 50 years of age. [23] This could be explained by the immune response induced by constant reexposure to the parasite over lifetime, or by the slow process of fibrosis formation. Therefore, younger individuals probably have not been exposed long enough to the cumulative effects of collagen deposition in the periportal tract. [24]

Many variables may influence the magnitude of the immune response in human schistosomiasis which includes gender and age, [25] intensity of infection, [26]-[28] and genetic characteristics of the population. [29] However, the reason why severe fibrosis develops only in a fraction of the population, which is under the same environmental conditions as others who do not develop fibrosis, remains not well understood. Moreover, individuals without periportal fibrosis had a higher parasite burden than individuals with incipient periportal fibrosis. A possible explanation for this observation is that chronic infection can lead to intestinal fibrosis that impairs the migration of eggs to the intestinal lumen and thereby decreases eggs count in parasitological exams. [30]

Schistosoma-associated fibrosis is influenced by several counter regulatory cytokines including IL4, IL13, TNF-α and IFN-α.[32]

TNF-α is a cytokine that may participate in the granuloma formation and evolution of fibrotic tissue process. Hoffmann and colleagues (1998) have demonstrated in experimental models that TNF-α exerts a protective effect, whereas other authors attribute to the TNF-α proinflammatory and profibrogenic effects. [33]

We have found in our study that the cells of individuals with incipient or moderate to severe fibrosis, even without antigenic stimuli, produced higher levels of TNF-α when compared to
those without fibrosis. Additionally, there was a positive association between serum levels of TNF-α and S. mansoni parasite burden, which suggests that this cytokine may contribute to the liver pathology observed in schistosomiasis [34].

In agreement of the role of TNF-α in the development of liver pathology due to schistosomiasis, a study conducted in a schistosomiasis endemic area in Brazil has demonstrated that individuals with moderate to severe periportal fibrosis have higher serum levels of TNF-α than those without fibrosis. [35] Considering that TNF-α was positively associated with S. mansoni parasite burden, they may represent biomarker for the progression of liver pathology in schistosomiasis. Larger casuistic further studies are needed however to confirm the role of this cytokines and chemokines in the development of periportal fibrosis in human schistosomiasis. In liver cirrhosis due to hepatitis C affection, increased levels of TNF-α could be explained by a different mechanism. As recovery requires hepatic regeneration, TNF-α was found to promote regeneration and hepatocyte proliferation. TNF-α control replication of the hepatocytes and of non parenchymal cells which constitute about 40% of liver cells. TNF-α may have both growth promoting and inhibitory properties on hepatocytes. [36] It can thus be concluded that the increased level of TNF-α might cause inhibition of the process of fibrogenesis in case of schistosomiasis, while in cirrhosis, it could inhibit fibrosis and stimulate hepatocyte regeneration and proliferation as well.

In the present study, the serum levels of TNF-α were significantly increased in both schistosomal and cirrhotic patients when compared to controls (p = 0.0001, p = 0.0001 respectively). The mean value was significantly higher in the cirrhotic group as compared to the schistosomal patients (p = 0.027) (Table 2). This comes in agreement with other studies. [37]-[39]. Also Vaillant B and co-workers [40] concluded that TNF-α upregulates extracellular matrix protein production. It is a potent inducer of the synthesis of matrix metalloproteinases (MMP), a family of endopeptidases involved in the metabolism of collagen. TNF-α, MMP, and their inhibitors (tissue inhibitors of MMPs [TIMPs]) were reported to be related to the risk of hepatic fibrosis due to schistosomiasis. However, other studies suggested that TIMPs do not inhibit fibrogenesis and the roles of MMP and TIMPS in increasing or decreasing the risk of hepatic fibrosis, respectively, were questionable. Accordingly, the functional role of TNF-α in the development of periportal fibrosis is still unknown. [38] Some previous human studies have pointed toward the involvement of TNF in hepatosplenic schistosomiasis. In a well-controlled study, Zwingenberger and colleagues [41] found higher TNF levels in serum of patients with hepatosplenic disease compared with patients without organomegaly. Similar observations were made on Egyptian schistosomiasis patients who were not controlled for age and intensity of infection. [42], [43] In addition, TNF secreted by nonstimulated monocytes and serum TNF was found to be elevated in S. haematobium-infected patients with carcinoma of the urinary bladder. [44] Other studies reported that the direct cause of hepatic periportal fibrosis is the T cell dependent granuloma that develops around Schistosoma ova. Granuloma and fibrosis are tightly regulated by cytokines and TNF-α was found to be associated with aggravation of disease. [45] During cirrhosis, there is always liver regeneration. TNF-α is required for normal hepatocyte proliferation during liver regeneration.[37] These pathophysiologic responses of the liver may exacerbate the disease process leading to increased fibrogenesis in cirrhosis and hepatomas. [36]

TNF-α has an antiapoptotic effect that leads to the induction of the transcription nuclear factor-kB. At the same time it is a mediator of hepatotoxicity by inducing hepatocyte apoptosis.[37] Hepatitis C proteins interact with TNF-α receptors but it is not clear whether this interaction promotes or prevents apoptosis.[46] It seems, that the level of TNF-α must be well modulated for the outcome to be effective regeneration rather than liver damage.[36].

5. CONCLUSION

TNF-α is significantly high in individuals with periportal fibrosis. Considering that it was positively associated with S. mansoni parasite burden, therefore it may represent biomarker for the progression of liver pathology in schistosomiasis. Larger casuistic further studies are needed however to confirm the role of these cytokines and chemokines in the development of periportal fibrosis in human schistosomiasis. In schistosomiasis and cirrhosis, the main effect of significantly increased level of TNF-α is important for the regeneration and proliferation processes. The main effect of the significantly increased level of TNF-α is inhibition of hepatocyte apoptosis (cell death) in a trial to protect the liver cells.

6. RECOMMENDATIONS

Based on our study we hope that:

6.1. More researches should be directed to better understand the role of TNF-α in periportal fibrosis due to Schistosomiasis.

6.2. TNF-α can be used as dependable marker in individuals with periportal fibrosis and for morbidity in hepatitis C+ve infection.

7. ACKNOWLEDGEMENTS

We wish to express profound gratitude to the management and staff of Ain shams university hospital and Ahmed Maher teaching hospital in particular the staff of the laboartory unit, and department of hepatology respectively for their immense support during the study.

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**Author Profile**

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**First Author Profile:** Manar ezz elarab ramadan said ,
Graduated from Ain Shams university, Faculty of Medicine,
December 1996(Very Good).
- Master degree of basic medical science, parasitology,
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- MD(Doctorate) degree (basic medical science,parasitology 2008),Faculty of Medicine Cairo university.
- Total Quality Management Diploma in healthcare from Arab Medical Union ,Arab Institute For Continuing Professional Development in collaboration with 6th October University from November 2010 to Jan 2012.
- Certified professional in healthcare quality(CPHQ),(NAHQH) (National Association for Healthcare Quality) 30/11/2012.-MY
- Current job is Parasitological Fellow in NHTRI,Egypt.

**Research work**

In 2005 to submit for the Master degree, it was(Sensitivity of trichrome stain versus ELISA in diagnosis of giardiasis) under supervision of Prof: Abdulla Michal Boghdadi, Prof: Amal Mohame Nour El Hoda and Mousa Abdel Gawd Moussa.

In 2008 to submit MD degree under supervision of Prof: Galila Amed Bassiony,Maysa Mohamed Kamel ,Amal Mohamed Nour El Hoda and Ahmed Hussein Mahmoud ,it was(circulating antigen levels in different clinical forms of schistosoma mansoni infections).

**Membership**

- Medical lab consultant from Egyptian medical syndicate since 2011.
- Member of ArCQQA(Arab Centre for Quality and Hospital Qualification for Accreditation)Arab Medical Union 2011.
- Member of African society of quality(non-profit and non-governmental registration number 3512of 2009,Giza,Cairo.

**Achievements:** I have experience in direct (microscopical) examinations, staining and indirect practical methods for dealing with specimens for parasitological diagnosis of human medical parasites.

-During my work at the department of parasitology in National Hepatology and Tropical Medicine Research institute(NHTRI)in Cairo, I trained on different recent techniques used in parasitology research work:
  a.ELISA.
  b.Dot-ELISA.
  c-Detection of blood parasites using different stains like Giemsa stain and safranin.
  d-Detection of protozoa using different stains like Iron Haemtoxylin and Trichrome stain.

-I have experience in training technicians working in the same field both practical and theoretical courses.

-Sharing in the practical part of the researches implemented in the NHTRI.

- I have experience in training for students at last year of Faculty of Science who learned parasitology.

-Sharing with health projects in MOH like prevalence of parasitological diseases among children in different governnorates.

-Excellent Dealing with computer skills (windows,words ,power point, excel and internet).

-Sharing In training and qualifications for hospitals seeking for accreditation in Egypt through ArcQQA(Arab center for quality and qualification of hospitals for accreditation),Arab Institute for continuous professional development(AICPD), Arab Medical Union.
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Achievements:
Have an Excellent Experience in ultrasound of liver and Liver biopsy, in Antiviral therapy (Pegylated Interferon), Proper selection of patients who are candidate for therapy, follow up, when to stop therapy to get a high response rate, in dealing with patient with focal lesion in the Liver and in Endoscope:
- Diagnostic upper GIT Endoscopy.
- Band ligation of esophageal varices.
- Sclerotherapy of esophageal varices.
- Histoacryl injection of fundal varices.
- Biopsy Taking.

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Membership: Egyptian Society of Hepatology – Member

Research work:
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Membership: Egyptian Society of Laboratory Medicine. Egyptian Society of Hematological Disease.

Achievements:
- I am One of the Initiative team for High Performance Liquid Chromatography (HPLC) in Ain Shams University Hospital.
- Assistant Director of Ain Shams Specialized University Hospital laboratory since 1/1/2011 till now.
- Supervising a lot of Thesis of Master and M.D. Degree in Clinical pathology, pediatric and Internal Medicine Departments.
- Attendance of annual symposium of Egyptian Society of Laboratory Medicine.
- Attendance of the last 4 years of Quality Improvement Week including this year (Patient Safety a challenge, a Commitment, a fulfillment).
- Sharing in Diagnostic Laboratory Medicine Seminars by giving a lecture about Laboratory Informatics.
- Sharing in continuous Education in Hera General Hospital/KSA by 2 Lectures:
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  b. Point of Care Testing.
- Speaker in Laboratory Slandered Implementation of Hera General Hospital/KSA by giving 4 Lectures:
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  b. Critical Values.
  c. Documentation of linearity limit.
  d. Utilization of QC runs.

Publications: