

1 Supplemental Case Examples:

2 *Case 1 (DILIN Case), Drug: amoxicillin-clavulanate*

3 This patient was a 64-year-old man who was found have hyperbilirubinemia and cholestatic liver
4 enzyme elevation 5 weeks after starting amoxicillin-clavulanate.

5 He had no prior liver problems. He was given amoxicillin-clavulanate for 7 days to treat an
6 infected pilonidal cyst. He took no other medications or herbal/dietary supplements. Twenty-
7 seven days after starting the antibiotic, he noted yellowing of his eyes. He went to his primary
8 care provider 8 days later, and his ALT was 109 U/L, AST 40 U/L, AP 312 U/L and bilirubin 9
9 mg/dL. R-value was 0.7. He was admitted for evaluation. Ultrasound and MRI of his liver were
10 unremarkable. Nevertheless, he had a laparoscopic cholecystectomy the next day. No stones were
11 found. An intra-operative liver biopsy was done, but the results were not able to be retrieved for
12 review. Over the next 4 weeks, his bilirubin climbed to 26 mg/dL and AP to 575 U/L. He
13 developed a rash and pruritus. Ten days after presentation he had decreased cognition, but his INR
14 remained normal. Anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HCV antibody, and HCV RNA
15 were negative. CMV and HEV serologies were negative. ANA, anti-smooth muscle antibody and
16 anti-mitochondrial antibody were all negative. He drank 10 alcohol equivalents per week. He was
17 treated with ursodiol, lactulose and rifaximin. A liver transplant evaluation was started, but he
18 improved rapidly after AP and bilirubin values peaked. AP fell by >50% from peak in 13 days and
19 bilirubin fell by >50% in 28 days. His symptoms resolved, and 112 days after onset his ALT,
20 AST, AP and bilirubin were normal.

21 Days from drug start to onset: 35

22 Days from drug stop to onset: 28

23 Days from peak to <50% peak AP: 13

24 LiverTox® category: A

25

RECAM	Points	RUCAM	Points
Domain		Criteria	
1a: Drug start to onset	4	1a: Drug start to onset	2
1b: Drug stop to onset	0	1b: Drug stop to onset	(1)^
2: Dechallenge	4	2: Course	3
3: Literature support	3	3: Risk factors**	1, 1
4: Competing diagnoses	0	4: Concomitant drugs	0
5: Additional data	0	5: Non-drug causes	1
		6: Previous information	2
		7: Rechallenge	0
Total	11	Total	10

DILI Diagnostic Category	High probable*	DILI Diagnostic Category	High probable
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26 *High probable is equivalent to DILIN's Highly likely or Definite; ^Not added to total; **alcohol,
27 age

28 Comment: DILIN Causality Committee felt this was definite DILI due to amoxicillin-clavulanate.
29 Both RECAM and RUCAM score this case as high probable DILI. However, the authors suggest
30 that this case would still be compelling for DILI had the patient been a 54-year-old, non-drinker.
31 In that case, the RECAM score would still be 11, while the RUCAM score would fall to 8, making
32 it probable instead of high probable.

33

34 *Case 2 (DILIN Case), Drug: doxycycline*

35 This patient was a 36-year-old Caucasian woman who developed high transaminases with jaundice
36 12 days after starting a 7-day course of oral doxycycline for a facial rash.

37 She noted scleral icterus within 4-5 days of starting doxycycline. She saw her primary care
38 provider 5 days after finishing her antibiotic course, and her ALT was 810 U/L, AST 1331 U/L,
39 AP 243 U/L and bilirubin 12.8 mg/dL. R-value 6.3. Evaluation testing included an ultrasound that
40 revealed cholelithiasis, but her bile ducts were small without signs of obstruction. Anti-HAV IgM,
41 HBsAg, anti-HBc IgM, anti-HCV antibody, HCV RNA and HEV testing were all negative.
42 Patient did not drink alcohol. ANA was positive at 1:640 and IgG level was over 4000 mg/dL
43 (upper limit of normal: 1600 mg/dL). A liver biopsy showed severe inflammation and necrosis
44 consistent with severe autoimmune hepatitis. Prednisone was started with fall in ALT to less than
45 50% of peak at 20 days. However, thereafter ALT remain elevated and mycophenolate mofetil
46 was started. Prednisone taper failed, and transition to azathioprine begun. At last follow-up, 233
47 days after onset, ALT had risen again from a low of 54 U/L to 151 U/L.

48 Days from drug start to onset: 12

49 Days from drug stop to onset: 5

50 Days from peak to <50% peak ALT: 20

51 LiverTox® category: B

RECAM	Points	RUCAM	Points
Domain		Criteria	
1a: Drug start to onset	4	1a: Drug start to onset	2
1b: Drug stop to onset	0	1b: Drug stop to onset^	(1)
2: Dechallenge	4	2: Course	2
3: Literature support	3	3: Risk factors**	0, 0
4: Competing diagnoses	-6*	4: Concomitant drugs	0
5: Additional data	0	5: Non-drug causes	1

		6: Previous information	1
		7: Rechallenge	0
Total	-6*	Total	6
DILI Diagnostic Category	Unlikely^^	DILI Diagnostic Category	Probable

52 *Stop warning for alternate diagnosis of autoimmune hepatitis; ^^Not added to total; **alcohol,
53 age.

54 Comments: DILIN Causality Committee felt this was unlikely DILI. In this case, the simplified
55 autoimmune hepatitis (AIH) score¹⁶ was 8, or definite for AIH, which triggered a RECAM
56 warning to stop, give a total score of -6 and assess the case as unlikely or excluded for DILI. The
57 RUCAM does not have stopping criteria and gave a score of 6 or probable DILI.

58

59 *Case 3 (Spanish Registry Case), amoxicillin-clavulanate*

60 A 54-year-old Caucasian male was admitted to the hospital because of a 3-day history of fever,
61 arthralgia and asthenia followed by dark urine 2 days later. Symptoms appeared 10 days after a 12-
62 day course of amoxicillin-clavulanate (875/125mg) three times daily prescribed for a dental
63 infection. On examination the subject was alert and slightly jaundiced. Liver biochemistries showed
64 an AST of 1832 U/L, ALT 3866 U/L, alkaline phosphatase 276 U/L, total bilirubin 7.85 mg/dL and
65 INR 1.28. An abdominal ultrasound was normal. Serologies excluded viral hepatitis A, B and C,
66 Epstein-Barr virus and cytomegalovirus infection. Autoantibodies were negative. The patient
67 improved with a progressive decrease of transaminases although total bilirubin peaked at 16.9 mg/dL
68 8 days after admission. Although amoxicillin-clavulanate hepatotoxicity was initially suspected,
69 HEV-IgM testing done with a second set of evaluation labs was positive.

70 Days from drug start to onset: 22

71 Days from drug stop to onset: 10

72 Days from peak to <50% peak ALT: 8

73 LiverTox® category: A

74

RECAM	Points	RUCAM	Points
Domain		Criteria	
1a: Drug start to onset	4	1a: Drug start to onset	2
1b: Drug stop to onset	-1	1b: Drug stop to onset^	(1)
2: Dechallenge	4	2: Course	3
3: Literature support	3	3: Risk factors**	0, 0
4: Competing diagnoses	-6*	4: Concomitant drugs	0
5: Additional data	0	5: Non-drug causes	-3
		6: Previous information	2

		7: Rechallenge	0
Total	-6*	Total	4
DILI Diagnostic Category	Unlikely	DILI Diagnostic Category	Possible

75 *Stop warning for alternate diagnosis of hepatitis E; ^Not added to total; **alcohol, age;
 76 ^^Unlikely included the category of excluded in the Spanish Registry

77 Comment: Expert opinion excluded DILI. RECAM gave a stopping score of -6 and assessed the
 78 case as Unlikely (or Excluded). RUCAM score was 4 with a diagnostic category of Possible.

79

80 *Case 4 (DILIN Case), Drug: isoniazid*

81 This patient was 58-year-old African American woman who developed high transaminases and
 82 mild hyperbilirubinemia 6 weeks after starting isoniazid.

83 She had no prior liver problems. She was exposed to a patient with tuberculosis at her work as a
 84 nurse and was started on isoniazid. Her ALT was normal at baseline. Forty-six days into therapy
 85 her ALT was 1609 U/L, AST 1400 U/L, AP 282 U/L and bilirubin 1.9 mg/dL. R-value was 21.4.
 86 Her isoniazid was stopped the next day. She was asymptomatic. She had received several days of
 87 ciprofloxacin 51 days before injury onset and gabapentin 90 days before onset. Her other
 88 medications had been taken for at least 3 years. She took acetaminophen as needed but never
 89 exceeded 2 tablets daily. She did not drink alcohol. Anti-HAV IgM, HBsAg, anti-HBc IgM, anti-
 90 HCV antibody, and HCV RNA were negative. CMV, EBV and HEV serologies were negative.
 91 ANA and ASMA were positive but at titers of <1:80. Ultrasound showed a normal liver. Her ALT
 92 and bilirubin increased modestly to 1649 U/L and 3.2 mg/dL over the next 2 to 8 days, but her
 93 AST fell to 644 in the same period. The patient did not get any follow-up labs until 109 days after
 94 onset and 107 days after peak ALT. Her ALT and AST were 13 U/L and 18 U/L respectively.

95 Days from drug start to onset: 46

96 Days from drug stop to onset: -1

97 Days from peak to <50% peak ALT: 107

98 LiverTox® category: A

RECAM	Points	RUCAM	Points
Domain		Criteria	
1a: Drug start to onset	4	1a: Drug start to onset	2
1b: Drug stop to onset	0	1b: Drug stop to onset^	(1)
2: Dechallenge	2	2: Course	0
3: Literature support	3	3: Risk factors**	0, 1
4: Competing diagnoses	0	4: Concomitant drugs	0
5: Additional data	0	5: Non-drug causes	1
		6: Previous information	2

		7: Rechallenge	0
Total	9	Total	6
DILI Diagnostic Category	High probable*	DILI Diagnostic Category	Probable

99 *High probable is equivalent to DILIN's Highly likely or Definite; ^Not added to total; **alcohol,
100 age

101 Comment: DILIN Causality Committee felt this was highly likely DILI due to isoniazid. Both
102 RECAM and RUCAM gave high scores, but the RECAM gave a higher diagnostic category of
103 high probable (i.e., DILIN highly likely or definite). Adding Criteria 1b (Drug stop to onset) to the
104 RUCAM would give a score of 7 which is still probable. The RECAM awarded more points for
105 latency and dechallenge compared to RUCAM. For the RUCAM Criteria 4, the authors thought
106 the latency for ciprofloxacin was too long and incompatible for DILI due to this drug.

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