Effect of Hemolysis, Icterus and Lipemia on Chemistry Tests and Association between the Amount of Interfering Substances and LIH Indices

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ABSTRACT

Background: Interference from endogenous substances is one of the leading source of errors that clinical laboratories frequently encounter at the pre-analytical phase of testing. Automated chemistry platforms allow accurate measurement of interferences due to endogenous substances such as hemolysis, icterus and lipemia utilizing semi-quantitative testing with indices. We evaluated the effect of hemolysis, icterus and lipemia on chemistry assays and further assessed the association between the amount of interfering substances and ordinal values reported by the automated chemistry analyzer as H-, I- and L-indices.

Methods: Three normal serum pools were prepared and supplemented with six increasing concentrations of hemolysate, bilirubin and triglyceride. These samples were then tested for 40 chemistry analytes for hemolysis, 38 chemistry analytes for icterus and 31 chemistry analytes for lipemia interferences on a Beckman Coulter AU5800 series analyzer. Results were compared to baseline values and acceptability of results were determined based on the total allowable error limits according to CAP and CLIA guidelines. Analytes showing a bias more than ±10% for lipemia were airfuged and reanalyzed. The amount of hemolysis, icterus and lipemia were measured using a semi-quantitative photometric test on the same instrument using the Beckman Coulter LIH reagent system. These values were assigned by the instrument on an ordinal scale as qualitative flag levels ("N", "+", "++", "+++", "++++" and "+++++") to reflect the degree of hemolysis, icterus and lipemia in a specimen. Visual detection of the hemolysis, icterus and lipemia was also performed independently on each aliquot in a blinded manner by three experienced technologists.

Results: Interference from hemolysis was detected for 20 of 40 tested analytes. Half of these twenty analytes were affected by gross hemolysis at hemoglobin concentrations of 798 mg/dL with ordinal values of "+++++" flag level. Only three analytes (aspartate aminotransferase, direct bilirubin and lactate dehydrogenase) were affected by slight hemolysis at hemoglobin concentrations of 76 mg/dL with ordinal values of "+" flag level. Aldolase was the only analyte that was affected at hemoglobin concentrations of 25 mg/dL. Interference from icterus was detected for 9 of 38 tested analytes. Three of these nine analytes were affected by gross icterus at bilirubin concentrations of 60 mg/dL with ordinal values of "+++++" flag level. Free glycerol was the only analyte that was affected by bilirubin concentrations of 3.7 mg/dL with ordinal values of "+" flag level. Interference from lipemia was detected for 9 of 31 tested analytes. There was no analyte that was affected by triglyceride concentrations of 300 and 600 mg/dL with ordinal values of "+" and "++" flag levels. BUN was the only analyte that was affected by gross lipemia at triglyceride concentrations of 2100 mg/dL with ordinal values of "+++++" flag level. Visual inspection results for hemolysis and lipemia showed good agreement between three technologists and were consistent with the corresponding ordinal values. Visual inspection results for icterus showed more variations between technologists and compared to ordinal values.

Conclusions: We have demonstrated that some of the chemistry analytes were affected by hemolysis, icterus and lipemia interferences. Generally, our results were consistent with manufacturer's claims. Our laboratory applied the results to determine the cut-off indices for hemolysis, icterus and lipemia on tested chemistry analytes using the robust measurement of the interferent provided by the automated chemistry analyzer. The implementation of the indices allows us to effectively determine the specimen integrity and prevent erroneous test results due to hemolysis, icterus and lipemia.

Introduction

- Clinical laboratory assays can be affected by various endogenous substances e.g. hemoglobin, bilirubin, lipids.
- Interferences due to hemolysis, icterus and lipemia can be accurately detected by automated chemistry analyzers.
- The aim of this study was to evaluate the effect of hemolysis, icterus and lipemia on chemistry assays and determine the cut-off indices above which these interferences impact the results of analysis.

Methods

- Three different serum pools were prepared.
- Each serum pool was spiked with increasing concentrations of hemolysate, commercially available bilirubin and triglyceride (human triglyceride-rich lipoproteins (Table 1).
- The degree of hemolysis, icterus and lipemia in each spiked sample were visually inspected in a blinded manner by three independent technologists.
- The amount of hemolysis, icterus and lipemia in each spiked sample were also measured semi-quantitatively using a photometric test on a Beckman Coulter AU5800 series analyzer. The LIH reagent system was used for this analysis.
    - The instrument assigns these values on an ordinal scale as "N", "+", "++", "+++", "++++" and "+++++" to be six different qualitative flag levels (Table 2).
- Each of the hemolysate, bilirubin and triglyceride supplemented samples were tested for 40 chemistry analytes for hemolysis, 38 chemistry analytes for icterus and 31 chemistry analytes for lipemia interferences on the same chemistry instrument.
    - Results were compared to baseline values and observed bias was determined.
    - Analytes showing a bias more than ±10% for lipemia were airfuged (30 PSI for 10 min) and reanalyzed.
    - The concentration of interferences that impacted the results was determined based on the total allowable error limits according to CAP and CLIA guidelines.
- The final cut-off indices were determined for each analyte at the concentration level of hemolysis, icterus and lipemia that affect the results of analysis.

Table 1. Target Concentrations of Hemoglobin, Bilirubin and Triglyceride in Each Serum Pool

Interferents	**Target Concentrations (mg/dL)**
Hemoglobin (Hemolysis)	25, 75, 150, 250, 400, 800
Bilirubin (Icterus)	1.0, 3.7, 7.5, 15, 30, 60
Triglyceride (Lipemia)	50, 300, 600, 1100, 1500, 2100

Table 2. Hemoglobin and Bilirubin Concentration Range at LIH Test and Associated Flag Levels

Hemoglobin Concentration (mg/dL) Range at LIH test	**Bilirubin Concentration (mg/dL) Range at LIH test**	**Triglyceride Concentration (mg/dL) Range at LIH test (Established at MRL)**	**Flag Level**
>500	>40	≥ 2016	+++++
300-500	20-40	≥1300-≤1979	++++
200-299	10-19.9	≥790-≤1255	+++
100-199	5-9.9	≥428-≤762	++
50-99	2.5-4.9	≥216-≤356	+
<50	<2.5	≤153	N
N: Normal			

Results

Table 3. Hemolysis Interference

Flag Level		N	+	++	+++	++++	+++++
Actual [Hb] (mg/dL)		25	76	150	249	399	798
ANALYTE	TaE	Bias (% or absolute)	Bias (% or absolute)	Bias (% or absolute)	Bias (% or absolute)	Bias (% or absolute)	Bias (% or absolute)
Albumin	±10.0%	-1.1%	-1.3%	-0.9%	0.7%	3.3%	10.2%
Aldolase	±20.0%	22.6%	111.5%	241.1%	N/A	N/A	N/A
ALP	±30.0%	-3.7%	-4.4%	-5.4%	-8.0%	-9.8%	-14.9%
ALT	±20.0%	3.2%	10.0%	13.3%	23.2%	31.4%	58.2%
Amylase	±30.0%	-0.2%	0.4%	-3.7%	-0.1%	15.6%	7.6%
AST	±20.0%	8.1%	27.9%	50.6%	87.3%	131.6%	263.2%
CO2	21.6%	-1.3%	-2.7%	-3.6%	-4.4%	-3.3%	-1.0%
Direct Bilirubin	±20.0%	-14.6%	-27.0%	-34.8%	-31.3%	-38.5%	-48.6%
Total Bilirubin	±0.4mg/dL	0.02	0.01	0.02	0.02	0.05	0.11
BUN	±9.0%	-0.6%	0.0%	0.8%	1.4%	2.4%	4.8%
Calcium	±1.0 mg/dL	0.01	0.09	0.05	0.00	-0.05	0.01
CK	±30.0%	2.4%	7.8%	17.7%	28.1%	44.5%	89.1%
Creatinine-Jaffe	±0.3 mg/dL	0.00	0.01	-0.03	-0.05	-0.02	0.06
Creatinine-Enzymatic	±0.3 mg/dL	0.00	-0.04	-0.09	-0.13	-0.21	-0.38
Fructosamine	9.9%	1.8%	5.8%	11.4%	13.7%	14.2%	0.4%
GGT	15.3%	1.7%	3.1%	3.7%	4.2%	13.1%	36.7%
Glucose	±10.0%	-0.1%	-0.4%	-0.6%	0.1%	0.2%	1.8%
LDH	±20.0%	18.3%	60.6%	113.8%	196.9%	276.0%	546.5%
Lipase	±30.0%	-0.8%	1.4%	1.6%	3.4%	3.6%	6.7%
Mg	±25.0%	0.5%	1.7%	4.2%	9.5%	15.7%	31.7%
Phosphorous	±10.7%	0.3%	2.1%	4.0%	5.9%	9.4%	17.9%
Total Protein	±10.0%	-0.3%	1.4%	2.0%	3.6%	6.1%	11.2%
Uric Acid	±17.0%	-0.1%	-1.2%	-1.8%	-3.3%	-3.9%	-6.5%
UIBC	20.7%	-0.6%	-1.1%	-2.8%	-7.9%	-12.1%	-24.2%
Cholesterol	±10.0%	-0.1%	1.9%	3.7%	9.1%	11.6%	26.1%
Triglyceride	±15.0%	1.1%	-0.5%	-0.4%	-1.2%	-1.3%	-3.6%
HDL-C direct	±13.0%	-0.1%	0.5%	-0.1%	0.0%	0.5%	0.0%
HDL-Cppt	±13.0%	1..5%	8.4%	14.0%	23.3%	37.3%	81.7%
Ethanol	Cut-off = 10 mg/dL	neg	neg	neg	neg	neg	pos
Iron	±20.0%	0.2%	-0.4%	-0.4%	-2.0%	-2.9%	-22.2%
Transferrin	±20.0%	0.3%	1.2%	-1.4%	-0.2%	-0.4%	-0.6%
LDL Cholesterol	±12.0%	0.3%	1.7%	-0.1%	-0.1%	-0.2%	-0.4%
Free Glycerol	±20.0%	-2.2%	-6.0%	-9.4%	-15.4%	-19.8%	-33.0%
Lactate	±0.4 mmol/L	0.00	-0.01	-0.01	-0.01	-0.01	-0.04
Lp(a)	52.2%	-2.5%	2.3%	1.2%	1.3%	-3.0%	-9.0%
Phospholipid	±20.0%	1.1%	0.7%	1.3%	1.9%	3.1%	5.5%
Free Cholesterol	±20.0%	0.3%	1.8%	3.1%	5.3%	8.8%	18.1%
K^+	±0.5 mmol/L	0.09	0.25	0.52	0.87	1.29	2.72
Na	±4.0 mmol/L	-0.06	-0.89	-0.28	0.02	-0.09	0.17
Cl	±5.0%	-0.2%	-0.6%	-0.2%	0.1%	0.4%	1.5%
		Results are listed as N/A if instrument was unable to determine the values due to instrument flags e.g. OD of reaction is higher than the maximum OD range. Results are colored in red when any of the listed results are outside the TaE limits.					

Table 4. Icteric Interference

Flag Level		N	+	++	+++	++++	+++++
Target [Bilirubin] (mg/dL)		1.0	3.7	7.5	15	30	60
ANALYTE	TaE	Bias (% or absolute)	Bias (% or absolute)	Bias (% or absolute)	Bias (% or absolute)	Bias (% or absolute)	Bias (% or absolute)
Albumin	±10.0%	-0.4%	-0.8%	-1.6%	-1.4%	-0.4%	-0.4%
Aldolase	±20.0%	12.2%	16.2%	9.4%	-1.5%	-6.9%	N/A
ALP	±30.0%	0.1%	0.5%	-0.2%	0.4%	-0.3%	-0.2%
ALT	±20.0%	7.1%	5.5%	5.5%	5.3%	5.9%	6.2%
Amylase	±30.0%	-0.9%	-0.4%	-0.3%	-7.2%	-14.0%	-22.6%
AST	±20.0%	4.6%	2.8%	4.0%	3.2%	3.4%	1.7%
CO2	21.6%	-5.2%	-5.9%	-6.1%	-5.2%	-2.1%	0.1%
BUN	±9.0%	-0.7%	-0.5%	-0.6%	-0.2%	-0.3%	-0.5%
Calcium	±1.0 mg/dL	-0.01	-0.02	-0.12	-0.11	0.13	0.08
CK	±30.0%	4.5%	3.8%	3.9%	4.3%	4.5%	3.3%
Creatinine-Jaffe	±0.3 mg/dL	0.01	-0.01	0.02	0.07	0.11	-0.09
Creatinine-Enzymatic	±0.3 mg/dL	0.00	0.00	0.00	-0.02	-0.04	-0.11
Fructosamine	9.9%	0.7%	7.8%	17.8%	35.2%	71.8%	171.3%
GGT	15.3%	5.1%	4.1%	2.0%	-3.8%	-14.4%	-21.3%
Glucose	±10.0%	0.8%	0.7%	0.4%	1.2%	0.8%	0.9%
LDH	±20.0%	3.8%	3.7%	4.2%	3.8%	4.1%	4.3%
Lipase	±30.0%	0.1%	-0.4%	-3.8%	-14.5%	-30.4%	-59.2%
Mg	±25.0%	0.7%	1.4%	2.0%	3.6%	6.7%	14.0%
Phosphorous	±10.7%	0.8%	-0.4%	-0.1%	1.5%	1.7%	1.2%
Total Protein	±10.0%	-0.5%	-1.1%	-2.3%	-4.0%	-8.3%	-17.9%
Uric Acid	±17.0%	-0.4%	-0.3%	-0.1%	0.0%	-0.6%	-2.2%
UIBC	20.7%	3.9%	2.7%	2.9%	2.2%	0.1%	-3.5%
Cholesterol	±10.0%	-0.5%	-4.1%	-7.1%	-14.9%	-31.7%	-60.5%
Triglyceride	±15.0%	1.5%	0.5%	0.6%	0.7%	-1.3%	-3.3%
HDL-C direct	±13.0%	-1.7%	0.0%	-1.7%	-2.1%	-2.0%	-5.2%
HDL-Cppt	±13.0%	-3.8%	-9.7%	-16.8%	-35.5%	-62.0%	-75.4%
Ethanol	Cut-off=10mg/dL	neg	neg	neg	neg	neg	neg
Iron	±20.0%	-0.9%	-0.7%	-1.1%	-0.3%	-0.6%	-1.0%
Transferrin	±20.0%	-0.9%	-0.4%	-1.6%	-1.2%	-0.5%	-1.3%
LDL Cholesterol	±12.0%	-1.1%	-0.2%	-1.4%	-0.5%	-0.8%	-0.8%
Free Glycerol	±20.0%	-12.4%	-43.5%	-72.5%	-95.1%	-60.7%	-72.3%
Lactate	±14.4%	-0.8%	-2.4%	-2.6%	-7.4%	-17.1%	-34.7%
Lp(a)	52.2%	2.5%	0.4%	-2.9%	1.0%	-6.4%	0.2%
Phospholipid	±20.0%	-0.1%	-0.7%	-1.3%	-2.6%	-6.0%	-13.7%
Free Cholesterol	±20.0%	-1.6%	-4.9%	-10.0%	-13.1%	-8.3%	-8.7%
K^+	±0.5 mmol/L	-0.01	-0.04	-0.02	-0.02	0.02	-0.02
Cl	±5.0%	-0.6%	-0.7%	-0.9%	-0.2%	0.1%	0.0%
		Results are listed as N/A if instrument was unable to determine the values due to instrument flags e.g. OD of reaction is higher than the maximum OD range. Results are colored in red when any of the listed results are outside the TaE limits.					

Table 5. Lipemia Interference

Flag Level		+	++	+++	++++	+++++
Target Trig (mg/dL)		300	600	1100	1500	2100
ANALYTE	TaE	Bias (% or absolute)	Bias (% or absolute)	Bias (% or absolute)	Bias (% or absolute)	Bias (% or absolute)
Albumin	±10.0%	-0.5%	-0.5%	1.8%	4.0%	8.1%
Aldolase	±20.0%	4.7%	8.9%	33.7%	67.7%	N/A
ALP	±30.0%	1.3%	1.1%	-0.9%	0.5%	-6.5%
ALT	±20.0%	5.7%	14.6%	31.1%	N/A	N/A
Amylase	±30.0%	-2.1%	-2.8%	-4.7%	-7.4%	-5.8%
AST	±20.0%	6.4%	24.2%	35.6%	N/A	N/A
CO2	21.6%	-7.1%	-7.0%	-8.8%	-10.5%	-20.4%
Direct Bilirubin	±20.0%	-3.7%	-9.2%	-12.6%	-18.1%	-25.4%
Total Bilirubin	±0.4mg/dL	0.00	-0.01	0.02	0.04	0.08
BUN	±9.0%	0.0%	0.3%	2.6%	2.9%	N/A
Calcium	±1.0 mg/dL	0.08	0.06	0.19	0.14	0.61
CK	±30.0%	-0.6%	-1.7%	-1.6%	-3.6%	-7.6%
Creatinine-Jaffe	±0.3 mg/dL	0.00	-0.01	0.00	-0.02	0.01
Creatinine-Enzymatic	±0.3 mg/dL	-0.01	-0.03	-0.05	-0.11	-0.10
Fructosamine	9.9%	2.1%	2.6%	6.5%	17.9%	31.4%
GGT	15.3%	-1.2%	-1.5%	-3.9%	-6.2%	-10.7%
Glucose	±10.0%	0.1%	0.8%	1.2%	1.4%	6.5%
LDH	±20.0%	-1.6%	-0.9%	-5.2%	-8.7%	-11.7%
Lipase	±30.0%	5.1%	9.6%	24.8%	51.0%	76.1%
Mg	±25.0%	1.3%	3.5%	8.3%	24.7%	44.2%
Phosphorous	±10.7%	-0.4%	-1.2%	-0.8%	-1.9%	3.0%
Total Protein	±10.0%	0.1%	0.5%	0.2%	1.6%	3.6%
Uric Acid	±17.0%	1.4%	1.9%	1.2%	-1.6%	-1.5%
HDL-C direct	±13.0%	-0.1%	-1.4%	-2.6%	-0.4%	-2.8%
Ethanol	Cut-off = 10 mg/dL	neg	neg	neg	neg	neg
Iron	±20.0%	-0.8%	-2.4%	-7.2%	-14.5%	-19.0%
UIBC	20.7%	0.4%	2.1%	3.4%	5.8%	5.8%
Transferrin	±20.0%	-0.5%	-1.4%	-2.2%	-3.9%	-0.6%
Free Glycerol	±20.0%	5.0%	8.9%	19.6%	31.5%	87.3%
Lactate	±0.4 mmol/L	-0.01	0.01	-0.02	-0.04	-0.05
K^+	±0.5 mmol/L	0.00	0.01	0.04	-0.03	0.02
		Results are listed as N/A if instrument was unable to determine the values due to instrument flags e.g. OD of reaction is higher than the maximum OD range. Used commercial triglyceride contains some of the analytes e.g. cholesterol, Lp(a), sodium therefore those analytes were excluded from the analysis. Results are colored in red when any of the listed results are outside the TaE limits.				

Table 6. Visual Assessment

LIH	Pool	Spike	Technologist #1			Technologist #2			Technologist #3		
			Hemolysis	Icterus	Lipemia	Hemolysis	Icterus	Lipemia	Hemolysis	Icterus	Lipemia
N	1	Neat	N	S	N/A	N	N	N/A	N	S	N/A
N	1	Normal	N	N	N	S	N	N	N	S	N
+	1	1+	S	S	S	S	N	S	S	N	S
++	1	2+	S	S	S	S	N	M	S	M	M
+++	1	3+	S	S	M	M	S	M	M	M	G
++++	1	4+	M	M	G	G	S	G	G	M	G
+++++	1	5+	G	M	G	G	M	G	G	G	G
N	2	Neat	N	S	N/A	N	N	N/A	N	S	N/A
N	2	Normal	N	N	S	N	N	N	N	S	N
+	2	1+	S	S	S	S	N	S	S	S	S
++	2	2+	S	S	M	S	S	S	S	S	M
+++	2	3+	M	S	M	M	S	M	M	M	M
++++	2	4+	M	M	M	G	S	G	M	M	G
+++++	2	5+	G	M	G	G	M	G	G	G	G
N	3	Neat	N	N	N/A	N	N	N/A	N	N	N/A
N	3	Normal	N	N	N	N	N	N	N	N	N
+	3	1+	S	S	S	S	N	S	S	S	S
++	3	2+	S	S	S	S	N	M	S	S	S
+++	3	3+	M	S	M	G	S	M	M	S	M
++++	3	4+	M	M	G	M	S	G	G	G	G
+++++	3	5+	G	M	G	G	M	G	G	G	G
			N: normal, S: slight, M: moderate and G: gross Neat and normal samples were the same for lipemia study hence results are listed as N/A for neat samples.								

Summary of Results

Hemolysis:

- Hemolysis affected 20 results out of 40 total tested analytes.
- For most of the assays, our data is in a good agreement with information provided by the manufacturers in the package inserts. However some assays are affected at higher hemolysis index values than the package inserts indicate.
  - The BUN insert states that results are not affected by hemolysis up to [Hb] of 500 mg/dL however our results show there is no interference by hemolysis up to [Hb] of ~800 mg/dL.
  - The UIBC and free glycerol inserts state that the results are not affected by hemolysis up to [Hb] of 200 mg/dL and 250 mg/dL, respectively. However our results show there is no interference until samples are grossly hemolysed at [Hb] of ~800 mg/dL.

- LDH and K^+ are most significantly affected analytes and should not be reported if qualitative hemolysis flag levels are ≥2+ and ≥4+, respectively.
- HDL-C measured by dextran sulfate precipitation and GGT are also significantly affected by hemolysis and should not be reported if samples are grossly hemolysed with a hemolysis flag level of 5+.
- 50% of tested analytes are not affected by hemolysis at any hemoglobin concentration levels including at hemoglobin concentrations of ~800 mg/dL.
- Visual inspection results for hemolysis showed good agreement between three technologists and when compared to corresponding flag levels.
- All three technologists were in agreement on 71.4% of results, while two technologists agreed on the remaining 28.6% of results.

Icterus:

- Icterus affected 9 results out of 38 total tested analytes.
- Almost all of our data for icterus agree with information provided by the manufacturers in the package inserts. However lipase assay is affected at higher icterus index values than the package insert indicates.
    - The lipase insert states that results are not affected by icterus up to [bilirubin] of 12 mg/dL however our results show there is no interference by hemolysis up to [bilirubin] of 30 mg/dL.
- Icterus has significant effect on HDL-C measured by dextran sulfate precipitation, cholesterol and free glycerol assays and should not be reported if samples are icteric with qualitative icterus flag level of ≥2+.
- Icterus significantly affects lipase results and should not be reported if qualitative icterus flag level is 3+ or more.
- GGT, fructosamine and aldolase are also significantly affected by icterus and should not be reported if samples are grossly icteric with qualitative icterus flag levels of ≥4+ for GGT and fructosamine and 5+ for aldolase.
- 76% of tested analytes are not affected by gross icterus at bilirubin concentrations of 60 mg/dL.
- Visual inspection results for icterus showed variations between technologists and compared to ordinal values.
- All three technologists were in agreement on 19% of results, while two technologists agreed on 71.4% of results. There was no agreement on 10% of results.

Lipemia:

- Lipemia affected 9 results out of 31 total tested analytes.
- Airfuging remedies well results of some of the assays (e.g. ALT, AST, BUN, LDH) while it moderately remedies others (e.g. bilirubin, fructosamine).
- Our results show that some assays (ALT, AST and lipase) are affected by lipemia at lower index values than the package inserts indicate.

- Lipemia significantly affects AST, ALT, lipase and aldolase results and should not be reported if the qualitative lipemia flag level is ≥2+ for AST and ≥3+ for ALT, lipase and aldolase.
- Fructosamine, free glycerol, Mg, D. Bili and BUN are also significantly affected by lipemia and results should not be reported if samples are grossly lipemic with qualitative lipemia flag levels of ≥4+ for fructosamine, free glycerol, Mg, D. Bili and 5+ for BUN.
- 67% of tested analytes are not affected by gross lipemia at triglyceride concentrations of 2100 mg/dL.
- Visual inspection results for lipemia showed good agreement between three technologists and when compared to corresponding flag levels.
- All three technologists were in agreement on 67% of results, while two technologists agreed on remaining 33% of results.

Conclusions

- Results of the current study show that 50% of tested chemistry analytes are affected by hemolysis, 29% are affected by lipemia, and 24% are affected by icterus.
- The automated chemistry analyzers provide a robust measurement of interferences compared to traditional visual inspection.
- The implementation of the cut-off indices allows clinical laboratories to accurately determine specimen integrity, assess the validitiy of results and prevent erroneous results.

References

1. Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition (EP7-A2)
2. 2017 CAP Survey