

## Supplementary Table 1 In-verbatim entry keyed into ChatGPT's interface

---

### In-verbatim entry keyed into ChatGPT's interface

---

#### Symptoms

- Severe abdominal pain
- Paralysis/ inability to move
- Inability to speak
- Chills
- Restlessness
- Progressive fluctuating high fever
- Progressive neurological degradation, delirium
- Excessive thirst

#### Plausible causes of Alexander the Great's death

##### 1. Poisoning

The circumstances surrounding Alexander the Great's potential poisoning evoke intriguing theories. The following are theories that explains why poisoning may be Alexander's cause of death.

##### a. Strychnine poisoning:

---

---

Graham Phillip's theory suggests that Alexander's wife, Roxanne, may have used strychnine, extracted from a plant found in the Indus Valley, to poison him. This theory is based on the belief that Roxanne, who was from Bactria in present-day Afghanistan, could have had knowledge of and access to the poison. Strychnine's bitter taste can be concealed with wine. The typical signs and symptoms of strychnine poisoning include violent seizures, muscle stiffness, rapid heart rate, fast breathing or absence of breathing, and eventually death. However, it's worth noting that Alexander's records don't mention convulsions and muscle rigidity, which are common effects of strychnine. Additionally, a gradual increase in fever and delirium are not typical of strychnine poisoning.

## 2. Styx river poisoning:

Theories from Greek and Roman writers propose the intentional poisoning of Alexander by Antipater, a Macedonia statesman and lieutenant. Antipater's motive to assassinate Alexander, stemmed from a deep-seated animosity attributed to Alexander's replacement of Antipater's managerial position in Europe, where he looked after Alexander's interest. This enmity led Antipater to plot an assassination, purportedly dispatching his son to retrieve water potentially tainted with calicheamicin bacteria from the mythical river Styx. This poison is said to be corrosive and have the strength to destroy bronze, glass and clay. The symptoms resulting from consuming this poison include severe pain, weakness, fatigue, swelling of mouth and throat, some of which are consistent with Alexander's symptoms in his final days. This poison is so lethal that it can result in massive organ failure and death. Some of the symptoms experienced by Alexander such as inability to speak coincides with the ancient Greek myths about water from the Styx.

## 3. White hellebore poisoning

---

---

Leo Schep, a toxicologist suggests that Alexander the Great may have consumed white hellebore, a harmless looking plant, during a banquet where he consumed an excessive amount of alcohol. This is made more possible since *Veratrum album* can be fermented as wine. The alkaloids present in various *Veratrum* species could induce symptoms akin to Alexander's 12-day illness, differing from the swift-acting strychnine. Instead, the slower-acting white hellebore, historically utilized for inducing vomiting, better corresponds with Alexander's reported symptoms: severe stomach distress, fever, nausea, and vomiting. Hellebore is also notorious for causing violent gastrointestinal symptoms and even death in weak patients. Leo Schep also states that fermented white hellebore is intensely bitter, possibly unnoticed due to Alexander's purported inebriation, offering a plausible explanation for his unwitting consumption.<sup>17</sup> These symptomatic parallels reinforce the plausibility of poisoning as a cause for Alexander's demise.

## 2. Acute pancreatitis from excessive alcohol consumption

The Court tradition suggests that Alexander's death was a result of acute pancreatitis, a condition inflaming the pancreas, induced by alcohol abuse. Historical records documents Alexander's excessive alcohol indulgence, reaching pathological intoxication during significant events, such as during his 33rd birthday, leading to erratic behavior, as evidenced by an instance where he fatally harmed a close friend during a drunken revelry. The last years of his life saw intensified symptoms of alcoholism, including extreme behavior, megalomania, and paranoia. In a feverish state, Alexander insisted on consuming a substantial amount of wine, potentially an acute case of alcohol withdrawal, exacerbating his condition, implicating alcohol as the prime contributor to Alexander's fatal illness. This theory is further supported by scholars who suggest that acute pancreatitis, possibly induced by excessive drinking, could lead to intra-abdominal sepsis and a fatal fever, taking around 10 days till death. His symptoms also include severe abdominal pain and high fever that escalated over approximately 11 days, which are consistent with signs of acute

---

---

pancreatitis. The flaws with this hypothesis is that Alexander's abdominal pain was transient and not constant and his fluctuating fever is not a characteristic of septic necrotizing pancreatitis.

### 3. Typhoid fever

Typhoid fever is a plausible cause for Alexander the Great's demise. This bacterial infection, caused by *Salmonella typhi*, induces symptoms such as progressively high fever, loss of appetite, weakness, headache, and constipation, aligning with Alexander's final days. In the second week, patients typically experience increasing fever and hot, dry skin. By the third week, fever escalation and serious complications, like enteric perforation, may arise, with a case-fatality rate of 10-30% without effective treatment, which is possible in Alexander's case given the lack of antibiotics in 323 B.C.. Key symptoms indicating enteric perforation is severe abdominal pain and high fever. Additionally, rarer symptoms like lack of muscle control and slurred speech are consistent with Alexander's paralysis and inability to speak, further support the typhoid diagnosis.

Another significant observation supporting typhoid fever as Alexander's cause of death, is the delay in typical signs of bodily decay post-mortem. In 2018, Dr Katherine Hall, a lecturer at Dunedin School of Medicine in New Zealand proposed that Alexander the Great had Guillain-Barré syndrome, an acute autoimmune condition that results in muscle paralysis. This syndrome, a rare neurological complication of typhoid fever can manifest with various clinical presentations: rapid onset of progressive, ascending paralysis, loss of deep tendon reflexes and paraesthesia. In severe cases, it can lead to a complete 'locked-in' syndrome, where the patient is conscious but unable to move or communicate due to paralysis. It is possible that Alexander developed Guillain-Barre syndrome as a complication of typhoid fever leading to paralysis and loss of reflexes, which may have been misinterpreted as his death, raising doubts about the accuracy of his death pronouncement.

---

---

#### 4. Malaria

Malaria is considered the most likely cause of Alexander's death due to several pieces of evidence. Firstly, Alexander had a history of contracting malaria, as he had collapsed from the disease in Cilicia in 333 BC. Additionally, malaria was endemic in Macedonia, where Alexander grew up. The symptoms of malaria, such as fever, chills, and fatigue align with the descriptions of Alexander's final illness. Furthermore, the absence of putrefaction in his body after his death, which is medically impossible, could be explained by the possibility that he had cerebral malaria, caused by infection with the protozoan parasite *Plasmodium falciparum*. Cerebral malaria presents clinically with decreased consciousness, seizures and coma. Hence, Alexander could be in a “deep” coma rather than actually deceased, explaining the delays of typical signs of decay postmortem. Overall, the prevalence of malaria in the region and the alignment of symptoms make it a plausible explanation for Alexander's death.

#### 5. West Nile Virus encephalitis

The theory proposing Alexander the Great's potential death from West Nile virus (WNV) stems from intriguing observations upon his arrival into Babylon. Notably, a peculiar event occurred involving a flock of ravens exhibiting abnormal behavior and dying in his presence, resembling avian illness seen before the first human cases of WNV in the United States. Coinciding with Alexander's illness during a period recognised for heightened WNV activity, this theory suggests that he might have succumbed to WNV encephalitis. The hypothesis draws parallels from studies from the 1999 WNV epizootic and epidemic in the U.S., highlighting symptoms observed in infected birds: abnormal head and neck posture, ataxia, tremors, circling, disorientation, and impaired vision. Drawing parallels, the authors speculate that the ravens' unusual behavior and subsequent death could indicate WNV infection in Babylon during Alexander's era. This conjecture postulates a scenario where WNV could have caused a significant

---

avian die-off in Babylon, possibly leading to sporadic human cases with fever and signs of encephalitis. These observations raise the possibility of WNV infection in Babylon during Alexander's time, hinting at a potential link between these events and his illness and death.

However, scientifically, the existence of WNV in its current form during 323 BC is improbable, ruling it out as the cause of Alexander's death. The WNV typically induces muscle failure and mental disturbances, symptoms absent in Alexander's case. His mental decline occurred around nine to ten days into the illness, inconsistent with the typical pattern of WNV.

Using the information above, which of the following causes of death most likely contributed to Alexander the Great's demise. Explain why with supporting evidence. Explain why the other causes are not plausible.

**Supplementary Table 2 Reviewer's comments and points system**

Nu mb er	Source citation	Autho r(s)	Sour ce type	Rater 1					To tal (R ate r 1)	Rater 2					To tal (R ate r 2)	Tota l (Ave rage )	Remar ks
				ChatG PT's summa ry of source	Clini cal Plaus ibilit y	Sour ce Relia bilit y	Cult ural - cont ext Fit	Rele vanc e		Clini cal Plaus ibilit y	Sour ce Relia bilit y	Cult ural - cont ext Fit	Rele vanc e				

1	Alexander the Great and the Guillain-Barré Syndrome Hypothesis. Ancient History Bulletin. 2018;32:1-10.	Hall K	Jour	Alexander the Great and the Guillain-Barré Syndrome Hypothesis	3	3	2	3	11	3	3	2	3	11	11	This source actually argues that C.jejuni is the cause of the GBS rather than Typhoid - while ChatGPT uses it
---	---	--------	------	--	---	---	---	---	----	---	---	---	---	----	----	---

---

to  
argue  
for  
typhoi  
d. It is  
a  
source  
that  
was  
taken  
out of  
contex  
t to  
suppo  
rt the  
argum  
ent  
that  
typhoi  
d

---



																	cause d GBS, when the paper argue d the oppos ite
2	Typhoid fever. Nat Rev Dis Primers. 2015;1:150 16.	Wain J, Hendr iksen RS, Mikole it ML, Keddy KH, Ochiai RL.	Jour nal	Clinical progres sion and sympto ms of typhoi d fever	2	3	1	3	9	2	3	1	2	8	8.5	Nil menti on of Typho id causin g GBS. It is also wrong ly	

																	cited as the paper was in the journa l Lancet not Natur e
3	Infectious causes of Guillain- Barré syndrome. Curr Opin Neurol. 2016;29(5): 419-425.	Willke A, Ergon ul O	Jour nal	Suppor ted the possibil ity of Guillai n-Barré syndro me as a compli	1	3	1	3	8	1	3	1	2	7	7.5	Nil menti on of typhoi d and wrong ly cited	

				cation of infectio ns like typhoi d.												
4	Alexander the Great: Murder in Babylon. London: Virgin Books; 2004.	Phillip s G	Book	Introdu ced strychn ine poisoni ng theory involvi ng Roxann e.	0	0	3	2	5	0	0	2	2	4	4.5	
5	Historical principles and	Wax PM	Jour nal	Genera l toxicol	0	0	0	0	0	0	0	0	0	0	0	Unabl e to locate



	902):697-700.	eamici n		Styx river poisoni ng theory.												
7	Was the death of Alexander the Great due to poisoning? Clin Toxicol (Phila). 2014;52(1):72-77.	Schep LJ, Slaugher RJ, Vale JA	Jour nal	Evaluat es the white hellebo re poisoni ng theory.	2	3	3	3	11	1	2	2	2	7	<b>9</b>	
8	Alexander of Macedon, 356-323	Green P.	Book	Provid ed backgr ound	0	2	3	0	5	0	2	2	0	4	<b>4.5</b>	

	B.C.: A Historical Biography . Berkeley: University of California Press; 1991.			and narrati ve of Alexan der's final days.												
9	Managem ent of acute pancreatiti s. N Engl J Med. 2016; 375(20):19 72–1981.	Forstm ark CE, Yadav D.	Jour nal	Suppor ted acute pancre atitis hypoth esis from excessi ve	2	3	2	3	10	2	3	2	2	9	9.5	



11	Pathogenesis, clinical features, and neurologic al outcome of cerebral malaria. Lancet Neurol. 2005;4 (12):827–840.	Idro R, Jenkins NE, Newton CR	Journal	Provided evidence supporting cerebral malaria as a cause of neurological symptoms.	2	3	1	3	4	0	1	1	1	3	3.5
12	Conquest and Empire: The Reign	Bosworth AB	Book	Historical reference for	0	2	2	2	6	0	2	2	2	6	6



	of Alexander the Great. Cambridg e: Cambridg e University Press; 1993.			Alexan der's campai gns and death context.												
13	Alexander the Great and West Nile Virus Encephalit is. Emerg Infect Dis. 2003;9(12): 1599-1603.	Marr JS, Calish er CH.	Jour nal	Propos ed West Nile virus enceph alitis theory.	1	2	1	2	6	0	2	1	1	4	5	

14	West Nile virus: primer for the clinician. Ann Intern Med. 2002;137(3):173-179.	Peters LR, Marfin AA.	Journal	Clinical backgr ound on WNV sympto ms	0	3	0	2	5	0	3	1	2	6	5.5
15	Life of Alexander. In: Parallel Lives. Translated by Perrin B. Cambridge (MA): Harvard University	Plutar ch.	Book (tran y slate d pri al sour ce)	Primar y historic al source detailin g events of Alexan	0	2	3	3	8	0	3	3	2	8	8

	Press;			der's												
	1919.			death.												
16	The Campaigns of Alexander (Anabasis Alexandri) . Translated by Hammond M. London: Penguin Classics; 1971.	Arrian	Book (translated by source d pri sour ce)	Primar y source docum enting Alexan der's militar y and health history.	0	2	3	3	8	0	3	2	2	7	7.5	
17	Ancient Medicine. 2nd ed.	Nutton V.	Book	Context for medica	0	0	3	3	6	0	1	3	2	6	6	

	London: Routledge; 2012.			l practic es and underst anding s in antiqui ty.												
18	Greek Fire, Poison Arrows, and Scorpion Bombs: Biological and Chemical Warfare in the Ancient	Mayor A.	Book	Insight into ancient bioche mical warfare and poison use.	0	2	2	0	4	0	2	2	1	5	4.5	

	World.															
	New York:															
	Overlook															
	Press;															
	2003.															
19	Alexander the Great: The Hunt for a New Past. London: Pan Macmillan ; 2004.	Cartle dge P	Book	Reinter prets Alexan der's life and legacy, includi ng his final illness.	1	2	3	1	7	1	2	2	1	6	6.5	
20	Alexander the Great: Man and God. Harlow:	Worthi ngton I.	Book	Provid es historic al analysi	0	2	2	0	4	0	1	2	0	3	3.5	



	Press; 1994.			historic al narrati ves.												
22	Who's Who in the Age of Alexander the Great: Prosopogr aphy of Alexander 's Empire. Oxford: Blackwell Publishing ; 2006.	Heckel W.	Book	Provid es biograp hical insights into Antipat er and others possibl y involve d in poisoni ng.	0	0	3	1	4	0	0	2	1	3	3.5	

23	Guillain-Barré Syndrome. Nat Rev Neurol. 2020;16(1):10-20.	Engel N	Journal	Contemporary clinical reference for GBS symptoms and progression.	0	0	0	0	0	0	0	0	0	0	0	Unable to locate source article. Citation likely to be erroneous
24	The Death of Alexander the Great: Rumour and Propaganda. Greece & Rome.	Parry RH	Journal	Explores the use of rumor and misinformation	2	1	2	1	6	1	1	2	1	5	5.5	



1963;10(1):	nding
14–22.	Alexan
	der's
	death.

*ChatGPT's in-verbatim output using Supplementary Table 1 prompt (3/6/25)*

Based on the evidence and symptoms outlined, **typhoid fever complicated by Guillain-Barré syndrome (GBS)** is the **most plausible explanation** for Alexander the Great's death. This theory not only aligns well with the **progression and combination of symptoms** he experienced but also explains the **unusual phenomenon of delayed bodily decay**, which has long puzzled historians and medical researchers.

☒ **Most Plausible Cause: Typhoid Fever with Guillain-Barré Syndrome**

**Supporting Evidence:**

- **Symptom match:** The progression of Alexander's illness — high fever, severe abdominal pain, chills, restlessness, and delirium — fits well with the known course of **typhoid fever**, particularly in its second and third weeks. Enteric perforation can cause severe abdominal pain and high fever.

- **Neurological degradation:** The eventual **paralysis, inability to speak, and restlessness** can be explained by **Guillain-Barré Syndrome (GBS)**, a rare but well-documented post-infectious complication of typhoid fever. GBS can cause ascending paralysis and “locked-in syndrome,” mimicking death.
- **Delayed decomposition:** GBS-induced paralysis could have led observers to mistakenly assume Alexander was dead. Ancient embalmers may not have detected vital signs, leading to reports that his body didn’t decay for days — now explainable by **being alive but paralyzed.**
- **Historical plausibility:** Typhoid fever was prevalent in the ancient world, especially in unsanitary urban centers like Babylon. Without antibiotics, the disease would have been highly lethal.

---

## ✕ Less Plausible Causes and Why They’re Unlikely

---

### *1. Poisoning Theories*

#### **a. Strychnine Poisoning**

- **Mismatch of symptoms:** Strychnine causes **violent convulsions, muscle rigidity, and quick death**, none of which were reported in Alexander's illness.
- **Slow progression:** Alexander's illness developed over several days, which does not align with the **rapid onset** of strychnine toxicity.

#### b. Styx River Poison (Calicheamicin-like theory)

- **Mythical basis:** This theory hinges on the **mythological River Styx**, with no credible evidence that water laced with such a bacteria or toxin was used.
- **Unverifiable agent:** No historical or biochemical support for such a toxin existing or being administered at the time.

#### c. White Hellebore Poisoning

- **Better symptom alignment** than strychnine, including vomiting, abdominal pain, and possible delirium.
- However, white hellebore typically leads to **rapid death** if a lethal dose is consumed, and its **gastrointestinal focus** does not explain the **neurological degradation** or delayed decomposition. Additionally, **paralysis and inability to speak** are not core

features of hellebore poisoning.

---

## *2. Acute Pancreatitis from Alcohol Abuse*

- **Some symptom overlap:** Severe abdominal pain, high fever, and alcohol abuse fit.
  - **Inconsistencies:** Abdominal pain in pancreatitis is usually **constant and severe**, whereas Alexander's was **transient**. Also, fluctuating fevers and progressive neurological symptoms are **not typical** of pancreatitis.
  - **Death from pancreatitis usually involves shock or sepsis**, not paralysis and locked-in syndrome.
- 

## *3. Malaria (especially Cerebral Malaria)*

- **Historical exposure** is plausible — malaria was endemic and Alexander had a past episode.

- **Symptom mismatch:** Cerebral malaria can cause fever and coma, but it usually presents **suddenly**, not over **11–12 days**. It also does **not** typically cause **ascending paralysis** or **inability to speak**.
  - **Delayed decay explanation** is speculative and better explained by GBS from typhoid.
- 

#### *4. West Nile Virus Encephalitis*

- **Coincidental bird behavior:** While the raven story is curious, it is not concrete evidence.
  - **Scientific implausibility:** WNV was **not documented in ancient Mesopotamia**, and its **neurological symptoms** typically appear much earlier in the illness.
  - Alexander's **late-onset mental degradation** is **not typical** of WNV.
- 

#### ☒ Conclusion

**Typhoid fever complicated by Guillain-Barré Syndrome** offers the best alignment with:

- The **timeline** of illness (progressive over ~12 days),
- The **constellation of symptoms** (abdominal pain, fever, delirium, paralysis, inability to speak),
- The **medical mystery** of delayed decomposition,
- And the **historical context** of disease prevalence and lack of modern treatment.

All other theories — though intriguing — fail to explain all of Alexander’s symptoms comprehensively or rely too heavily on speculation or myth.

Certainly! Below is a list of **scholarly sources, historians, and medical experts** whose work or hypotheses are referenced or aligned with the conclusions in your analysis of Alexander the Great’s death. Where possible, I’ve cited names, works, and affiliations. These are organized by the theory they support:

---

☒ **Typhoid Fever + Guillain-Barré Syndrome**

**Primary Researcher:**

- **Dr. Katherine Hall**, Dunedin School of Medicine, University of Otago (New Zealand)
  - **Paper:** Hall, K. (2018). *Alexander the Great and the Guillain-Barré Syndrome Hypothesis*.
  - Published in *The Ancient History Bulletin*.
  - Hypothesized that Alexander suffered from GBS as a complication of typhoid fever, explaining his paralysis and delayed decomposition.

#### Supporting Medical Literature:

- Wain, J., Hendriksen, R. S., Mikoleit, M. L., Keddy, K. H., & Ochiai, R. L. (2015). *Typhoid fever*. Nature Reviews Disease Primers, 1, 15016.
- Willke, A., & Ergonul, O. (2016). *Infectious causes of Guillain-Barré syndrome*. Current Opinion in Neurology, 29(5), 419–425.

---

#### ✕ Poisoning Theories

### a. Strychnine Poisoning

#### Proponent:

- **Graham Phillips**, British author and journalist
  - Book: *Alexander the Great: Murder in Babylon* (2004)
  - Proposed that Roxanne poisoned Alexander using strychnine derived from Indian plants.

#### Toxicology Reference:

- Wax, P. M. (1999). *Historical principles and perspectives in toxicology*. Toxicologic Pathology, 27(2), 129-138.

---

### b. Styx River / Calicheamicin-like Toxin

#### Source:

- Classical references from **Plutarch** and **Diodorus Siculus**, who noted rumors of poisoning and mention of Antipater's motives.



- The modern calicheamicin comparison is speculative and is not linked to specific historical texts but draws analogy from:
    - Zein, N., Sinha, A. M., McGahren, W. J., & Ellestad, G. A. (1989). *Calicheamicin  $\gamma$ 11: An antitumor antibiotic that cleaves double-stranded DNA*. *Science*, 244(4902), 697–700.
- 

### c. White Hellebore Poisoning

#### Proponent:

- **Dr. Leo Schep**, toxicologist at the National Poisons Centre, University of Otago
  - Featured in several interviews and publications (2014)
  - Suggested **Veratrum album** (white hellebore) as a plausible poisoning agent.

#### Published in:

- Schep, L. J., Slaughter, R. J., & Vale, J. A. (2014). *Was the death of Alexander the Great due to poisoning?* Clinical Toxicology, 52(1), 72–77.

---

## ✗ Acute Pancreatitis

### Historians Referenced:

- Peter Green, *Alexander of Macedon, 356–323 B.C.: A Historical Biography* (1991)
  - Chronicles Alexander's excessive alcohol use and erratic behavior.

### Medical Sources:

- Forsmark, C. E., & Yadav, D. (2016). *Management of acute pancreatitis*. The New England Journal of Medicine, 375(20), 1972–1981.

---

## ✗ Malaria (esp. Cerebral Malaria)

### Medical Literature:

- World Health Organization. (2023). *Malaria Fact Sheet*.
- Idro, R., Jenkins, N. E., & Newton, C. R. (2005). *Pathogenesis, clinical features, and neurological outcome of cerebral malaria*. *The Lancet Neurology*, 4(12), 827–840.

### Historical Context:

- Bosworth, A. B. (1993). *Conquest and Empire: The Reign of Alexander the Great*
  - Mentions Alexander's illness in Cilicia, possibly malaria-related.

---

### ✕ West Nile Virus (WNV) Encephalitis

#### Proponent of theory:

- Marr, J. S., & Calisher, C. H. (2003). *Alexander the Great and West Nile Virus Encephalitis*. *Emerging Infectious Diseases*, 9(12), 1599-1603.
  - Hypothesized a link based on bird die-off observed upon Alexander's arrival in Babylon.

### Epidemiological Reference:

- Petersen, L. R., & Marfin, A. A. (2002). *West Nile virus: A primer for the clinician*. *Annals of Internal Medicine*, 137(3), 173-179.

---

### ! Note on Delayed Decomposition

The idea that Alexander's body did not decay for several days is recorded in ancient sources such as:

- Plutarch, *Life* of Alexander
- Arrian, *Anabasis* of Alexander
- These accounts may be mythologized but formed the basis for modern medical reinterpretations.

---