

Appendix Table 9. Therapeutic Phlebotomy Studies for Key Question 2*

Study, Year (Reference)	Setting and Study Design	Population	Inclusion Criteria	Control Group	Follow-up	Treatment	Measure and Results	Adverse Events	Quality																																						
Adams et al., 1991 (25)	Specialty clinic Canada Retrospective case series	n = 85 Probands: 48 Discovered family members: 37 Men: 53 Arthritis: 40 Diabetes: 18	Diagnosed between 1958 and 1989 Diagnosis was based on clinical history, physical examination, SF levels, and TS and was confirmed through liver biopsy Patients with iron-loading anemias, transfusional iron overload, and dietary iron overload were excluded	Survival was compared against provincial life-table data matched for age and sex	Mean: 8.1 (SD, 6.8) y Analysis was censored at 20 y because only 5 patients were followed for >20 y	500 mL blood/wk until SF level < 30 µg/L or patient became anemic Mean number of treatments: 43 (SD, 51) Treatment resumed if SF levels became elevated	Deaths: 17 Cumulative survival: 5 y: 87% 10 y: 81% 20 y: 71% Expected survival: significantly decreased survival at all times except 1 y and >14 y No significant difference between noncirrhotic patients and hypothetical cohort of age- and sex-matched patients Adjusted RR for death: Cirrhosis: 5.54 Arthritis: 0.24	NR	Fair																																						
Bomford and Williams, 1976 (59)	Specialty clinic United Kingdom Case series	n = 111 Patients diagnosed through routine clinical practice who received treatment Treated: 85 Untreated controls: 26	Excluded persons with secondary iron overload. Diagnosis made "by clinical, biochemical and where possible histological criteria"	26 untreated historical controls who were not comparable to treated patients	1937 to approximately 1975	600 mL was removed weekly until hemoglobin ≤ 10 g/dL and serum iron level decreased to <10 µmol/L Biopsy usually repeated after completion of treatment. Treatment resumed if chelatable body iron levels increased to >1000 µg/kg body weight 79 of 85 completed full course	Diabetes: 56 Improved: 16 of 56 Worsened: 7 of 56 New cases: 3 Liver histology: 75 Improved: 5 of 75 No definite change: 68 of 75 Worsened: 2 of 75	NR	Fair																																						
Niederer et al., 1996 (60)	Diagnosed patients from primary care clinics Germany Retrospective case series	n = 251 Mean age: 45.7 (SD, 10.8) y Men: 224 Noncirrhotic: 109 Asymptomatic: 41 Family screening: 15 Cirrhotic: 142 Asymptomatic: 7 Diabetic: 120 2 lost to follow-up	Diagnosed between 1947 and 1991 Patients were diagnosed on basis of clinical features and biochemical test results: liver function, serum iron, TS, and SF. Confirmed by liver biopsy	Expected deaths were calculated for a German normal population that was age- and sex-matched for time period of observation	Mean: 14.1 (SD, 6.8) y	From 1979 on, patients were treated 1–2 times/wk by TP (500 mL) until SF levels were normal 185 patients with documented iron depletion received mean of 84.8 (SD, 4.4) treatments to achieve depletion All patients underwent 4–12 TPs per y after depletion	Cumulative survival: 5 y: 93% 10 y: 77% 20 y: 55% 30 y: 20% Significantly reduced compared with expected survival in matched population Liver iron concentration at diagnosis per fibrosis stage: <table border="1"> <thead> <tr> <th>Stage</th> <th>Pts, n</th> <th>Liver Iron (SD), µmol/g</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>7</td> <td>11.6 (1.8)</td> </tr> <tr> <td>1</td> <td>10</td> <td>13.9 (1.1)</td> </tr> <tr> <td>2</td> <td>9</td> <td>16.9 (1.4)</td> </tr> <tr> <td>3</td> <td>15</td> <td>22.4 (2.0)</td> </tr> <tr> <td>All</td> <td>41</td> <td>16.1 (1.6)</td> </tr> </tbody> </table> Changes in fibrosis stage after iron depletion: <table border="1"> <thead> <tr> <th>Stage</th> <th>I, n</th> <th>W, n</th> <th>U, n</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>0</td> <td>1</td> <td>20</td> </tr> <tr> <td>1</td> <td>10</td> <td>1</td> <td>21</td> </tr> <tr> <td>2</td> <td>20</td> <td>0</td> <td>19</td> </tr> <tr> <td>3</td> <td>12</td> <td>0</td> <td>81</td> </tr> </tbody> </table> Sign/Symptom AD, % I, % U, % W, % Weakness/lethargy 80 55 40 6 Abdominal pain 56 68 29 1 Arthralgia 45 30 50 20 Elevated AST or ALT level 81 73 25 2 Pigmentation 68 68 32 0 Loss of potency (163 men) 40 19 69 12 Electrocardiographic changes 35 34 61 5 Diabetes mellitus 44 41 53 6 Impaired glucose tolerance 15 37 56 7	Stage	Pts, n	Liver Iron (SD), µmol/g	0	7	11.6 (1.8)	1	10	13.9 (1.1)	2	9	16.9 (1.4)	3	15	22.4 (2.0)	All	41	16.1 (1.6)	Stage	I, n	W, n	U, n	0	0	1	20	1	10	1	21	2	20	0	19	3	12	0	81	NR	Fair-poor
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McDonnell et al., 1999 (55)	Population-based mailings to all known patients with HC and organizations with access to patients with HC in United States, Canada, Australia, and northern Europe. Patients from ≥17 countries, including United States (84%), Australia (6%), United Kingdom (6%), and Canada (4%). Retrospective cross-sectional study.	n = 2851 patients (80% of all surveys mailed). White: 99%. Men: 62%. Diagnosis made 1990 or later: 70%. Diagnosis made before 1980: 6%.	Led to diagnosis: 35% from symptoms related to hereditary HC, 45% from routine or ancillary laboratory test, 20% from diagnosis of family member. 56% diagnosed by primary care physician. 67% initially diagnosed with alternate condition to explain symptoms. Mean age at symptom onset: 41 (SD, 14) y. Mean age when sought treatment: 43 (SD, 14) y. Mean age at diagnosis: 50 (SD, 13) y.	None	NA	Location at which patient had TP: physician's office/hospital (73%), blood bank (25%), home (0.1%).	Some or all symptoms improved with therapy: 86%. Mean time for improvement: 39 (SD, 67) wk. New symptoms developed despite treatment: 33%. <table border="1"> <thead> <tr> <th>Sign/Symptom</th> <th>RS, n (%)</th> <th>I, n %†</th> <th>W, n %‡</th> </tr> </thead> <tbody> <tr> <td>Fatigue</td> <td>1296 (45.5)</td> <td>705 (54.4)</td> <td>223 (17.2)</td> </tr> <tr> <td>Joint pain</td> <td>1241 (43.5)</td> <td>115 (9.2)</td> <td>422 (34.0)</td> </tr> <tr> <td>Impotence/loss of libido</td> <td>735 (25.8)</td> <td>93 (12.7)</td> <td>204 (27.8)</td> </tr> <tr> <td>Skin bronzing</td> <td>733 (25.7)</td> <td>431 (58.8)</td> <td>30 (4.1)</td> </tr> <tr> <td>Heart fluttering</td> <td>679 (23.8)</td> <td>42 (6.2)</td> <td>69 (10.1)</td> </tr> <tr> <td>Depression</td> <td>592 (20.8)</td> <td>242 (40.8)</td> <td>61 (10.3)</td> </tr> <tr> <td>Abdominal pain</td> <td>578 (20.3)</td> <td>129 (22.3)</td> <td>69 (11.9)</td> </tr> </tbody> </table> <p>Compared with NHANES II and III, similar proportion of patients reported arthritis, liver or gallbladder disease, and extreme fatigue as general population.</p>	Sign/Symptom	RS, n (%)	I, n %†	W, n %‡	Fatigue	1296 (45.5)	705 (54.4)	223 (17.2)	Joint pain	1241 (43.5)	115 (9.2)	422 (34.0)	Impotence/loss of libido	735 (25.8)	93 (12.7)	204 (27.8)	Skin bronzing	733 (25.7)	431 (58.8)	30 (4.1)	Heart fluttering	679 (23.8)	42 (6.2)	69 (10.1)	Depression	592 (20.8)	242 (40.8)	61 (10.3)	Abdominal pain	578 (20.3)	129 (22.3)	69 (11.9)	65% of patients with symptoms said the benefit of treatment outweighed difficulties. 20% found the process routine and expressed indifference. 12% expressed a negative attitude toward TP that they attributed to poor venous access, time involved, dissatisfaction that the removed blood was discarded.	Fair
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Powell et al., 2006 (58)	First-degree relatives of C282Y homozygotes with clinical HC or screened population with elevated serum iron measures. Australia. Prospective cross-sectional study.	n = 672. 401 from family screening; 271 from primary care screening. Underwent biopsy after TP: 25. Patients were those with "uncertainty about cirrhosis or persistently abnormal liver enzyme levels". White: predominantly. Men: 53%.	Homozygotes identified from family or primary care screening. Those with high alcohol intake were not analyzed for changes in cirrhosis/fibrosis (n = 5).	None	Up to 24 years	TP until TS < 0.15 or SF level ≤ 20 µg/L.	NR because of high alcohol intake: 5 of 25 (20%). Improved fibrosis score: 19 of 20 (95%). No change in cirrhosis: 1 of 20 (5%).	NR	Fair																																

* AD = at diagnosis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HC = hemochromatosis; I = improved; NA = not available; NHANES = National Health and Nutrition Examination Survey; NR = not reported; Pt = patient; RR = relative risk; RS = reported symptom; SF = serum ferritin; TP = therapeutic phlebotomy; TS = transferrin saturation; U = unchanged; W = worse.

† Improved with therapy.

‡ Worsened despite therapy.