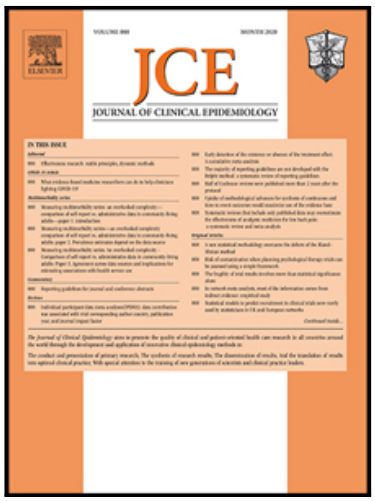

The possible effects of iron loss from bloodletting on mortality from pneumonia in the nineteenth century

Bernard Brabin

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Highlights

- The benefits of bloodletting for pneumonia in the nineteenth century were hotly debated.
- Pneumonia case fatality, recovery times and iron losses are here calculated from available historical data.
- Early bloodletting and higher iron losses were associated with shorter recovery times, despite higher average case fatality with bloodletting.

The possible effects of iron loss from bloodletting on mortality from pneumonia in the nineteenth century.

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Abstract

Objective. To estimate iron losses and disease severity following 19th century bloodletting in patients with pneumonia.

Study design and setting. Benefits of bloodletting in pneumonia patients were contested during the 19th century. Although large blood volumes during infection were removed there was no systematic data collection assessing efficacy and knowledge of iron composition of blood was rudimentary. This observational analysis of historical data quantifies iron losses in pneumonia cases in relation to disease severity.

Results. Based on one detailed case series average blood volume removed for survivors was 830 ml (range 114 - 2272 ml), and mean recovery times were shorter in patients bled within 2 days of illness ($p<0.001$). Average iron removed was 446 mg with phlebotomy done ≤ 2 days of illness presentation and 347 mg after >2 days of illness ($p=0.012$). Across several European hospitals average case fatality in pneumonia patients receiving phlebotomy was higher than in those treated without phlebotomy (19.9% vs 12.8%, OR 1.55, 95% CI 1.38-1.74, $P<0.001$).

Conclusion. Variable efficacy for bloodletting could at least in part be explained by altered iron status.

Key words: Bloodletting, iron, pneumonia, inflammation, efficacy, mortality.

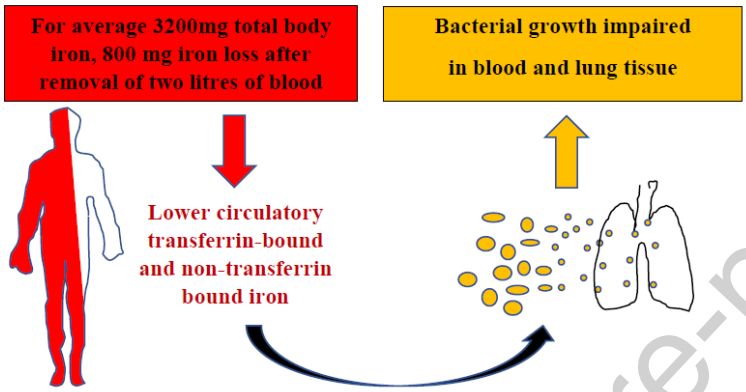
Word count: 2918

Running title: Iron losses from bloodletting and pneumonia

What is New

- The benefits of bloodletting for pneumonia in the nineteenth century were hotly debated.
- Pneumonia case fatality, recovery times and iron losses are here calculated from available historical data.
- Early bloodletting and higher iron losses were associated with shorter recovery times, despite higher average case fatality with bloodletting.

Graphical abstract



1. Introduction

For many centuries bloodletting, or the taking of blood from a patient with therapeutic intent, was practised to treat illnesses associated with inflammation and fever.[1] Following the 16th century it was widely used in Western Europe, as it followed Galenic principles by removing excess heat from febrile patients and possibly putrid matter.[2] The Flemish physician Jan Baptist van Helmont (1578-1644), was an iatrochemist who opposed bloodletting in the 17th century. He

developed an alternative system of medicine which considered serum as a product of the formation of blood, with disease resulting from an influence on a vital principle in the body to which bloodletting would be detrimental.[3, 4] He proposed a randomised trial to establish if case fatality was reduced from bloodletting by treating fever, with or without bloodletting as the standard therapy.[5] No records are available to confirm whether this experiment was ever undertaken, but its theoretical undertones questioned whether phlebotomy impaired vital principles in blood which would otherwise be beneficial to recovery. This early example indicated a more scientific approach to understanding how blood constituents reacted during infection. The practice of bloodletting remained the key principle in anti-phlogistic therapy for treating fever and inflammation (phlogistos = inflammation) up to the early 19th century.

Although physicians attested their belief in its value, especially for chest infections, it still lacked an evidence base as efficacy was not addressed until the twentieth century. By 1860 knowledge related to blood constituents was increasing and provided insights into the cellular response to infection. Virchow had applied Schwann's concept of the cell to pathology, but only rudimentary laboratory methods for investigation were available, which resulted in a more speculative pathology of mechanism.[6, 7] Large blood volumes blood between one to three litres were often removed within hours of presentation for many complaints which included inflammation and fever. Underlying concerns on use of bloodletting were stronger for their rhetoric rather than statistics and have been characterised as a clash between established and emerging medical practice.[8] A theoretical understanding was developing of the potential dangers associated with loss of blood nutrients, in particular iron, about which little was known at the time. The action of iron biomarkers in blood and their influence on infection severity was potentially enormous. It can be estimated that iron losses with two litres venesection would remove almost 900 mg of body iron, a quarter of the total iron content of an average male person.[9] Repeated bloodletting in pneumonia patients pneumonia would induce hypoferraemia, leading to immune function abnormalities and an anti-inflammatory effect by limiting bacterial access in the blood to extracellular iron.[10, 11]

In this paper 19th century historical data on pneumonia case fatality is analysed to estimate bloodletting efficacy in relation to mortality outcomes and iron deficits and potential implications for patient outcomes.

2. Search strategy

Physical searches for 19th century historical information used library resources, inter-library loan facilities and the Archive collection at the University of Liverpool. For recent publications electronic databases were examined for historical and scientific content, including PubMed, Scopus and ISI Web of knowledge, using the search terms: bloodletting, venesection, pneumonia, infection and mortality. Reference lists from general medical and historical journals were searched. A summary of the debate between the merits of clinical decisions versus the scientific approach to the use of bloodletting in pneumonia current in mid-19th century is outlined in supplementary File 1. [12, 13] The best pneumonia outcome data came from Pierre-Charles-Alexandre-Louis. In general outcomes were more often reported for acute pneumonia than other conditions.

3. Pierre-Charles-Alexandre-Louis and management of pneumonitis by bloodletting

Questions about bloodletting in chest infections initially arose in 1828 when Pierre-Charles-Alexandre-Louis (1787-1872) published his original findings on the efficacy of bloodletting in patients with pneumonitis (pneumonia) treated at the Hôpital de la Charité in Paris. His observations were unique as he selected patients who were previously in good health and who had a uniform definition of acute pneumonia which reduced misclassification.[14] His findings were re-published in 1835, with further observations from cases under his care admitted to the Hôpital de la Pitié in Paris.[15] Surviving patients were grouped by the number of times phlebotomy was used, illness duration and time of first bleeding and, for La Charité information was provided for patients who died. Figure 1 shows the distribution of blood volumes venesected for 101 pneumonia patients listed in his report, both survivors and deaths. Their estimated iron losses in milligrams are

derived based on the volumes reported by Louis for an average single bleeding of between 10 and 15 ounces, or 12.5 ounces per bleed (355 mls).[16] Mean phlebotomy volume was around 800 ml. For comparison blood volumes phlebotomy during the last fatal illnesses of President George Washington (1732-1799), (2365 mls) and Wolfgang Amadeus Mozart (1756-1791), (1800 mls) are also shown on Figure 1.

The information available from his published report is summarised in Table 1. Also shown are comparative pneumonia cases treated by phlebotomy in Boston at the Massachusetts General Hospital by James Jackson (1777-1867). These cases were reported alongside the original Louis series in the English translation published in the United States.[15] The average blood volume removed for survivors was 830 mls (range 114 to 2485 mls) and the average iron removed (mg) was between 347 mg and 446 mg using the same method as above.[16] Mean phlebotomy volume for patients who died at La Charité Hôpital was greater (1024 mls) than that for survivors, which equates to higher loss of body iron. Statistical comparison of these patient classes is suggestive (see footnote p values Table 1) but limited due to possible confounding. Sample sizes were small, younger patients were likely to recover more quickly and survivors were younger than case fatalities. Also varying proportions of patients were bled within two or four days of their presentation.

Re-calculation from the original data of mean recovery times (in days) comparing patients bled within two days of illness presentation with those bled after two days consistently shows in survivors shorter illness duration with earlier bleeding (Table 1). In cases from La Charité hospital venesection in the first few days was associated with higher mortality, and re-analysis of this data by Morabia showed the odds of death were more than halved compared to those bled late. [17] Early copious bleeding with its associated higher mortality risk might result from more severe disease in some of these cases. Nevertheless, Louis concluded that, while pneumonitis was not arrested by bloodletting, those bled during the first four days recovered (other things being equal) four or five days sooner than those bled at a later period. His general conclusion was that that ‘bloodletting had no appreciable influence on the progress of the disease’, but this was based mainly on his findings in patients with erysipelas and angina tonsillaris. James Jackson attributed the shorter mean duration of illness in his cases at the Massachusetts General Hospital (13 days, Table 1) not to early intervention, but to better general care in a smaller hospital with higher ward temperatures than the colder Parisian

hospitals. That apart, the clinical profiles of Jackson's pneumonia cases showed these were, on average, several years younger than Paris cases, which could favour recovery. Theoretically there is some justification from the data in Table 1 that the earlier average time of bleeding for the American cases shortened their recovery compared to the Parisian series.

The findings presented by Louis invoked strong professional opposition as they undermined current medical practice and de-emphasised the traditional anti-phlogistic treatment which bloodletting was thought to provide by correcting imbalances in body secretions. That organised epidemiological enquiries or experimental science could govern therapeutic practice had fundamental implications for professional identity. A fundamental problem was the absence of an accepted avenue for calling into question the utility of practices such as bloodletting. Lack of knowledge on pathophysiological mechanisms prevented insight into the possible effects of loss of normal blood constituents, including red cell iron, on the inflammatory response to infection. The histological appearances of blood were yet to be described, its corpuscular nature was still ill-defined, and the haematological and haemorheological consequences on blood viscosity were completely unknown.[18] However, Louis' report on pneumonia mortality following bloodletting catalysed an imperative to report pneumonia case fatalities, and within twenty years publications from Austria, Sweden, Germany, England, Scotland, Holland and France addressed this question.

4. Pneumonia case fatality in European hospital patients treated with and without bloodletting

During the first two decades after the publication of Louis' findings further clinical studies became available on case fatality in patients with pneumonia following bloodletting. Most had small sample sizes with imprecise clinical details. Overall case fatality and percentage bled were reported, but without case fatality data for patients who did or did not receive phlebotomy and no analyses of efficacy based on cases and controls. During the nineteenth century, lack of reliable statistical methods precluded measurement of efficacy which, in this context, is the percentage reduction in case fatality in pneumonia in cases treated with phlebotomy compared to cases not receiving venesection. An accepted formula for efficacy estimation had not yet been proposed. Greater scientific rigour in data collection

was also required. Blood volumes collected were often unmeasured or unrecorded. The vigour with which phlebotomy was practised differed, being judged by the character of the pulse, degree of flushing of the patient, viscosity and appearance of the blood, and onset fainting. Without this rigour, the interpretation of pneumonia case fatality reports was often confounded due to differences in case definition, possible misclassification and varied use of drug treatments. Nevertheless, the evidence base was increasing and for European hospital cases is summarised in Table 2.

This compares case fatality of patients with predominantly acute pneumonia, in the period between 1820 and 1859, who were treated with or without phlebotomy and for whom treatment group was clearly stated. The table includes the patient deaths reported by Louis, but not those listed by James Jackson at the Massachusetts General Hospital, as details were not provided for the four deaths he reported.[8] Other studies during this period were derived from published lectures or identified in French and German textbooks. The 1866 publication by John Hughes Bennett on the restorative treatment of pneumonia included his cases from patient reports from the Edinburgh Royal Infirmary between 1839 and 1863.[19] Fourteen studies were identified in which all pneumonia cases were treated by phlebotomy, and eleven in which pneumonia patients only received alternative treatments. These variously included antimonials, tartar emetics, narcotics, digitalis, citrates, alcoholic drinks, calomel and saline purges, or nutritive broths, some of which may have been tried in phlebotomy cases. None of these investigations used a case control design, as patients who did not receive phlebotomy were mostly studied at a later date after reductions in phlebotomy as standard therapy. Age and sex were inconsistently recorded and while some children or adolescents may have been included, patients with chronic symptoms seem to have been excluded as, probably, were pregnant women.

Average case fatality was seven percent higher in patients receiving phlebotomy (risk ratio 1.55, 95% CI 1.38-1.74, P<0.001), which is a percentage reduction in case fatality of 35% by avoiding phlebotomy (95% CI 28% - 43%). In his 1866 report, John Hughes Bennett compared case fatality expressed as percentages for several of the investigators referenced in Table 2 with his own data from the Edinburgh Royal Infirmary collected between 1839 and 1865.[19] He did not summate

findings across studies and used death:survivor ratios to conclude that extreme treatment with phlebotomy was attended with a mortality of about one in three cases, although with less extreme application this fell to between one in five to one in thirteen. He attributed variations to weakness induced in the patient by phlebotomy and associated treatments and noted improved outcomes in children and adolescents.

Amongst the alternative interventions he used were restorative nutritional treatments which resulted in a mortality ratio of approximately one in 33 cases, and even these deaths were reported to be due to complications unconnected with the pneumonia. By improving patient diets Bennett attributed recovery to restoring the 'nutritive power of the system'. Although he recommended and prescribed 'beef tea' for some pneumonia patients, he neither mentioned iron losses incurred by phlebotomy, nor improved iron intakes with recovery, in support of this remedy. His appreciation of the importance of nutritional therapy was considerable and although the amount of iron in blood had yet to be determined he concluded in 1842 that 'blood circulating to every part of the living organism carried with it the principles of nutrition'.[20] This theme he developed into a nutritional theory explaining the process of inflammation which he later used as the main scientific rationale for abandoning phlebotomy in the treatment of infection.[21] The specific role of iron would not be evident without a clearer understanding of blood composition, but by the mid-1850's, comparative case fatality statistics indicated that removing large volumes of the patient's blood during pneumonia infection was often, although not always, detrimental. In the context of bloodletting the argument centred round the nature of inflammation.

Although it was recognised by almost all that inflammation involved buffed blood (the top layer of white blood cells on standing) and excess fibrin, no further investigations ensued. These changes in febrile cases led Emile Bertin (born 1832) to conclude, in a dictionary of science published in 1878, that bloodletting was still relevant as it helped to deplete these factors.[22] The value of iron compounds in reviving blood was recognised, but only after 1860 was the role of iron in blood becoming understood. Prior to then it was linked to apathy, melancholia, anorexia and poor appetite, all of which were often associated with anaemia.

5. Haematological and cardio-pulmonary effects of bloodletting

Anaemia was a confusing issue because the difference between nutritional anaemias such as iron deficiency, and inflammatory anaemia which occurred with infection, was unknown. The clinical and functional significance of fewer red cells was unclear without information on the constitution of blood in patients and how these characteristics related to disease severity. A more comprehensive clinical picture of anaemia, iron deficiency and the potential effects of blood loss did not emerge until the early 20th century. Bloodletting was often used for treatment of fever in plethoric patients, while in those with pallor, although improved nutrition was recognised, venesection was still used to remove morbid factors. As a result, the possible effects of bloodletting on body iron were unappreciated and potentially beneficial cardio-pulmonary effects with acute venous congestion could not be distinguished.

The result was a confusing picture. Paradoxically, by the late 19th century, prescribing of iron supplements in patients with a variety of acute and chronic infections was frequent.[23] Figure 2 shows an example promoting use of Iron Bitters, a popular therapy in America and recommended as a cure for intermittent fevers, malaria, dyspepsia and weakness. In contrast, although use of bloodletting declined, as late as 1892, the first edition of Sir William Osler's (1849-1919) textbook on the Practice of Medicine recommended moderate venesection (~500 ml) in pneumonia. [24] Osler's recommendation continued through several editions of his textbook until 1947 (16th edition) based on venesection to reduce venous pressure in congestive heart failure complicating pneumonia. By the mid-20th century Paul Wood (1907-1962), the greatest British cardiologist of his time, commented that although venesection had fallen out of favour, it should not be abandoned offering a quick and sure way of lowering venous pressure. [25]

6. Conclusions

William Markham commented in his Gulstonian lecture of 1864, that '--- never, perhaps, has more blood flowed from the veins and arteries of mankind, under the authority of medicine, than during the first quarter of the present century'.[26] The mid-century decline in its use was fostered by evidence that overall case fatality

tended to be higher with venesection, despite Louis' findings that bloodletting for pneumonia within 2-4 days of presentation lead to shorter recovery times. The possibility that blood constituents directly influenced the inflammatory response was only raised by Bennett, who recognised that lower blood volumes altered blood constituents. While he did not mention blood iron or body iron losses, he recognised the potential role of 'molecules', as well as nutrition, in affecting the inflammatory response to infection. A remarkable foresight in this pre-Pasteurian period.

Opinions on the efficacy of bloodletting in the treatment of pneumonia in the mid-19th century led to conflicts which were poised between the clinical experience of early 19th century physicians and scientific insights arising later in the century. Blurring of case definitions, combined with variable use of small, moderate or large volume venesection at differing times following presentation, altered risk-benefit ratios. Early bloodletting of moderate volume in patients without cardiac complications could have a beneficial effect related to bacterial iron restriction, whereas large volume losses over a longer period could be detrimental due to dehydration, poor oxygen saturation, anaemia and lower blood volumes. Experience dictated the importance of bleeding during the early stages of disease before overt signs of inflammation were apparent, although the rationale for this remained unclear. Use of comparative observational case fatality statistics with such mixed groups of patients inevitably led to unreliable conclusions, although in retrospect the data in Table 2 arguably suggests overall case fatality from bloodletting in pneumonia was detrimental. The paradox is, that while rapid removal of iron by moderate bloodletting during acute infection may in certain circumstances be beneficial, to this day no randomised controlled trial has ever assessed this in patients with pneumonia.

Competing interests

The author declares that he has no competing interests

Author contributions

I conceived, undertook the research, and wrote the manuscript

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Figure Legends

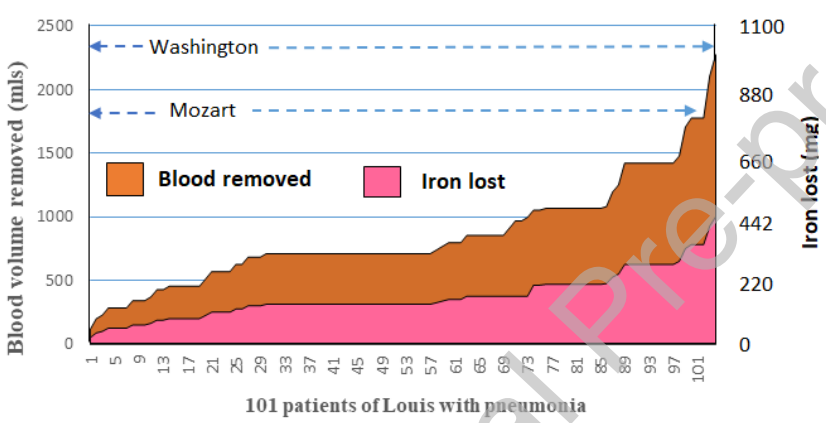

Figure 1 Phlebotomy volumes and estimated iron losses in Louis' patients with pneumonia

Sources: Louis PCA, reference 8; Haskins et al, reference 9; Morens DM. Death of a President. New England Journal of Medicine 1999;341:1845-1850; Drake ME. Mozart's chronic subdural hematoma. Neurology 1993; 43;2400-2403.

Figure 2 Nineteenth century promotion of iron supplementation for infective illness

The text at the side of the desk reads: Brown's iron bitters has cured the whole family of malaria and as a personal tonic we believe it has no equal.

Baltimore: Brown Chemical Co. trade card [ca.1880], New York: Burrow Giles Lith; image is in the public domain.

Table 1 Summary characteristics of pneumonitis patients and their phlebotomy volumes with resultant iron losses at La Charité and La Pitié Hospitals, Paris and Massachusetts General Hospital, Boston and published in the years 1835 and 1836

Variable	Survivors				Deaths [a]
	Charité	Pitié	MGH	All	Charité
Patient profile					
Number	49	25	29	103	27
Mean age, years	35.3	40.8	25.6	33.9	48.8
Mean day of first bleeding after onset of illness	5.2	5.0	4.2	4.8	4.1
Mean number of bleedings	2.4	1.8	2.0	2.1	2.8
Bled within 2 days of disease onset, %	10.2	12.0	44.8	20.4	22.2
Bled within 4 days of disease onset, %	44.9	52.0	75.9	55.3	66.6
Mean illness duration, days (SD)	19.3 (7.4)	17.1 (6.2)	13.0 (3.9)	17.1 (6.9)	19.3 (14.3)
Mean duration if bled within 2 days of disease onset, days SD (n)	11.6 (5)	14.0 (3)	11.6 (13)	11.9 ± 2.7 (21) [b]	18 ±16.0 (6)
Mean duration if bled after 2 days of disease onset, days SD (n)	20.2 (44)	17.5 (22)	14.2 (16)	18.3 ± 7.1 (82)	19.7 ± 14.1(21)
Mean phlebotomy volume, ml (SD) [c]	859 (325)	749 (266)	851 (539)	830 (390)	1024 (524)
range, ml	114 - 1775	114 - 1420	227 - 2272	114 - 2272	355 - 2485
Estimated mean iron removed (mg) by phlebotomy [d]					
Phlebotomy done ≤ 2 days after onset of illness, ± SD (n)	343(5)	342 (3)	510 (13)	446 ± 263 (21) [e]	599 ± 318 (6) [f]
Phlebotomy done after 2 days of disease onset, (n)	382 (43)	328 (22)	277 (16)	347 ± 144 (81)	394 ± 174 (21)

SD: standard deviation; Charité: Hôpital de la Charité, Paris; Pitié: Hôpital de la Pitié, Paris; MGH: Massachusetts General Hospital, Boston. Red highlighting indicates estimated iron losses in mgs.

[a] In addition four deaths at La Pitié: mean age 61 years and mean disease duration of 13 days; 3 bled after 4 days. Also four deaths at MGH with no further details available. Phlebotomy volumes not reported for these deaths.

[b] For survivors mean difference in duration by T test between ≤2 days and > 2 days for all hospitals: one-tailed with unequal variance, P < 0.001; one tailed with equal variance P <0.001.

[c] Converted from ounces reported in original publication. For La Charité and La Pitié hospitals between 10 – 15 ounces taken at each bleeding and a mean of 12.5 ounces (355 ml) used for phlebotomy volume estimates for these hospitals. For La Charité one phlebotomy volume not reported.

[d] Assumed haematocrits (packed red cell volume) were 40% at baseline. All estimates expressed in terms of mg, iron, using a value of 1.1 mg iron/1.0 ml packed red cells. (Haskins et al).

[e] For survivors mean difference in iron losses by T test between ≤2 days and > 2 days for all hospitals: one-tailed with unequal variance, P = 0.058; one tailed with equal variance P = 0.012.

[f] For deaths mean difference in iron losses by T test between ≤2 days and > 2 days for La Charité Hospital: one-tailed with unequal variance, P = 0.120; one tailed with equal variance P = 0.039.

Sources: Pierre-Charles-Alexandre-Louis, *Researches on the Effects of Bloodletting in some Inflammatory Diseases and on the Influence of Tartarised Antimony and Vesication in Pneumonitis. Translated by C.G. Putnam with a Preface and Appendix by James Jackson*, Boston: Hilliard Gray and Company, 1836; D. Haskins, A.R. Stevens Jr, S.C. Finch, C.A. Finch, 'Iron metabolism. Iron stores in man as measured by phlebotomy', J Clin Invest 1972; 31:543-47.

Table 2 Case fatality in hospital patients with pneumonia treated with and without phlebotomy

Investigator	Source [a]	Period enrolled	Location	Pneumonia category	Cases	Deaths	Case fatality %
			Patients with phlebotomy				
Enrico Acerbi (1785-1827)	1	Pre-1820	Milan, Maggiore Hospital	All [b]	142	16	11.1
René Laennec (1781-1826)	2	Pre-1826	Paris	All	-	-	12.0 -16.0
William Pulteney Alison (1790-1859)	3	Post-1822	Edinburgh Royal Infirmary	All	8	2	25.0
Jean-Baptiste Bouillard (1796 -1881)	4	1831-1834	Paris, Hôpital de la Charité	All	102	12	11.8
Gabriel Andral (1797-1876)	5	Pre- 1834	Paris, Hôpital de la Charité	Uncomplicated Complicated	29 36	14 22	48.3 61.1
Pierre-Charles-Louis (1787-1872)	6	1828-1835	Paris, Hôpital de la Charité Paris, Hôpital de la Pitié	All All	76 29	27 4	35.5 13.8
James Jackson (1777-1867)	7	1825-1834	Massachusetts General Hospital	All	33	4	12.1
John Hughes Bennett (1812-1875)	8	1812-1837	Edinburgh Royal Infirmary	All	50	19	38.0
Pierre Briquet (1796 -1881)	9	1836-1839	Paris, Hôpital Cochin	All	140	29	20.7
Józef Dietl (1804-1878)	10	Pre-1840 [c]	Vienna, Wieden Hospital	Mostly large bleedings. 7 uncomplicated cases	85	17	22.0

John Hughes Bennett	11	1839-1849	Edinburgh Royal Infirmary	All	648	222	34.3
Magnus von Huss (1807-1890)	12	1840-1847	Stockholm, Seraphim-Lazarethe Hospital	Also with local bleedings. Two-thirds uncomplicated	1040	120	11.5
Robert Bentley Todd (1809 -1860)	13	1840-1847	London, King's College Hospital	-	25	4	16.0
Hermann Lebert (1813-1878)	14	1853-1859	Zurich Hospital	4 cases complicated	205	15	7.3
All investigators					2648	527	19.9
			Patients without phlebotomy				
John Rasori (1767-1823)	15	Pre-1823	Milan, Santa Corona Hospital	-	648	143	22.1
M. Grisolle (1811-1869)	16	Pre- 1841[c]	Paris, L'Hôtel-Dieu	Uncomplicated 1st stage [d] Uncomplicated 2nd stage	50 182	5 32	10.0 17.6
Józef Dietl	17	Pre-1840 [c]	Vienna, Wieden Hospital	Deaths all complicated	295	36	12.2
John Hughes Bennett	18	1849-1863	Edinburgh Royal Infirmary	All	115	3	2.6
Karl Kissel	19	1852 [e]	Germany, location not specified	Iron acetate orally if alkaline urine	112	5	4.5
Magnus von Huss	20	1848-1855	Stockholm, Seraphim Lazarethe Hospital	Two thirds uncomplicated cases	1576	161	10.2
Karl Heinrich.Thielmann (1802-1872)	21	Pre-1852 [c]	St Petersburg, Peter and Paul's Hospital,	57 1st stage (no deaths) 32 2nd stage (3 deaths) 24 3rd stage (8 deaths)	113	11	9.7
F.J.J.Schmidt	22	1851-1854	Rotterdam Krankenhuis	-	37	4	10.8
Heinrich von Bamburger (1822-1888)	23	1857 [c]	Wurzburg, Julius Hospital	Few leeches applied in minority	186	21	11.3
Professor Dr Rigler	24	1856-1858	Gratz, General Hospital	Venesection in only 4 cases; leeches in several	119	20	16.8
Robert Bentley Todd	25	1847-1859	London, King's College Hospital	-	53	6	11.3
All investigators					3486	447	12.8

[a] Details of References for sources listed in supplementary file 1.

[b] All indicates both uncomplicated and complicated cases

[c] Uncertain period of enrolment, probably before 1840

[d] Stages following presentation: first is initial 24 hours; second is 2nd - 3rd days; third is 4th - 6th days

[e] Date of publication, not date of patient recruitment.