Heighten Science PUBLICATIONS Corporation

ISSN
2639-6653

Case Report

Complicated Hepatitis A Virus Infection: A Report of Three Cases from Single Tertiary Referral Center

Omkolsoum M Alhaddad[1], Maha M Elsabaawy[1]*, Khalid A Gameel[1], Marwa Elfauomy[1], Olfat Hendy[2] and Eman A Rewisha[1]

[1]Departments of Hepatology, National Liver Institute, Menoufia University, Shibin El Kom 234511, Egypt

[2]Department of Clinical Pathology, National Liver Institute, Menoufia University, Shibin El Kom 234511, Egypt

***Address for Correspondence:** Dr. Maha M Elsabaawy, National Liver Institute, Shibin El-kom, Menoufia, Egypt, Tel: 020482223216; Email: maha.ahmed@liver.menofia.edu.eg

Submitted: 16 December 2016
Approved: 28 December 2016
Published: 30 December 2016

ABSTRACT

Hepatitis A virus (HAV) infection is the commonest form of acute viral hepatitis all over the world. Complicated HAV cases had been reported with evolving presentations. This is a report of three cases of non-fulminant HAV infections annotating rare non hepatic sequalae.

INTRODUCTION

Hepatitis Virus A is a single-standard, linear RNA measuring 27nm hepatovirus belonging to the family of Picornaviridae [1,2]. It is the commonest form of orally transmitted hepatitis viruses [3]. This single serotyped virus was firstly isolated by Purcell in 1973 in the stool of patients by electron microscopy allowing future serologic testing discovery [1,3,4]. Since the great advent of the effective HAV vaccination in 1995, the disease becomes more controllable [2,5]. Being non enveloped virus, HAV is considered one of the most surviving viruses, necessitating sophisticated infection control measures [5,6]. Genotype IA is the most prevalent of the three genotypes. Egypt as a Mediterranean country is specified by the subtype IB [7,8]. In spite of being benign disorder, critical complications had been occasionally encountered and require special medical care.

CASE DESCRIPTIONS

Case 1

A 19 years old lady had presented to National Liver Institute (NLI) hospital-Menoufia University with jaundice, dark urine and easy fatigability. The condition started five days before admission, and was not preceded by any constitutional symptoms. Itching and slight right hypochondrail pain were reported. Jaundice and pallor and right hypochondrial tenderness were the relevant clinical finding. A picture of acute hepatitis was depicted by elevated serum bilirubin and transaminases along with the slightly raised cholestatic enzymes (Table 1). Normocytic normochromic anemia (Hemoglobin 8gm/dl) and severe thrombocytopenia (platelets 38000/cc) and

How to cite this article: Alhaddad OM, Elsabaawy MM, Gameel KA, Elfauomy M, Hendy O, et al. Complicated Hepatitis A Virus Infection: A Report of Three Cases from Single Tertiary Referral Center. J Clin Intensive Care Med. 2016; 1: 014-020. https://doi.org/10.29328/journal.jcicm.1001003

Table 1: Laboratory data of the patient.

	On admission	Day 2	Day 7 (initiation of methylprednisone)	Day 14	Day 20	Day 30
Bili-t (mg/dl)	49,8	36.9	13.5	10.3	5.3	1.7
BILI D (mg/dl)	34.5	30.3	10.5	8.2	3.2	0.9
ALB (g/dl)	4.1	2.8	3.1	3.6	3.9	3.9
AST(IU/l)	351	235	234	88	36	
ALT(IU/l)	1133	535	543	170	47	
ALP(IU/l)	317	201	132	118		
GGT(IU/l)	151	89	120	268		
Hb (g/dl)	8.7	5	5.2	11.1	11.5	11.8
WBC (10^3/dl)	8.6	9.8	10.5	11.7	12.1	6.9
Platelets (10^3/dl)	38	15	17	192	547	420
Urea (mg/dl)	29	18	14			
Creatinine (mg/dl)	0.8	0.6	0.6			
INR %	1.2	1.39	1.2	1.23		
LDH (iu/l)	2100	1915	5200	1587		
Ferritin (ng/ml)	2119	2000	2200	1800	1400	800
Triglycerides (mg/dl)	350	505	520	472	300	280

Billi-t: Bilirubin total, Bili-D: Bilirubin direct, ALB: Albumin, AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferee, HB: Haemoglobin, WBCs: White blood cells, INR: International normalized ratio, LDH: Lactic dehydrogenase

normal white cell counts were evident. Both direct and indirect coombs tests were negative along with normal reticulocytic count. Antiplatelet antibodies were proved to be negative. Abdominal ultrasonographic examination concealed homogenous liver with peri-cholycystic edema and minimal pelvic, perisplenic and peri-hepatic ascites. She was negative for hepatitis B surface antigen (HBsAg) anti-hepatitis B core (HBc)-IgG, anti-HBc-IgM, anti-EBV-IgM, anti-CMV-IgM, anti-HIV-Ab, and anti-HSV-IgM), and polymerase chain reaction (PCR) for HCV-RNA. Hepatitis A IgM (HAV-IgM) proved to be positive. Serum ceruplasmin and copper along with urinary copper all were within normal ranges. Antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-mitochondrial antibody (AMA), and anti-liver-kidney microsomal antibody (anti-LKM-1) were negative, and perinuclear anti-neutrophil cytoplasmic antigen (p-ANCA).

Anemia and the consistent decrease in platelet counts necessitated transfer of the patient to the intensive care unit for close monitoring, red blood cells and platelet transfusions, and best of care management. The progressive rising of serum ferritin and triglycerides along with persistent thrombocytopenia had inquired bone marrow examination. Bone marrow aspiration, the less invasive technique, revealed hyper cellular bone marrow with hemophagocytic activity (1.7% of nuclear cell count) against both erythrocytes, and platelets with absence of dysplastic cells. Intravenous methyl prednisolone 1gm per day for three days was prescribed, followed by oral prednisolone 60mg daily. Rapid recovery of hematological derangements and slow drop of serum ferritin and triglycerides were documented in the following days as shown in table 1.

Case 2

A 20 year old gentleman presented with 15 days jaundice, dark urine, normal colored stools and mild itching. The condition was preceded by one week of constitutional symptoms: fever, anorexia, and vomiting. Physical examination was unremarkable with fair general condition and vital signs but the patient was deeply jaundiced. On admission, laboratory tests revealed positive serology for HAV IgM, high serum transaminases, serum bilirubin, hypoalbuminemia, and unexpectedly raised renal function tests (Table 2). The past and drug history were irrelevant. The patient has neither diabetes nor hypertension and no recent history of renal troubles or exposure to

Table 2: Laboratory data of case 2.

	On admission	Day 2	Day 5	Day 7	Day 10
Total Bili (mg/dl)	13	10.5	7.6	6.3	5.3
Diredt BIL (mg/dl)	9	9.2	6.6	8.2	3.2
ALB (g/dl)	3.9	3.7	4.1	3.6	
AST(IU/l)	97	62	67	36	
ALT(IU/l)	295	200	139	47	
ALP(IU/l)	337	281	228	118	
GGT(IU/l)	465	368	290	268	
Hb (g/dl)	8.7	5	11	12.1	11.5
WBC (10^3/dl)	8.6	9.8	10.5	11.7	12.1
Platelets (10^3/dl)	507	409	401	356	287
Urea (mg/dl)	60	43	29	26	35
Creatinine (mg/dl)	3.2	2.2	1.6	1.4	0.9
INR%	0.9	1.18			
Crp (iu/l)	3				
LDH(iu/l)	322				
S Ca(g/l)	10.4	10.2	10.5	10	10.2
NA(iu/l)	130	132	134	133	135
K (mg/l)	4.9	4.3	4	4.3	4.2
Phosph (mg/l)	3.5				
Ferritin (ng/l)	1900	1756	1456	500	398

Billi-t: Bilirubin total, Bili-D: Bilirubin direct, ALB: Albumin, AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferee, HB: Haemoglobin, WBCs: White blood cells, INR: International normalized ratio, LDH: Lactic dehydrogenase, CRP: C - reactive protein

nephrotoxic agents. Sonography revealed normal study including normally appearing kidneys. Urine analysis showed absent proteinuria and inflammatory markers with normal complement 3 and 4 measures. The patient received best of care management and by the second day post admission, serum creatinine started normalization along with liver enzymes. Serum creatinine became normal by day 10, and serum bilirubin returned to normal values 3 weeks later.

Case 3

A 25 year old gentleman had presented with jaundice, dark urine, normal colored stools, and itching and marked epigastric pain for 15 days. This condition was preceded by short term fever and anorexia. Jaundice and hepatomegaly were the only physical findings. Laboratory study demonstrated a picture of acute liver injury (Table 3). Hepatitis A IgM antibody was the only positive among hepatitis viral markers. Severe thrombocytopenia (23000/dl) was evident with normal red and white blood cell counts. Progressively rising platelet counts on the following days along with improving liver function testing had negated further investigations.

DISCUSSION

In HAV infection, progression from the concealed incubation period to the preicteric and icteric phases up to the convalescence phase largely portrayed the well-known excellent outcome. However the outcome may occasionally be hindered by fulminant disease as well as the prolonged cholestatic and relapsing forms [6]. In addition many extrahepatic disorders of HAV had been mentioned in many case reports verifying acute renal failure, carditis, pancreatitis, red blood cell aplasia, Guillain Barré syndrome, Still's disease as copresentation to HAV infection [9].

The reported mean peak of total bilirubin in acute spontaneously resolved HAV infection is less than 10mg/dl [10]. In this report, the three cases were suffering from higher serum levels of hyperbilirubinemia in particular the first case reflecting

Table 3: Laboratory data of case 3.

	On Admission	Day 2	Day 5	Day 7	Day 10	Day 15
Bili-t (mg/dl)	24.7	22.9	15.1	9.4	4.9	3.1
BILI D (mg/dl)	17.9	13.3	6.6	4.9	3.1	2.4
ALB (g/dl)	3	2.8		2.9	3	3.7
AST(IU/l)	557	226	108	34	32	29
ALT(IU/l)	443	322	99	39	34	24
ALP(IU/l)	80	79		90	81	60
GGT(IU/l)	24	14		13	12	10
Hb (g/dl)	13.9	13.4	12.6	12.7	12.6	12.8
WBC (10^3/dl)	6.7	7.9	5.7	6	6.4	5.9
Platelets (10^3/dl)	23	86	97	125	167	198
INR %	1.07	0.9	0.7	0.5		
LDH (iu/l)	322	264	133	124	123	
S CA (gm/l)	10.4	10.3	10.3		10.3	
K (mg/l)	3-5					
Phosph (gm/l)	3.5	3.3	3.4	3.2		3.5
Ferritin (ng/ml)	1900	2200	900	800	568	344
Triglycerides (mg/dl)	420	350	230	190		

Billi-t: Bilirubin total, Bili-D: Bilirubin direct, ALB: Albumin, AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferee, HB: Haemoglobin, WBCs: White blood cells, INR: International normalized ratio, LDH: Lactic dehydrogenase

a potential liability for extraordinary presentations.Prolonged cholestasis had been mentioned to occur in 10% of HAV cases and would be an indication for corticosteroid treatment [11]. In case one, pruritus, conjugated hyperbilirubinemia of more than 10mg/dl and elevated cholestatic enzymes were evident, however the expected prolonged course might be aborted by early interference with corticosteroids targeting the possible hemophagocytic syndrome rather than cholestasis.

Maiga et al. 1997 had reported three cases of mild HAV infections associated with hematological disturbances and thrombocytopenia. Similarly, none of the three cases in this report had shown severe or fulminant course [12].

Macrophage activation syndrome (MAS) is the acquired form of the Hemophagocytic syndrome, which also referred to as Haemophagocytic lymphohistiocytosis (HLH). Macrophage activation syndrome represents huge immune system activation secondary to many illnesses and characterized by enormous elevation of serum ferritin and severe hypercytokinemia [13]. An early and dramatic fall in platelet counts is characteristic and bone marrow showing numerous macrophages that actively phagocytosing hematopoietic elements is mentioned as pathognomonic feature of the syndrome [13]. Yet, this feature is just supportive for the diagnosis and being absent may be false negative finding due to elusive nature of the condition as well sampling errors.

Interestingly, ferritin is primarily produced by splenic macrophages through a non-classical secretory pathway and a very high ferritin level strongly suggests macrophage activation and diagnosis of MAS [14]. Case 1 in this report exhibited continuous rise in serum ferritin levels that parallels rising in serum bilirubin and worsening of the bicytopenia.

In a similar way hypertriglyceridemia is considered as a feature of the macrophage activation syndrome although it may be a marker of severe liver involvement. In a study that included 28 patients diagnosed as having macrophage activation syndrome secondary to various conditions including virus infections; hypertriglyceridemia was notifiable on diagnosis and during the entire disease period [15].

Hemophagocytic syndrome is a well-known association to viral infections; nominated virus-associated hemophagocytic syndrome (VAHS). Linkage to HAV had been mentioned in few case reports. Watanabe et al. 2002, mentioned two cases of hepatitis A virus-associated hemophagocytic syndrome (HAV-AHS) with no morbidity [16]. Unlike VAHS's fatal destiny with other viruses, HAV-AHS is usually a resolved sequalae. In case 1, the association of hyperferrtinemia and elevated triglycerides with the severe bicytopenia had directed the team to search for Hemophagocytic syndrome, which was confirmed by the presence of hemophagocytic activity in bone marrow aspiration. It is not well settled whether the condition was the same in case 3 or not; the monocytopenia and the rapid resolution negated this assumption.

Reportedly, HAV was said to induce autoimmune hemolytic anemia [17]. However, the negative Coomb's test along with negative autoantibodies had denied this possibility in case one and addressing the presenting anemia as a part of the hemophagocytic syndrome. However, thrombocytopenia as a preceding manifestation of VAHS can be an overlooked diagnosis. This might be related to unawareness of this association, and the latency in such a way that an invasive diagnostic bone marrow examination in critically ill subjects is non-feasible. Further investigations are necessary to clarify the clinical features of HAV-AHS in more patients.

As a challenging disorder; early recognition of HAV-MAS along with prompt initiation of treatment in case 1 along with supportive measures had contributed to recovery of the case.

Fulminant hepatitis had been reported to complicate less than 1% of HAV infections [18]. The linkage between renal failure and HAV infection was limited to fulminant cases except in very few reports [19-21]. Meanwhile, in HAV infections that are exhibiting benign course, renal disorders are rare to occur and only few reports had mentioned this particular complication in mild HAV infections [22,23,9]. Various pathogenic mechanisms have been suggested for acute kidney injury in fulminant cases starting by the nephrotoxic effects of high bilirubin and bile acids, and ending by description of immune complex mediated disease and mesangial proliferative glomerulonephritis in such cases [24]. In absence of renal functional impairment as in case 3 raised serum creatinine can be explained by bilirubin induced acute tubular injury. Tubulopathy and intra renal bile casts have recently been described as the pathogenic background for renal injury in severely jaundiced patients. In a recent case report; renal histology showed many tubular green casts, tubular injury and bilirubin composition of the tubular casts with Hall stain in a patient with calcular biliary obstruction and acute kidney injury [25]. The removal of the bile duct obstruction was followed by improvement of renal function. In a recent case report; renal histology showed many tubular green casts, tubular injury and bilirubin composition of the tubular casts with Hall stain in a patient with calcular biliary obstruction and acute kidney injury. The removal of the bile duct obstruction was followed by improvement of renal function [25]. Cholestatic hyperbilirubinemia either through the direct toxic effect of bilirubin salts or the bilirubin and bile acids ischemic potentiating effect also presented a challenging offender [23]. In a recent case report; a patient with calcular biliary obstruction and acute kidney injury, improvement was linked to removal of the bile duct obstruction [25]. However, the multifactorial dehydration (anorexia, vomiting, developing endotoxaemia) taking place in those ill patients is considered added confounder to the condition [26]. The direct cytopathic effect of the virus is also said to be involved [26]. Exclusion of other causes of renal injury as: sepsis, shock, drug toxicity, bacterial infections, and rhabdomyolysis represented a challenging diagnostic must in these cases.

Acute tubular necrosis (ATN) is the most frequently reported histopathological variant of kidney injury associating HAV infection. Acute interstitial nephritis, and

mesangial proliferative glomerulonephritis were also reported as single cases [27]. Only a report described a copresentation of interstitial nephritis and ATN associating nonfulminant hepatitis A [28].

In case 3, the acute renal insult could be attributed to either prerenal, direct cytopathic or immune mediated as the bilirubin levels were not so high to vindicate such an insult. The rapid recovery of kidney function in case 3 was paralleling the improvement in liver function and the drop of serum bilirubin levels. Also, laboratory data showed normal complement levels and didn't support the diagnosis of immune or non-immune mediated acute glomerular injury. The rapidly resolved renal condition made the kidney biopsy unjustifiable. This fruitful outcome connected to improved bilirubin levels was similar to what's mentioned in literature except for the temporary need of hemodialysis in some cases [20,21]. Nevertheless, improved renal disorders associating HAV infections following corticosteroids treatment had been reported [29]. Dissimilarly, were the results of Jung et al. who signified the need of hemodialysis in more than half of the patients with evidenced delayed anti-HAV IgM seroconversion, prolonged cholestasis. However correction of cholestasis is always accompanied with amelioration of kidney dysfunction [25].

In conclusion, renal and hematological evaluations are mandated in every single case of HAV infection, even non fulminant and non-severe cases.

REFRENCES

1. Nainan OV, Xia G, Vaughan G, Margolis HS. Diagnosis of hepatitis a virus infection: a molecular approach. Clin Microbiol Rev. 2006; 19: 63-79. Ref.: https://goo.gl/pNpS6p
2. Martin A, Lemon SM. Hepatitis A virus: from discovery to vaccines. Hepatology. 2006; 43: 164-172. Ref.: https://goo.gl/fPRJm7
3. McCaustland KA, Bond WW, Bradley DW, Ebert JW, Maynard JE. Survival of hepatitis A virus in feces after drying and storage for 1 month. J Clin Microbiol. 1982; 16: 957-958. Ref.: https://goo.gl/nxoOJF
4. Anne Marie Roque-Afonso, Delphine Desbois, Elisabeth Dussaix. Hepatitis A Virus: Serology and Molecular Diagnostics. Future Virology. 2010; 5: 233-242. Ref.: https://goo.gl/RqFC67
5. Centers for Disease Control and Prevention (2016) Hepatitis Surveillance Guidelines, Atlanta, USA.
6. Lahmidani N, Najdi A, Benbrahim Z. Update on clinical and epidemiological features of viral hepatitis A. Gastroenterol hepatol open access. 2016; 5: 00144. Ref.: https://goo.gl/O6Htcm
7. Coudray Meunier C, Fraisse A, Mokhtari C, Martin Latil S, Roque Afonso AM, et al. Hepatitis A Virus Subgenotyping Based On RT-qPCR Assays. BMC Microbiol. 2014; 14: 296-301. Ref.: https://goo.gl/EYAjce
8. Wang X, Ren J, Gao Q, Hu Z, Sun Y, et al. Hepatitis A Virus And The Origins Of Picornaviruses. Nature. 2015; 517: 85-88. Ref.: https://goo.gl/xa47RH
9. Lapp RT, Rochling F. Acute Cholestatic Hepatitis A Virus Infection Presenting with Hemolytic Anemia and Renal Failure: a Case Report. Case Reports Hepatol. 2013. Ref.: https://goo.gl/F11fwf
10. Rozen P, Korn RJ, Zimmerman HJ. Computer analysis of liver function tests and their interrelationships in 347 cases of viral hepatitis. Isr J Med Sci. 1970; 6: 67-79. Ref.: https://goo.gl/NZLxN8
11. Kemmer NM, Miskovsky EP. Hepatitis A. Infect Dis Clin North Am. 2000; 14: 605-615. Ref.: https://goo.gl/t6V10x
12. Maiga MY, Oberti F, Rifflet H, Ifrah N, Calès P. Hematologic manifestations related to hepatitis A virus. 3 cases. Gastroenterol clin biol. 1997; 21: 327-330. Ref.: https://goo.gl/6kiyq4
13. Larroche C. Hemophagocytic lymphohistiocytosis in adults: diagnosis and treatment. Joint Bone Spine. 2012; 79: 356-361. Ref.: https://goo.gl/D8eyBi
14. Cohen LA, Gutierrez L, Weiss A, Leichtmann-Bardoogo Y, Zhang DL, et al. Serum ferritin is derived primarily from macrophages through a nonclassical secretory pathway. Blood. 2010; 116: 1574-1584. Ref.: https://goo.gl/79fEsb
15. Okamoto M, Yamaguchi H, Isobe Y, Yokose N, Mizuki T, et al. Analysis of triglyceride value in the

diagnosis and treatment response of secondary hemophagocytic syndrome. Intern Med. 2009; 48: 775-781. Ref.: https://goo.gl/IlyU6c

16. Watanabe M, Shibuya A, Okuno J, Maeda T, Tamama S, et al. Hepatitis A virus infection associated with hemophagocytic syndrome: report of two cases. Intern Med. 2002; 41: 1188-1192. Ref.: https://goo.gl/MDSfMf

17. Tibble JA, Ireland A, Duncan JR. Acute auto immune haemolytic anaemia secondary to hepatitis A infection. Clin Lab Haematol. 1997; 19: 73-75. Ref.: https://goo.gl/KsfjY8

18. Jung YM, Park SJ, Kim JS, Jang JH, Lee SH, et al. Atypical manifestations of hepatitis A infection: A prospective, multicenter study in Korea . J. Med. Virol. 2010; 82: 1318-1326. Ref.: https://goo.gl/wTmoVF

19. Shroff GR, Badve SV, Joshi AG, Desai DG, Abrahim P, et al. Acute renal tubular injury with acute hepatitis A infection: is it just a coincidence? Nephrology (Carlton). 2004; 9: 44-46. Ref.: https://goo.gl/ars7tN

20. Yasar B, Akbayir N, Celik S, Ozgil D, Akkan Z, et al. Acute oligo-anuric renal failure during the course of non-fulminant hepatitis A in a patient with anorexia nervosa. Turk J Gastroenterol. 2002; 13: 164-167. Ref.: https://goo.gl/lDM8OX

21. Vesely DL, Dilley RW, Duckworth WC, Paustian FF. Hepatitis a induced diabetes mellitus, acute renal failure and liver failure. Am J Med Sci. 1999; 317: 419-424. Ref.: https://goo.gl/Prfj4D

22. Lin CC, Chang CH, Lee SH, Chiang SS, Yang AH. Acute renal failure in non-fulminant hepatitis A. Nephrol Dial Transplant. 1996; 11: 2061-2066. Ref.: https://goo.gl/2dc6oU

23. Adas M, Tanakol R, Yarman S, Boztepe H, Ecder T, et al. Acute renal failure associated with nonfulminant hepatitis A virus infection. Ren Fail. 2002; 24: 97-102. Ref.: https://goo.gl/XcCpaH

24. van Slambrouck CM, Salem F, Meehan SM, Chang A. Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction. Kidney Int. 2013; 84: 192-197. Ref.: https://goo.gl/1r1YXA

25. Aniort J, Poyet A, Kemeny J, Philipponnet C, Heng E. Bile cast nephropathy caused by obstructive cholestasis. American Journal of Kidney Diseases. 2016; 69: 143-146. Ref.: https://goo.gl/w8LWnQ

26. Sarawgi S, Gupta AK, Arora DS, Jasuja S. Acute renal failure associated with nonfulminant acute viral hepatitis A. Indian J Nephrol. 2008; 18: 77-79. Ref.: https://goo.gl/Hqyghp

27. Faust RL, Pimstone N. Acute renal failure with non-fulminant hepatitis A viral infection. Am J Gastroenterol. 1996; 91: 369-372. Ref.: https://goo.gl/JELv4d

28. Vaboe AL, Leh S, Forslund T. Interstitial nephritis, acute renal failure in a patient with nonfulminant hepatitis A infection. Clin Nephrol. 2002; 57: 149-153. Ref.: https://goo.gl/NvmXRB

29. Bhatt G, Sandhu VS, Mitchell CK. A rare presentation of hepatitis a infection with extrahepatic manifestations. Case Rep Gastrointest Med. 2014. Ref.: https://goo.gl/SMRQZf

30. US Center for Disease Control and Prevention (2010) Illinois Department of Public Health. In: Heymann DI (Ed.), Control of Communicable Diseases in Man. (19th Edn), Washington, DC: American Public Health Association, USA.