

6. Maple Syrup Urine Disease (MSUD)

6.0 Introduction

Screening for maple syrup urine disease (MSUD) began in some screening programs in the 1960's although most programs now screening developed their programs later. The relatively low incidence of MSUD has made it a controversial disorder for inclusion in many newborn screening programs. Those that screen uniformly use the bacterial assay for leucine and even though there are relatively few programs screening, there is some disagreement on screening cutoff levels and definitions. All data reported here was collected from questionnaires submitted to programs as noted in Chapter 3. Only programs noting MSUD as included in their testing scheme are listed in the Tables.

6.1 Definitions for Maple Syrup Urine Disease

Programs were asked to give the definition used by their program to define maple syrup urine disease. There is still not general agreement among programs as to the level of leucine to be used for defining possible cases of MSUD, either 2 mg/dL or 4 mg/dL. It is hoped that eventually programs can come to a consensus as to the best definition to use and the extent to which a metabolic specialist should be involved in the final diagnosis. From the definitions submitted, it is the usual case that a specialist is consulted to make the final diagnosis and program guidance is limited.

6.2 Laboratory Techniques

In order to identify laboratory techniques in use, programs were asked to report their laboratory protocols. These data are reported in Table 6.02.

6.3 Initial Screening Results

In order to ascertain the effectiveness of screening for MSUD, programs were asked to report their findings on initial screening. Initial

screening was defined as the first reportable test, and programs were asked not to include duplicate screenings. By reviewing the number of infants screened and confirmed, versus the number of positive tests reported, the efficiency of the testing protocol may be evaluated.

Additionally, programs were asked to report the number of positive patients 'lost to follow-up' as a means of evaluating the follow-up procedures. These data are reported in Table 6.03. Programs wishing to explain some of their responses included information as footnotes to the table. Because programs continue to report inaccurate or inappropriate data in some of their responses, no totals were given in some columns of the table. Care should be taken in using these data, since not all programs reported data.

6.4 Second Screen Results

Please see Section 3.6 for a more complete discussion of the data on second screening tests. Second screen data are divided on the basis of whether the second screens are required on all newborns ('required') or are obtained on some other basis ('discretionary') when a second test is performed without regard for the initial screening result. Programs that requested a second screen because of either a certain result on the first screen that acted as impetus for a second screen or because of an unsatisfactory first screen (usually due to sample condition or early collection) were asked to report these data as 'repeat screens.'

For each case, the data requested included the total infants tested, the total with findings considered not normal, and the number of confirmed cases divided by type of clinical finding. It should be recognized that this is a different way of reporting these data than previously and may, therefore, be somewhat confusing. It is hoped that these data better represent the findings from additional screens. Once again, the reader is cautioned about using the data without regard to notes of explanation.

6.5 Cases of MSUD Divided by Sex and Race/Ethnicity

Programs were asked to report the total of all confirmed cases of MSUD, whether detected on first or second screen, divided by sex and race/ethnicity. The term race/ethnicity was used because some states with high Hispanic populations maintain Hispanic data in much the same way that other states maintain racial data. These data are reported in Table 6.05. For comparative data about the breakdown of births in all states and territories, the reader is referred to the tables in Chapter 1.

6.6 Time Until Treatment

In order to look at overall program efficiency, programs were asked to report the number of days from birth until treatment of MSUD. The definition of treatment used in the questionnaire was “initiation of dietary or drug regimen” and programs using a different definition were asked to report their definition for inclusion as a footnote to the tabulation. Similarly programs were asked to provide footnote information for any cases not treated within the first 21 days of life. These data are reported in Table 6.06.

6.7 Historic Data

In order to document the value of screening for MSUD, programs were asked to supply whatever historic data they could on their screening program. In particular, they were asked to give the date the program began and the number of cases detected over the years. These data are given in Table 6.07.

6.8 Total Newborns Screened

Table 6.08 gives a summation of the data contained in Tables 6.03 and 6.04 along with the number of births in each state or territory as reported in Table 1.01. This table was included so that tabulation of these data could be viewed without having to refer to several tables.

6.9 Summation of Results

Table 6.09 sums the significant testing data from this Chapter. It includes the total births from Table 1.01, the total infants reported as being screened, and the testing data reported in Tables 6.03 and 6.04. Comparative percentages have been provided at the request of a number of readers, but in many cases these data are based on estimates or on data that appear to contain duplicate information, thus total compliance percentages may exceed 100% in some cases.

Table 6.01: Definitions for Maple Syrup Urine Disease

State/Territory	Definition for Maple Syrup Urine Disease
1 Alaska	Branched chain Amino Acids elevated above normal on diet and infant symptomatic.
2 Arizona	Serum leucine \geq 4 mg/dL.
3 Connecticut	Classified by treatment center.
4 District of Columbia	Elevated leucine.
5 Georgia	Branched chain amino acids significantly elevated confirmed by plasma amino acid analysis.
6 Hawaii	Branched chain amino acids elevated above normal and infant symptomatic.
7 Idaho	Branched chain Amino Acids elevated above normal on diet and infant symptomatic.
8 Indiana	Leucine \geq 4.0 mg/dL on screen. Confirmation by medical consultant and diagnostic tests.
9 Maine	Leucine < 6 mg/dL on screen with confirmation by medical consultant and/or reference lab performing diagnostic tests.
10 Maryland	Leucine >2 mg/dL on screen, elevated leucine, valine and isoleucine on amino acid profile.
11 Massachusetts	Diagnosis and classification determined by metabolic consultant.
12 Michigan	Deficiency in the enzyme BCKAD resulting in elevations in serum (leucine, isoleucine, valine).
13 Nevada	Branched chain amino acid elevated above normal on diet and symptomatic.
14 New Hampshire	Diagnosis and classification made by metabolic consultant.
15 New York	Diagnosis and classification determined by treatment center.
16 North Carolina	Diagnosis and classification made by medical consultant.
17 North Dakota	Diagnosis determined by medical consultant.
18 Oregon	Branched chain Amino Acids elevated above normal on diet and infant symptomatic.
19 Pennsylvania	An autosomal recessive disorder of branched chain ketoacid decarboxylation resulting in high body fluid levels of leucine.
20 Rhode Island	Diagnosis and classification determined by metabolic consultant.
21 Vermont	Persistent leucine elevation > 6 mg/dL.
22 Virginia	Branched-chain Keto acid decarboxylase deficiency resulting in elevated leucine levels.
23 Wyoming	Leucine > 400 increased allisoleucine, decreased branched chain ketoacid dehydrogenase in fibroblasts.
24 Virgin Islands	> 4 mg/dL.

Table 6.02: Maple Syrup Urine Disease - Laboratory Testing

State/Territory	Leucine BIA Assay	Other	Definition of NOT NORMAL (mg/dL) <i>Requiring Further Filter Paper Testing</i>	Definition of NOT NORMAL (mg/dL) <i>Requiring Immediate Serum Follow-up</i>
1 Alaska	X			≥4 mg/dL Leucine (all elevations require phone calls).
2 Arizona	X		None	≥ 4 mg/dL
3 Connecticut	X			≥ 4 mg/dL
4 District of Columbia		MS/MS		Leucine - > 400 μM/L.
5 Georgia	X		Leu ≥ 4 mg/dL without symptoms but < 6 mg/dL	Leucine ≥ 6 mg/dL or Leucine ≥4 mg/dL with symptoms.
6 Hawaii	X		> 4 mg/dL (all elev. Require phone calls) if on hyperal repeat filter paper	> 4 mg/dL if not on hyperal and symptomatic
7 Idaho	X			≥ 4 mg/dL % all elevations require phone notification.
8 Indiana	X		Leucine ≥ 4.0 < 5.9 mg/dL	Leucine ≥ 6.0 mg/dL.
9 Maine		MS/MS		
10 Maryland	X	HPLC	> 2 mg/dL and < 4 mg/dL	> 4 mg/dL
11 Massachusetts		MS/MS	≥ 6 mg/dL	≥ 6 mg/dL, all elevations reported by phone.
12 Michigan		a	5.5 - 6.9 if ≤ 8 days old	≥ 7.0 if < 8 days old, > 8.0 if > 8 days old.
13 Nevada	X		Leucine 4 mg/dL	Leucine ≥ 4 mg/dL
14 New Hampshire		MS/MS	≥ 6 mg/dL	≥ 6 mg/dL, All elevations reported by phone.
15 New York	X		≥4 mg/dL	> 4 mg/dL
16 North Carolina		MS/MS	≥ 3.51 mg/dL (300μM)	5.86 mg/dL (500 μM)
17 North Dakota	X		≥ 4 mg/dL	≥ 6 - 8 mg/dL
18 Oregon	X			≥4 mg/dL (all elevations require phone calls).
19 Pennsylvania		MS/MS		
20 Rhode Island	X		≥ 5 mg/dL	> 6 mg/dL
21 Vermont		MS/MS	< 6 mg/dL	> 6 mg/dL
22 Virginia	X	HPLC	≥ 4 mg/dL	≥ 6 mg/dL
23 Wyoming	X		DA	Leucine ≥ 4 mg/dL
24 Virgin Islands	X		> 4 mg/dL	

a = fluorometric since 6-14-00.

Table 6.03: Initial Screening Results - Maple Syrup Urine Disease

State/Territory	Number of Newborns Screened	Number of Newborns with <u>NOT NORMAL</u> Test Results	Number of Newborns with <u>NOT NORMAL</u> Test Results Lost to follow-up	Number of Newborns Confirmed with MSUD
1 Alaska	9,821	0		0
2 Arizona	81,956	4	0	1
3 Connecticut	43,722	32	0	0
4 District of Columbia	15,125	0	NA	0
5 Georgia	189,498	0	0	2
6 Hawaii	17,612	5	2 c	0
7 Idaho	20,254	2	0	0
8 Indiana	87,639	68	3	1
9 Maine	13,341	0	0	0
10 Maryland	72,390	108	4	2
11 Massachusetts	82,703	37	0	0
12 Michigan	134,022	120	0	0
13 Nevada	30,659	5	0	0
14 New Hampshire	13,879	4	0	0
15 New York	258,449	131	ND	0
16 North Carolina	114,389	NC	NC	0
17 North Dakota	9,815	1	0	0
18 Oregon	46,879	5	0	0
19 Pennsylvania	145,874	6	0	2
20 Rhode Island	13,150	0	0	0
21 Vermont	6,040	0	0	0
22 Virginia	99,410	42	0	0
23 Wyoming	~ 1,530	0	0	0
24 Virgin Islands	1,851	8	0	0
TOTAL	a	a	a	8 b

a = totals not given - too many programs reported inaccurate or inappropriate data; **b** = total given does not include all states; **c** = expired.

Table 6.04: Second Screens for Maple Syrup Urine Disease

R = Required Second Screens D = Discretionary Second Screens P = Repeat Second Screens

State/Territory	Newborns Receiving Required Second Screen	Newborns Receiving Discretionary Second Screens	Newborns Receiving Repeat Second Screens	Total 2nd Screens	Number of Newborns with <u>NOT NORMAL</u> Test Results				Number of Newborns with <u>NOT NORMAL</u> Test Results Lost to Follow-up				Number of Newborns Confirmed with MSUD			
	R	D	P		R	D	P	Total	R	D	P	Total	R	D	P	Total
1 Alaska		7,759	216	7,975		0		0								
2 Arizona		57,352		57,352		3		3								
3 Connecticut			235	235			2	2		0		0		0		0
4 District of Columbia			287	287				0	0		0					0
5 Georgia			ND	ND												
6 Hawaii			189	189												
7 Idaho		13,804	199	14,003												
8 Indiana			DA 31,782	31,782			25	25			2	2				0
9 Maine																
10 Maryland	61,152			61,152	7			7	5			5				
11 Massachusetts			8,818	8,818			50	50				0				0
12 Michigan				0			0	0			0	0		1		1
13 Nevada	25,668			25,668												
14 New Hampshire		815		815												
15 New York			DA	0		DA	N/C			DA	N/C			DA	N/C	
16 North Carolina																
17 North Dakota			DA 2,647	2,647		DA	1	1		DA	0	0		DA	0	0
18 Oregon	43,423		864	44,287	1		0	1								
19 Pennsylvania																
20 Rhode Island		N/C	N/C 427	427												
21 Vermont			326	326												
22 Virginia			12,648	12,648			12	12		0	0	0		0	0	0
23 Wyoming			DA NC			DA	N/C			DA	N/C					
24 Virgin Islands			8	8												
Total	a	130,243	79,730	58,646	b			b				b	0	1	0	1 c

a = totals given reflect program responses and should be viewed as estimates only, given the number not reporting and the number of caveats listed;

b = totals not given - too many programs reported inaccurate or inappropriate data; **c** = totals given do not include all states.

Table 6.05: Cases of Maple Syrup Urine Disease

Total detected on initial and second screens

Subdivided by Sex and Race/Ethnicity

State/Territory	White		Black		Asian or P. Islander		Native American		Other		Unknown		Total.....		Hispanic				
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Total	Male	Female	Total	
1 Alaska																			
2 Arizona									1				1	0	1				
3 Connecticut																			
4 District of Columbia																			
5 Georgia		1											0	1	2	³	1	1	
6 Hawaii																			
7 Idaho																			
8 Indiana		1											0	1	1				
9 Maine																			
10 Maryland	1			1									1	1	2				
11 Massachusetts																			
12 Michigan	1												1	0	1				
13 Nevada																			
14 New Hampshire																			
15 New York																			
16 North Carolina																			
17 North Dakota																			
18 Oregon																			
19 Pennsylvania	1	1											1	1	2				
20 Rhode Island																			
21 Vermont																			
22 Virginia																			
23 Wyoming																			
24 Virgin Islands																			
TOTAL	3	3	0	1	0	0	0	0	1	0	0	0	4	4	9	0	1	1	

¹did not report a breakdown of Race/Ethnicity.

²total reported is from Table 6.03 and Table 6.04; therefore total does not equal or may differ from data given in Table 6.05 and denotes a problem in reliability.

³Ethnicity counted as a Race and is included in total

Table 6.06: Days from Birth Until Treatment Initiated for Maple Syrup Urine Disease
Total detected on initial and second screens

(blank spaces mean that no infants fell into these categories)

State/Territory	≤ 3	4	5	6	7	8	9	10	11	12	13	14	15-21	>21	Unk.	TOTAL
1 Alaska																0
2 Arizona					1											1
3 Connecticut																0
4 District of Columbia																0
5 Georgia													2			2
6 Hawaii																0
7 Idaho																0
8 Indiana							1									1
9 Maine																0
10 Maryland					1	1										2
11 Massachusetts																0
12 Michigan														1		1
13 Nevada																0
14 New Hampshire																0
15 New York																0
16 North Carolina																0
17 North Dakota																0
18 Oregon																0
19 Pennsylvania	1						1									2
20 Rhode Island																0
21 Vermont																0
22 Virginia																0
23 Wyoming																0
24 Virgin Islands																0

Table 6.07: Summation of Years Covered and Number of Cases Detected by Program

State/Territory	Maple Syrup Urine Disease		
	Year Started	Total Years	Total Cases
1 Alaska	1987	13	0
2 Arizona	1994	6	2
3 Connecticut	1993	7	0
4 District of Columbia	1996	4	0
5 Georgia	Sep-78	21 1/4	19
6 Hawaii	Jul-97	2 1/2	2
7 Idaho	1962	38	0
8 Indiana	Jul-85	15 1/2	2
9 Maine	1976	24	0
10 Maryland	1972	28	14
11 Massachusetts	1963	37	19
12 Michigan	1987	13	8
13 Nevada NR			
14 New Hampshire	1983	17	0
15 New York	1968	32	26
16 North Carolina NR			
17 North Dakota	1992	8	0
18 Oregon NR			
19 Pennsylvania NR			
20 Rhode Island NR			
21 Vermont	Jul-89	11 1/2	0
22 Virginia	1984	16	3
23 Wyoming	Apr-79	17 3/4	0
24 Virgin Islands NR			

Table 6.08: Total Newborns Screened for Maple Syrup Urine Disease

State/Territory	Total Births	Number of Newborns with <u>NOT NORMAL</u> Test Results	Number of Newborns with <u>NOT NORMAL</u> Test Results Lost to follow-up	Number of Newborns Confirmed with MSUD
1 Alaska	9,866	0	0	0
2 Arizona	85,470	7	0	1
3 Connecticut	43,370	34	0	0
4 District of Columbia	15,159	0	0 N/A	0
5 Georgia	133,524	0	0	2
6 Hawaii	17,638	5	2 b	0
7 Idaho	19,863	2	0	0
8 Indiana	87,891	93	5	1
9 Maine	13,462	0	0	0
10 Maryland	69,574	115	9 c	2
11 Massachusetts	82,673	87	0	0
12 Michigan	134,889	120	0	1
13 Nevada	30,387	5	0	0
14 New Hampshire	13,987	4	0	0
15 New York	259,995	131	N/D	0
16 North Carolina	121,347	0	0	0
17 North Dakota	8,847	2	0	0
18 Oregon	46,790	6	0	0
19 Pennsylvania	146,857	6	0	2
20 Rhode Island	13,180	0	0	0
21 Vermont	6,277	0	0	0
22 Virginia	96,755	54	0	0
23 Wyoming	5,847	0	0	0
24 Virgin Islands	1,851	8	0	0
TOTAL	1,465,499	679	16	9 a

a = totals given do not include all states; **b** = expired; **c** = 4 expired.

Table 6.09: Summation Results of Testing for Maple Syrup Urine Disease

State/Territory	Total Births	Total Newborns Receiving Initial Screen	% of Newborns Receiving Initial Screening calculated	Total Newborns Receiving Required 2nd Screen	% of Newborns Receiving Required 2nd scrn. (calc'd)	Total Newborns Receiving Discretionary 2nd Screen	% of Newborns Receiving Discretionary 2nd scrn. (calc'd)	Total Newborns Receiving Repeat 2nd Screen	% of Newborns Receiving Repeat 2nd scrn. (calc'd)
1 Alaska	9,866	9,821	99.54%			7,759	78.64%	216	2.19%
2 Arizona	85,470	81,956	95.89%			57,352	67.10%		
3 Connecticut	43,370	43,722	* 100.81%					235	0.54%
4 District of Columbia	15,159	15,125	99.78%					287	1.89%
5 Georgia	133,524	189,498	* 141.92%						
6 Hawaii	17,638	17,612	99.85%					189	1.07%
7 Idaho	19,863	20,254	* 101.97%			13,804	69.50%	199	1.00%
8 Indiana	87,891	87,639	99.71%					31,782	36.16%
9 Maine	13,462	13,341	99.10%						
10 Maryland	69,574	72,390	* 104.05%	61,152	87.89%				
11 Massachusetts	82,673	82,703	* 100.04%					8,818	10.67%
12 Michigan	134,889	134,022	99.36%						
13 Nevada	30,387	30,659	* 100.90%	25,668	84.47%				
14 New Hampshire	13,987	13,879	99.23%			815	5.83%		
15 New York	259,995	258,449	99.41%						
16 North Carolina	121,347	114,389	94.27%						
17 North Dakota	8,847	9,815	* 110.94%					2,647	29.92%
18 Oregon	46,790	46,879	* 100.19%	43,423	92.80%			864	1.85%
19 Pennsylvania	146,857	145,874	99.33%						
20 Rhode Island	13,180	13,150	99.77%					427	3.24%
21 Vermont	6,277	6,040	96.22%					326	5.19%
22 Virginia	96,755	99,410	* 102.74%					12,648	13.07%
23 Wyoming	5,847	1,530	26.17%						
24 Virgin Islands	1,851	1,851	100.00%					8	0.43%
TOTAL	a 1,465,499	1,510,008	b	130,243	b	79,730	b	58,646	b

* Percentage > 100% denotes inability of program to separate newborns screened from specimens received; **a** = totals should be viewed as a rough estimate due to inability of many states, to know actual number of newborns screened. Many programs count samples received but cannot eliminate duplication when multiple samples are received; **b** = cannot calculate due to inaccurate data.