

## Optimum Sequence of Liver Serology in an Inpatient Setting

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### ABSTRACT

**AIMS:** To investigate the most cost effective and highest diagnostic yield of sequential vs. 'shotgun' approach when evaluating the cause of elevated liver biochemistries in the inpatient setting as it relates to Wilson's Disease (WD) and Alpha-1 Antitrypsin Disease (AATD).

**MATERIALS AND METHODS:** Inpatients without chronic liver disease were evaluated for acute elevated liver biochemistries and stratified into two cohorts: sequential and 'shotgun'. Sequential had only an acute viral hepatitis panel ordered initially while 'shotgun' included the viral hepatitis panel and ceruloplasmin and/or alpha-1 antitrypsin level/phenotype. Diagnostic yield, length of stay, hospital

acquired infections, and overall cost were evaluated. Secondary analysis evaluated how often each approach was used by different types of providers and hospital setting.

**RESULTS:** 738 patients were evaluated, 23% using the 'shotgun' approach. Neither approach diagnosed WD or AATD. Patients in the sequential approach were discharged 1.06 days later ( $p = 0.052$ ), contributing to \$2337 more per patient. There was no difference in the number of hospital acquired infections between approaches ( $p = 0.36$ ).

**CONCLUSION:** In the inpatient setting the yield of screening for WD or AATD in patients presenting with elevated liver biochemistries is low, however if these tests are ordered, it is more cost effective to use a 'shotgun' approach.

**Key words:** Alpha 1 Antitrypsin; Ceruloplasmin; Wilson's Disease; Liver Biochemistries; Viral Hepatitis

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### INTRODUCTION

With the popularization of electronic medical records it has become more convenient to use 'order sets' which can lead to inappropriate testing<sup>[1]</sup>. In the evaluation of abnormal liver biochemistry levels two predominant strategies are utilized: a sequential evaluation based on pretest probability and a 'shotgun' approach, where all diagnostic testing is ordered on initial evaluation. In clinical practice the 'shotgun' approach is more likely to be utilized in the inpatient setting possibly due to illness acuity<sup>[2]</sup>.

Evaluation for acute elevated liver biochemistries in our community hospital typically includes the tests listed in Figure 1, which corresponds to what has been observed in general practice<sup>[3]</sup>. Two diagnoses that are often sought, but infrequently encountered are Wilson's Disease (WD) and Alpha-1 Antitrypsin Deficiency (AATD)<sup>[4,5]</sup>.

Pretest probability should guide the clinician's diagnostic algorithm, and ordering of these lower yield tests during the initial

work-up may lead to increased cost and length of stay (LOS) without improving diagnostic yield. For elevated liver biochemistry tests, sequential algorithms have been designed for outpatient evaluation, but no standard approach has been described for the inpatient setting<sup>[1]</sup>. The low positive predictive value of testing and low prevalence of WD and AATD would make investigation of these pertinent only in very specific circumstances<sup>[4,5]</sup>. Wilson's disease is rarely encountered with a prevalence of 30 per million and has great clinical variability<sup>[4]</sup>. The overall prevalence of AATD is estimated between approximately 1:3000 to 1:5000<sup>[5]</sup>, and 10 percent of which are estimated to develop liver disease at some point in their disease course<sup>[6]</sup>. Both AATD and WD are usually considered to be third tier testing in sequential evaluation of abnormal liver biochemistries<sup>[7,8]</sup>, and therefore it is debatable whether they should be included during initial evaluation within the inpatient setting.

We sought to investigate the most cost effective and best diagnostic yield approach (sequential vs. 'shotgun') when evaluating the cause of increased liver biochemistries in the inpatient setting as it relates to WD and AATD.

## METHODS

IRB approval was obtained (869082-3) for this retrospective study. We identified patients from Genesys Regional Medical Center, a 400 bed community teaching hospital in Grand Blanc, Michigan, United States. Patients without prior diagnosis of chronic liver disease were evaluated for acute elevated liver biochemistries via International Classification of Diseases (ICD) codes 9 and 10 (Figure 2).

Patients were excluded if they did not have an acute viral hepatitis panel ordered and if they had a history of chronic liver disease, defined as: cirrhosis, fibrosis (F1-F4), ascites, longstanding alcohol abuse, variceal bleed, hepatic encephalopathy, NAFLD, NASH, liver cancer, chronic hepatitis B, chronic hepatitis C, and hemochromatosis. Data was collected for male and non-pregnant female patients age 18 or older who were admitted between July 2011 and May 2016.

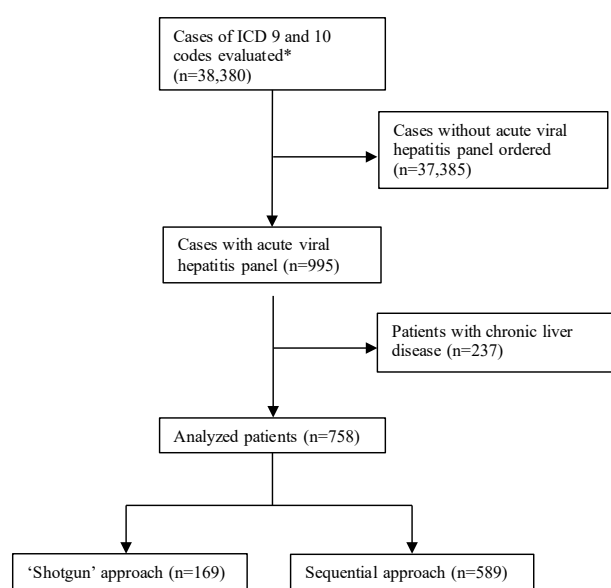
Patients were stratified into two cohorts by the approach of liver biochemistry evaluation: sequential and 'shotgun'. The sequential approach was defined as an acute viral hepatitis panel (Hep A Ab IgM, Hep B Surface Antigen, Hep B Core Ab IgM, Hep C Ab) ordered without evaluation of ceruloplasmin or alpha-1 antitrypsin level and/or phenotype (A1ALP) on the initial evaluation of raised liver biochemistries. In the sequential approach patients may or may not have had subsequent ceruloplasmin and or A1ALP ordered. The 'shotgun' approach was defined as having the acute viral hepatitis panel ordered on the same day as the serum ceruloplasmin and/or A1ALP.

The length of stay was evaluated with a two-sample T-test between the means. The number of hospital acquired infections was compared using McNemar's test. Length of stay and infection rates were examined at the aggregate level. The outcome measures are a proxy based on the average within each population. No statistical analysis was performed on diagnostic yield of each approach as there were no positive cases of WD or AATD detected. Hospital acquired infections were defined as central line associated bloodstream infection, catheter associated urinary tract infection, and Clostridium difficile associated diarrhea.

The overall cost of laboratory testing and length of stay was estimated using national averages. We evaluated the cost of screening and confirmatory tests for AATD and WD. At Genesys hospital's laboratory the cost of Ceruloplasmin, 24 hour urine copper, Alpha-1

**Figure 1** Elevated Liver Biochemistries Workup.

Complete Metabolic Panel
Complete Blood Count
Coagulation Profile
Gamma-Glutamyl Transpeptidase
Acetaminophen Level
Salicylate Level
Urine Toxicology
Acute Viral Hepatitis Panel
Right Upper Quadrant Ultrasound with Doppler Flow
Iron Studies
ANA, ASMA (F-Actin), Total IgG
Alpha-1 Antitrypsin Phenotype
Ceruloplasmin
CMV/EBV/HSV



**Figure 2** Patient Selections. \*ICD 9 codes evaluated include transaminitis (790.4), abnormal LFTs (794.8), liver failure (573.8), jaundice (782.4), hepatic encephalopathy (572.2), and RUQ abdominal pain (789.00-789.09). ICD 10 codes evaluated include abnormal LFTs (R94.5), nonspecific elevation of levels of transaminase and lactic acid dehydrogenase (R74.0), hepatic failure (K72, K72.90, K72.91), alcoholic hepatic failure (K70.4), jaundice (R17), RUQ abdominal pain (R10.11), acute hepatitis (K75.9), ascites of liver (K70.31), cirrhosis (K74.69), choledocholithiasis (K80.50), cholecystitis (K81.0), liver mass (R16), alcoholic liver disease (K70.9), and cholangitis (K83.0).

Antitrypsin level, and Alpha-1-Antitrypsin phenotype are \$45.36, \$9.00, \$56.73, and \$26.00 respectively. The average cost of a 24-hour stay in the hospital in the United States in 2013 was \$2289<sup>[9]</sup>. These values were used to make estimates regarding cost differential between the two groups.

Secondary analyses included how each of these groups is affected by the background of ordering provider: gastroenterologist (GI), general surgeon (GS), and other provider (OP) as well as the hospital setting: intensive care (ICU), general floor, observation and emergency department. In order to determine if these tests were ordered with pretest probability in mind, we stratified patients evaluated with A1ALP and ceruloplasmin according to epidemiological characteristics of these diseases. For AATD this included age 40 or greater, male sex, and Hispanics and Caucasians<sup>[10]</sup>. For WD this included age less than 40 and female sex<sup>[11]</sup>.

## RESULTS

There were 758 patients who met inclusion criteria, 589 in the sequential group and 169 in the ‘shotgun’ group (Figure 2). The average age of patients was 54, ranging from 18 to 96. 54% of patients were female, 89% were Caucasian. The only statistical difference between groups was in the Hispanic/Latino race, however the sample size was too small to draw comparisons (Table 1).

The primary end points were length of stay, diagnostic yield, and hospital acquired infections. The mean (standard deviation) length of stay did not differ significantly between the sequential group (6.14 ± 7.22 days) compared to the ‘shotgun’ group (5.10 ± 5.28 days) ( $p=0.082$ ). There were 0 patients diagnosed with WD and there were 0 patients diagnosed with AATD. The incidence of hospital acquired infections was 2.4% in the sequential group and 3.0% in the ‘shotgun’ group (Table 2).

In secondary analysis (Table 3), GI providers utilized a ‘shotgun’ approach (34.1%,  $n = 116$ ) significantly more often than the OP (12.6%,  $n = 48$ ) ( $p < 0.01$ ). There was no difference in how often each approach was utilized between GS and OP ( $p = 0.84$ ) or GI and GS ( $p = 0.39$ ). Providers were found to utilize a ‘shotgun’ approach more often in the observation unit (31.2%) as compared to the general floor (22%) ( $p < 0.001$ ), or the ICU (15.8%) ( $p < 0.001$ ).

We analyzed demographic characteristics to see if providers used pretest probability to aid in their test ordering. Patients screened for Wilson’s on average were significantly younger ( $p < 0.001$ ). There was no difference in ethnicity between those screened for WD and those who were not ( $p = 0.11$ ). Females were more likely to be screened for WD ( $p = 0.047$ ).

In the AATD group, there was no difference in ethnicity ( $p = 0.68$ ), gender ( $p = 0.35$ ), or age (0.89) between those screened for AATD and those who were not screened.

Direct costs were estimated between the two groups. The calculation with these estimates demonstrated that the sequential method cost \$2337 more per patient than the ‘shotgun’ method (Figure 3).

## DISCUSSION

Neither ‘shotgun’ nor sequential approach led to a diagnosis of WD or AATD when evaluating inpatients with elevated liver biochemistry tests. This suggests that when evaluating inpatients with elevated liver biochemistries, testing for WD and AATD, may not be cost effective. However, due to the low incidence of WD and AATD, the study was not powered to draw this conclusion.

The very low incidence of these conditions makes testing for them

in the acute setting inappropriate without the proper pretest probability. Historically, Wilson’s disease has been a diagnostic challenge<sup>[12]</sup>. WD is rarely encountered with a prevalence of 30 per million and has great clinical variability<sup>[4]</sup>. Typically, the disease presents between the ages of 5 and 25<sup>[13]</sup>, nonetheless it has the potential to present at any age<sup>[11,14]</sup>. The American Association for the Study of Liver Diseases recommends that clinicians consider the diagnosis of WD in all patients under age 40 and those older than 40 if liver biochemistries remain elevated when other more common diseases have been excluded<sup>[13,15]</sup>. The disease is screened for by the serum marker, ceruloplasmin. Ceruloplasmin is an acute phase reactant<sup>[16]</sup>, which can result in an increased proportion of false negative results. The screening marker may be falsely positive due to chronic liver disease, malabsorptive syndromes, nephritic syndromes, and malnutrition<sup>[16]</sup>. The serum marker has a low positive predictive value (8.4%) and false-positive rate as high as 98.1% if patients are not carefully selected, especially if no confirmatory testing is pursued<sup>[2]</sup>.

**Table 1** Baseline Characteristics.

	‘Shotgun’ Approach	Sequential Approach	p value
Mean Age	51.64 (18-96)	54.72 (18-95)	0.052
<b>Gender</b>			
Male	69	280	0.13
Female	100	309	0.12
<b>Ethnicity</b>			
Caucasian	154	521	0.31
American Indian/Alaskan Native	0	4	0.28
Black/African American	10	49	0.31
Hispanic/Latino	4	2	0.01
Asian	0	3	0.35
Non-Disclosed	1	9	0.35
Other	0	1	0.59

**Table 2** Primary Endpoints.

	‘Shotgun’ method	Sequential method	P
Total Number	169	589	
WD and AATD diagnoses	0	0	
Hospital Acquired Infections	5	14	0.667
Length of Stay	5.102 (days)	6.142 (days)	0.082

**Table 3** Secondary Endpoints.

Providers	‘Shotgun’ Approach	Sequential Approach
Gastroenterologist (GI)†	116 (34.1%)	224 (65.9%)
General Surgery (GS)	5 (15.6%)	27 (84.4%)
Other Providers (OP)†	48 (12.6%)	333 (87.4%)
<b>Floor</b>		
General Floor‡	101 (22.0%)	358 (78.0%)
ICU*	23 (15.8%)	123 (84.2%)
Observation‡ *	39 (31.2%)	86 (68.8%)
ER	6 (22.2%)	21 (77.8%)
<b>Level of Ordering</b>		
Attending	69	255
Resident	45	250
Fellow	52	76

† GI used ‘shotgun’ approach more than OP ( $p < 0.001$ ), ‡ ‘Shotgun’ approach was used more frequently in Observation vs General Floor ( $p < 0.03$ ), \* ‘Shotgun’ approach was used more frequently in Observation vs ICU ( $p < 0.03$ ).

$$\text{Cost differential of methods} = \frac{(A \times B) + (C \times D)}{E} - \frac{(F \times B) + (G \times D)}{H}$$

A=number of patients in the sequential cohort who had a ceruloplasmin checked;  
 B=cost of the ceruloplasmin lab test;  
 C=number of patients in the sequential cohort who had an alpha-1 antitrypsin level checked;  
 D=cost of the alpha-1 antitrypsin lab test;  
 E=total number of patients in the sequential cohort;  
 F=number of patients in the ‘shotgun’ cohort who had a ceruloplasmin checked;  
 G=number of patients in the ‘shotgun’ cohort who had an alpha-1 antitrypsin level checked;  
 H=total number of patients in the ‘shotgun’ cohort).

**Figure 3** Cost Calculation.

Similar concerns arise with respect to Alpha-1 Antitrypsin Deficiency. AATD has typically been a disease of interest in the pulmonary field. Most of the recommendations in the gastrointestinal literature are cited from the pulmonary guidelines, particularly those of the American Thoracic Society (ATS). Not all individuals with liver disease will have concomitant pulmonary manifestations since the pathogenesis of pulmonary and hepatic disease are different<sup>[17]</sup>. AATD typically presents with an obstructive lung disease in younger individuals who may not have any smoking history<sup>[18]</sup>. ATS guidelines suggest providers evaluate for AATD in patients with otherwise unexplained liver disease<sup>[5]</sup>. Patients with liver disease will typically present with chronic hepatitis, cirrhosis, or hepatocellular carcinoma<sup>[19]</sup>. Among patients with AATD, transaminase levels do not significantly differ between patients with and without liver disease. The sensitivity of alanine aminotransferase in detecting liver disease in patients with AATD has been shown to be less than 12 percent<sup>[6]</sup>.

Three strategies are employed for the diagnosis of AATD; alpha 1 antitrypsin serum level (AAT level), alpha 1 antitrypsin phenotype, and alpha 1 antitrypsin genotype. When screening for AATD, many clinicians will check a serum AAT level. AAT level has been shown to be an acute phase reactant and may not accurately detect disease in heterozygous individuals, therefore ATS suggests checking both AAT level as well as the phenotype<sup>[20]</sup>. Phenotyping can be challenging to interpret and cannot readily differentiate a homozygous deficiency state from a heterozygous allele paired with a null allele. In addition, phenotyping is unable to detect PI NULL alleles, as these variants produce no circulating protein<sup>[20]</sup>.

The third test, genotyping is only used to detect the most common variants. The most common genotype is PiZZ, which has a bimodal distribution and a variable presentation with adults diagnosed in the 5<sup>th</sup> decade of life<sup>[10]</sup>. Furthermore, the relationship between patients with heterozygous alleles and risk of developing liver disease is controversial<sup>[21]</sup>.

Patients who had a sequential diagnostic evaluation for elevated liver biochemistries did have a longer LOS, by one full day. However, the difference did not reach statistical significance ( $p = 0.082$ ). The extra wide standard deviation in the sequential group may have masked an otherwise significant difference. It is important to note that the intention of this examination was not to apply grouped results to the individual level. Rather it was to determine if there were differences in the two populations at an aggregate level for comparative purposes and to generate new hypotheses. Differences between populations at this level may be larger than they would be at the individual level. Nonetheless, the observed difference was not significant for LOS regardless.

Further, we extrapolated cost based on the trend toward increased LOS between the two groups (this assumes there is causality between order of testing and LOS). Given the substantial difference in cost between the extra time spent in the hospital versus the cost of screening for WD and AATD, ordering the tests in a 'shotgun' method may be more cost effective than a sequential method.

We expected to see a greater rate of infections in the sequential group given the longer LOS. Yet the results show a greater rate of infection in the 'shotgun' group, which had a shorter LOS. We suspect that this discrepancy is due to relatively small number of hospital acquired infections, since it is shown that longer LOS correlates with higher hospital acquired infections<sup>[22]</sup> as we do not expect the method by which the tests are ordered to affect the infection rate.

We also attempted to find differences in ordering patterns by location and type of provider. The observation unit at our hospital encompasses patients who are not admitted, but evaluated over a 48-hour

period. More providers used the 'shotgun' approach in this setting as compared to ER, ICU, or general floor. It was noted that in the observation unit the 'shotgun' method was the preferred method of screening for WD or AATD. The 'shotgun' approach may be a more conducive option than the sequential approach in the observation unit due to the 48-hour time restriction.

We found that more gastroenterologists ordered the 'shotgun' approach compared to other providers. This may have had to do with familiarity with testing and broader differential diagnosis. They may have also had more pressure to come up with a diagnosis as they were consulted to answer why patients had elevated liver biochemistries.

This was the first study to evaluate different methods of ordering liver serology specifically for screening of WD or AATD in the inpatient setting. Recently, a similar investigation has been conducted in the outpatient setting and focused on a broad array of liver serology tests and drew similar conclusions as our study<sup>[23]</sup>. Likewise, in 2016, Chadwick and colleagues performed a comparable study in the inpatient setting<sup>[3]</sup>, however they evaluated fewer patients, investigated a broad array of liver serologies, and did not draw firm conclusions on the method (sequential vs 'shotgun') of ordering. Chadwick and colleagues at the end of the study<sup>[3]</sup> did propose an algorithm for the inpatient setting for elevated liver biochemistries, which has not been validated and favors the sequential approach. Further, in 2009, O'Brien highlighted the type of work-up that is suggested in the inpatient setting for elevated liver biochemistries<sup>[24]</sup> but did not make recommendations on the ordering pattern (sequential vs 'shotgun' approach). Additionally, this study also evaluated multiple disciplines, multiple settings within the hospital, and multiple levels of providers in a community hospital setting; making the data more applicable to general practice within the inpatient setting.

We recognize that there were several limitations in this study. Our study was underpowered to detect differences in WD or AATD yield. A retrospective design was used and thus patients were not randomized to their respective groups. ICD-9 and 10 codes were used to collect patient data which may not have reflected the true clinical assessment, however, charts were reviewed in an effort to find and reconcile possible discrepancies. Additionally, the cost of hospitalization was estimated based on national and local averages and may not reflect the true cost at individual hospitals. We extrapolated the difference in cost between the two groups, which increases the risk of type I error. Further, we assumed that the trend towards the increase LOS in the sequential group was due to the method of ordering, which also increases the risk of type I error. Our study was not designed to evaluate whether the method of test ordering affected length of stay. We did not follow up on subsequent testing from positive screening results; since this would have affected both groups equally.

In an inpatient setting, the yield of screening for WD or AATD in patients presenting with elevated liver biochemistries is quite low. However, if these diagnoses are being pursued, we recommend screening for them using a 'shotgun' method rather than a sequential method.

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## REFERENCES

1. Arnold et. al. Should Patients with Abnormal Liver Function Tests in Primary Care be Tested for Chronic Viral Hepatitis: Cost Minimisation Analysis Based on a Comprehensively Tested Cohort. *BMC Family Practice* 2011, **12**: 9. [PMID: 21371303]
2. Tapper EB, Rahni DO, Arnaout R, Lai M. The overuse of serum ceruloplasmin measurement. *Am J Med.* 2013; **126(10)**: 926.e1-5. [PMID: 23953876]
3. Chadwick A, Marks M. Low yield of unselected testing in patients with acutely abnormal liver function tests. *JRSM Open.* 2016; **7(1)**: 2054270415611309. [PMID: 26770816]
4. Cauza E, Maier-Dobersberger T, Polli C, Kaserer K, Kramer L, Ferenci P. Screening for Wilson's disease in patients with liver diseases by serum ceruloplasmin. *J Hepatol* 1997; **27**: 358-362. [PMID: 9288611]
5. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med* 2003; **168**: 818. [PMID: 14522813]
6. Clark VC, Dhanasekaran R, Brantly M, Rouhani F, Schreck P, Nelson DR. Liver test results do not identify liver disease in adults with  $\alpha(1)$ -antitrypsin deficiency. *Clin Gastroenterol Hepatol.* 2012; **10(11)**: 1278-83. [PMID: 22835581]
7. Daniel S, Ben-menachem T, Vasudevan G, Ma CK, Blumenkehl M. Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients. *Am J Gastroenterol.* 1999; **94(10)**: 3010-4. [PMID: 10520861]
8. Skelly MM, James PD, Ryder SD. Findings on liver biopsy to investigate abnormal liver function tests in the absence of diagnostic serology. *J Hepatol.* 2001; **35(2)**: 195-9. [PMID: 11580141]
9. Centers for Medicare & Medicaid Services. Medicare Provider Utilization and Payment Data. <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/medicare-provider-charge-data/index.html>. August 8, 2017. Accessed November 15, 2017. [PMID: 31859664]
10. Fairbanks KD, Tavill AS. Liver disease in alpha 1-antitrypsin deficiency: a review. *Am J Gastroenterol.* 2008; **103(8)**: 2136-41. [PMID: 18796107]
11. Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: an update. *Hepatology.* 2008; **47(6)**: 2089-111. [PMID: 18506894]
12. Gow PJ, Smallwood RA, Angus PW, Smith AL, Wall AJ, Sewell RB. Diagnosis of Wilson's disease: an experience over three decades. *Gut* 2000; **46**: 415-419. [PMID: 10673307]
13. Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's Gastrointestinal and Liver Disease- 2 Volume Set: Pathophysiology, Diagnosis, Management, 10e (Gastrointestinal & Liver Disease (Sleisenger/Fordtran)) 10th Edition; page 1247. [DOI: 10.1136/gut.2007.121533]
14. EASL Clinical Practice Guidelines: Wilson's disease. *J Hepatol.* 2012; **56(3)**: 671-85. [PMID: 22340672]
15. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology.* 2011; **54(1)**: 328-43. [PMID: 21452290]
16. Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's Gastrointestinal and Liver Disease- 2 Volume Set: Pathophysiology, Diagnosis, Management, 10e (Gastrointestinal & Liver Disease (Sleisenger/Fordtran)) 10th Edition; page 1270. [DOI: 10.1136/gut.2007.121533]
17. Alpha-1 Antitrypsin Deficiency. NORD (National Organization for Rare Disorders). <https://rarediseases.org/rare-diseases/alpha-1-antitrypsin-deficiency/>. Accessed November 17, 2017. [PMID: 11778003]
18. Needham M, Stockley RA. Alpha 1-antitrypsin deficiency. 3: Clinical manifestations and natural history. *Thorax.* 2004; **59(5)**: 441-5. [PMID: 15115878]
19. Bals R. Alpha-1-antitrypsin deficiency. *Best Pract Res Clin Gastroenterol.* 2010; **24(5)**: 629-33. [PMID: 20955965]
20. Lee JH, Brantly M. Molecular mechanisms of alpha1-antitrypsin null alleles. *Respir Med.* 2000; **94 Suppl C**: S7-11. [PMID: 10954248]
21. Bell H, Schruppf E, Fagerholm M. Heterozygous MZ alpha 1-antitrypsin deficiency in adults with chronic liver disease. *Scand J Gastroenterol* 1990; **25**: 788-92. [PMID: 2402584]
22. Rahmqvist M, Samuelsson A, Bastami S, Rutberg H. Direct health care costs and length of hospital stay related to health care-acquired infections in adult patients based on point prevalence measurements. *Am J Infect Control.* 2016; **44(5)**: 500-6. [PMID: 26988332]
23. Tapper EB, Saini SD, Sengupta N. Extensive testing or focused testing of patients with elevated liver enzymes. *J Hepatol.* 2017; **66(2)**: 313-319. [PMID: 27717864]
24. O'Brien CB. The hospitalized patient with abnormal liver function tests. *Clin Liver Dis.* 2009; **13(2)**: 179-92. [PMID: 19442913]