



Fatal waterhouse–friderichsen syndrome at autopsy: a systematic review and forensic diagnostic framework

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Abstract

Waterhouse–Friderichsen syndrome (WFS) represents a fulminant septic condition characterized by bilateral adrenal hemorrhage and rapid clinical deterioration. Although classically associated with meningococcal infection, fatal cases occur across multiple infectious etiologies and heterogeneous clinical contexts. In forensic practice, diagnosis frequently relies on post-mortem interpretation rather than clinical recognition, making consistent pathological assessment essential. A systematic review was conducted according to PRISMA guidelines to identify autopsy-confirmed fatal cases consistent with WFS. PubMed/MEDLINE and Scopus were searched from database inception to 21 February 2026, with a supplementary search conducted in Google Scholar. Eligible studies included fatal human cases with bilateral adrenal hemorrhage documented at autopsy and sufficient pathological and/or microbiological data. Data were extracted on clinical course, gross and histopathological findings, microbiological investigations, pathogens, and predisposing factors. Owing to marked heterogeneity of case-level reporting, qualitative synthesis and semi-quantitative descriptive analysis were performed. Sixty-five studies, encompassing 86 individual fatal cases, met the inclusion criteria. Bilateral adrenal hemorrhage consistently occurred within a broader systemic septic pattern characterized by multiorgan congestion, hemorrhagic manifestations, and variable disseminated intravascular coagulation-related changes. Histopathological and microbiological findings were heterogeneous, with frequent discrepancies between culture-based and molecular results and recurrent diagnostic limitations related to post-mortem microbiology. The synthesis of evidence supports interpreting WFS as a recurrent forensic-pathological pattern rather than a single morphological diagnosis. Based on key findings identified across cases, practical forensic frameworks were developed to support autopsy interpretation, microbiological sampling, and differential diagnosis. Integration of morphology, histopathology, microbiology, and circumstantial data may improve consistency and reproducibility in the medico-legal evaluation of sudden septic deaths.

Keywords Waterhouse–Friderichsen syndrome · Bilateral adrenal hemorrhage · Forensic pathology · Autopsy · Fulminant sepsis · Disseminated intravascular coagulation · Post-mortem microbiology

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Introduction

Waterhouse–Friderichsen syndrome (WFS) is a rare but frequently fatal clinicopathological condition characterized by acute bilateral adrenal hemorrhage occurring in the setting of overwhelming infection and septic shock. Traditionally associated with meningococcal disease, WFS is currently regarded as a pathological response to severe systemic infection, resulting from the interaction between sepsis, coagulopathy, and circulatory collapse rather than being linked to a single specific pathogen [1]. The syndrome represents a dramatic endpoint of fulminant infection, in which rapid progression and nonspecific early manifestations may hinder timely clinical recognition and contribute to high mortality [2].

From a forensic and pathological perspective, WFS represents a complex interpretative scenario. Fatal cases have been described in association with a broad range of infectious agents and clinical contexts, extending beyond classical meningococcal septicemia. At autopsy, bilateral adrenal hemorrhage is considered a key finding; however, it is not pathognomonic and must be interpreted within the broader pattern of forensic-pathological findings, including systemic hemorrhagic manifestations, disseminated intravascular coagulation (DIC), and multiorgan involvement [3]. In addition, risk factors such as functional or anatomical hyposplenism and other conditions predisposing to overwhelming infection may further complicate clinical and forensic interpretation [4].

A further challenge concerns the interpretation of microbiological findings in the post-mortem setting. Negative cultures, prior antimicrobial therapy, post-mortem bacterial translocation, and contamination may complicate the diagnosis of fatal sepsis, requiring integration of microbiological results with autopsy, histopathological, and circumstantial evidence [5–7].

Despite the recognized medico-legal relevance of WFS, the available evidence remains fragmented and largely limited to isolated case reports and small case series, with heterogeneous reporting of autopsy findings, histopathology, and microbiological investigations. Consequently, a systematic synthesis focused on autopsy-confirmed fatal cases is needed to identify recurring forensic-pathological patterns and to support a more consistent interpretative approach in routine medico-legal practice.

Previous reviews have primarily focused on the clinical presentation, pathophysiology, and management of WFS or on broader aspects of post-mortem sepsis investigation. In contrast, the present review specifically examines autopsy-confirmed fatal cases from a forensic-pathological perspective, aiming not only to summarize the available evidence but also to identify recurrent post-mortem patterns and translate them into practical interpretative tools for medico-legal practice.

Materials and methods

Study design

This study was designed as a systematic review of the literature aimed at identifying and synthesizing autopsy-confirmed fatal cases of WFS. The primary objective was to identify recurrent post-mortem patterns and ancillary findings, including histopathological and microbiological data, supporting an interpretation consistent with WFS, and to translate these findings into an evidence-informed forensic diagnostic framework applicable to medico-legal practice. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The review protocol was prospectively registered on the Open Science Framework (OSF) prior to data extraction. Materials related to the review are available in view-only format on the OSF repository (https://osf.io/9uaeq/?view_only=3b6e536e63b546999e235cf504f36f74).

Search strategy

A systematic literature search was conducted in PubMed/MEDLINE and Scopus from database inception to 21 February 2026. Search strategies were developed using combinations of keywords and free-text terms related to Waterhouse–Friderichsen syndrome, bilateral adrenal hemorrhage, purpura fulminans, sepsis or infection, and autopsy, post-mortem examination, or forensic pathology. Boolean operators (AND/OR) were applied and the search syntax was adapted to the requirements of each database. The complete database-specific search strategies are reported in Supplementary Table S1. In addition, Google Scholar was searched to identify additional case reports and historical publications not captured through database searching, particularly older or non-indexed forensic reports. No language restrictions were applied during study selection. Articles published in languages other than English were assessed for eligibility using available abstracts, bibliographic information, and translation tools when necessary.

Eligibility criteria

Studies were considered eligible when they described human subjects and reported fatal cases of WFS supported by autopsy findings. For the purposes of this review, WFS was operationally defined as fatal sepsis associated with bilateral adrenal hemorrhage documented at autopsy, in the absence of a more plausible non-infectious explanation for the adrenal lesions. Classical meningococcal WFS, fatal sepsis with bilateral adrenal hemorrhage caused by other

pathogens, and cases explicitly described by the original authors as consistent with WFS were all considered eligible, provided that autopsy findings supported the diagnosis.

Inclusion required documentation of bilateral adrenal hemorrhage, identified either macroscopically or histologically, together with sufficient pathological and/or microbiological information to support an interpretation consistent with WFS in the setting of overwhelming infection or sepsis, including features such as DIC, purpura fulminans, microthrombosis, or pathogen identification. Studies were excluded when they reported non-fatal cases, survivals, or lacked autopsy confirmation. Reviews, editorials, letters without original case-level data, and conference abstracts without full case documentation were also excluded. Cases describing unilateral adrenal hemorrhage without evidence supporting WFS, reports lacking sufficient forensic-pathological or microbiological information, and cases in which an alternative non-infectious cause of bilateral adrenal hemorrhage was clearly established were not included.

Study selection

All records retrieved through database searches were imported into a reference manager (Zotero), and duplicate entries were removed. Titles and abstracts were independently screened by two reviewers to identify potentially eligible reports, in accordance with PRISMA recommendations. Discrepancies were resolved through discussion and consensus.

Data extraction

Data were extracted using a predefined standardized form. For each eligible case, bibliographic information, including first author, year of publication, and country, was recorded together with demographic data such as age and sex. Clinical and circumstantial information was collected whenever available, including prodromal symptoms, suspected infection focus, timing of symptom onset to death, and whether death occurred in-hospital or out-of-hospital. Cutaneous findings such as purpura fulminans, petechiae, and ecchymoses were documented, as well as gross autopsy findings including bilateral adrenal hemorrhage, adrenal enlargement or necrosis, hemorrhages in other organs, serous effusions, and organ congestion or edema. Histopathological findings were recorded with particular attention to hemorrhagic necrosis of the adrenal cortex and medulla, fibrin microthrombi, small-vessel thrombosis, DIC-related changes, and skin lesion pathology when available. Microbiological investigations, including culture, PCR or other nucleic acid amplification techniques, immunohistochemistry, sampling

sites, and timing relative to death, were collected together with the identified pathogens. Findings were interpreted within a clinicopathological context rather than as stand-alone diagnostic evidence. Predisposing conditions such as asplenia, immunosuppression, pregnancy or postpartum status, adrenal disease, anticoagulant therapy, or recent infections were also recorded.

Data synthesis

Given the rarity of fatal WFS and the marked heterogeneity of case-level reporting, statistical pooling and meta-analysis were not considered appropriate. Data were therefore synthesized qualitatively, with emphasis on identifying recurring forensic-pathological patterns observed at autopsy, evaluating the relationship between adrenal findings and systemic manifestations of sepsis and DIC, and assessing the contribution and limitations of post-mortem microbiology and ancillary testing. These elements were integrated to support consistent interpretation of forensic-pathological findings consistent in suspected WFS.

Quality assessment and limitations of evidence

Because the available literature primarily consisted of single case reports and small case series, formal risk-of-bias tools developed for analytical studies were considered inappropriate. Therefore, a structured qualitative appraisal, informed by the CARE reporting guidelines for case reports, was performed.

Each included report was assessed across five domains considered relevant to forensic interpretation: (1) completeness of clinical and circumstantial information; (2) clarity and completeness of autopsy findings, including documentation of bilateral adrenal hemorrhage; (3) availability and adequacy of histopathological examination; (4) microbiological investigations and reporting of diagnostic methods; and (5) etiological attribution and consideration of major alternative causes of adrenal hemorrhage.

To improve transparency, reporting completeness was additionally categorized according to these predefined domains. Reports documenting all five domains were considered high-completeness reports, whereas reports with incomplete documentation in one or more domains were considered moderate-completeness reports. No included reports were classified as low-completeness because studies lacking essential forensic-pathological information were excluded during the eligibility assessment process.

Reporting completeness was used to contextualize the strength of case-level evidence and to guide interpretation during qualitative synthesis. Findings derived from reports with incomplete pathological, histopathological,

or microbiological documentation were interpreted with greater caution.

Overall, the available evidence is limited by retrospective publication, heterogeneity of post-mortem protocols, variability in reporting standards, and potential publication bias. Consequently, the proposed forensic diagnostic framework should be interpreted as an evidence-informed diagnostic support tool rather than as formal diagnostic criteria.

Development of the interpretative frameworks

The proposed diagnostic algorithm, autopsy sampling strategy, and differential diagnostic framework were developed through qualitative synthesis of recurrent forensic-pathological, microbiological, and clinical patterns identified across the included cases. Framework construction was informed by systematic review of the extracted data and complemented by the authors' forensic pathology expertise to translate recurring observations into practical medico-legal tools.

These frameworks were not generated through formal consensus methodology, external validation, or quantitative modeling. Accordingly, they should be interpreted as evidence-informed interpretative tools intended to support forensic decision-making in suspected cases of WFS, rather than as validated diagnostic criteria.

Results

Study selection

The systematic search identified a total of 225 records, including 209 records retrieved from database searching (139 from Scopus and 70 from PubMed/MEDLINE) and 16 additional records identified through Google Scholar. Among the 209 records retrieved through database searching, 82 duplicates were removed, leaving 127 records for title and abstract screening. Following this phase, 20 records were excluded because they were not relevant to fatal WFS or did not meet the predefined eligibility criteria.

A total of 107 reports identified through database searches were sought for full-text retrieval. Of these, 73 reports were successfully retrieved and assessed for eligibility, whereas 34 could not be accessed despite multiple retrieval attempts. For records not readily available, additional efforts included institutional library resources, inter-library loan services, DOI-based searches, Google Scholar, ResearchGate, and alternative bibliographic sources. Many of the non-retrieved reports were historical publications dating from the 1970s–1980s or articles published in languages other than English with limited electronic availability.

In parallel, 16 reports identified through Google Scholar were assessed at full text. Full-text evaluation resulted in the exclusion of studies lacking autopsy confirmation, reporting non-fatal cases, representing reviews without original case-level data, or providing insufficient forensic-pathological information to substantiate an interpretation consistent with fatal WFS.

Overall, 65 studies, encompassing 86 individual fatal cases, met the inclusion criteria and were included in the qualitative synthesis. Of these, 56 studies were identified through PubMed/MEDLINE and Scopus, whereas 9 additional studies were retrieved through Google Scholar [3, 4, 8–70]. The study selection process is summarized in the PRISMA 2020 flow diagram (Fig. 1). Although formal meta-analysis was not feasible because of the marked heterogeneity of the available evidence, a semi-quantitative synthesis of the included cases was performed. An overview of the included studies is reported in Table 1, whereas individual case-level data are reported in Supplementary Table S2 and aggregated semi-quantitative findings are summarized in Table 2. Regarding reporting completeness, 58 of the 65 included studies (89.2%) were classified as high-completeness reports, whereas 7 studies (10.8%) were classified as moderate-completeness reports. No included study was classified as low-completeness.

General characteristics of included cases

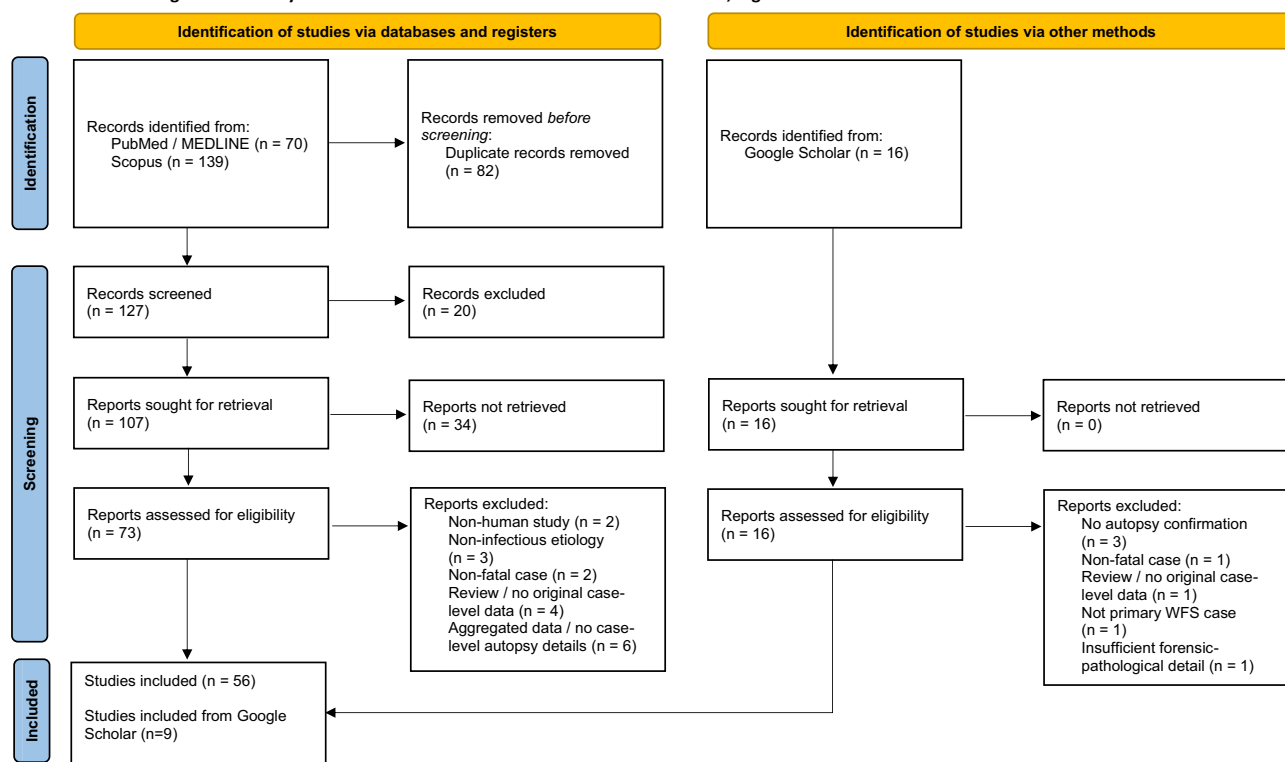
The included studies comprised fatal cases reported across a wide temporal range, reflecting both historical and contemporary forensic literature. Among the 86 cases, adults accounted for 62.8% and pediatric patients for 33.7%; age was not reported in 3.5% of cases. Among cases with available age data ($n = 83$), the mean age was 31.7 ± 25.4 years. Most reports consisted of single case descriptions, while a minority presented small case series.

Geographically, cases originated from multiple countries across Europe, North America, Asia, and other regions, reflecting the global occurrence of WFS in medico-legal practice. The majority of reports described hyperacute clinical courses characterized by rapid deterioration and death within hours to a few days from symptom onset, frequently before definitive clinical diagnosis could be established.

Pathogens and microbiological findings

A wide spectrum of pathogens was identified across included cases. The most frequently identified pathogens were *Neisseria meningitidis* and *Streptococcus pneumoniae* (23/86 cases each, 26.7%), followed by *Capnocytophaga canimorsus* (8/86, 9.3%). However, several cases involved

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

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Fig. 1 PRISMA 2020 flow diagram

other pathogens, including group A streptococci, *Haemophilus influenzae*, and other bacterial species, highlighting the etiological heterogeneity of fatal cases.

Microbiological investigations showed substantial variability in methods and reporting. Microbiological confirmation frequently relied on multimodal approaches, with combined microbiological investigations reported in 43/86 cases (50.0%). Several reports described negative cultures despite pathological findings strongly suggestive of fulminant sepsis, emphasizing the importance of integrated clinical-pathological interpretation.

Gross autopsy findings

Bilateral adrenal hemorrhage was consistently documented in all included cases, representing the defining pathological feature supporting interpretation consistent with WFS. The extent of adrenal involvement ranged from focal cortical hemorrhage to massive bilateral hemorrhagic necrosis with near-complete destruction of adrenal architecture.

In addition to adrenal findings, recurrent gross features included multiorgan congestion, pulmonary edema, serosal petechiae, and diffuse visceral hemorrhages. Hemorrhagic cutaneous manifestations were reported in 67/86

cases (77.9%), most commonly purpura or purpuric lesions (43/86, 50.0%) and petechiae (30/86, 34.9%).

Histopathological findings

Histopathological examination commonly demonstrated hemorrhagic necrosis of the adrenal cortex and medulla, often associated with fibrin microthrombi and small-vessel thrombosis consistent with DIC, which was documented in 36/86 cases (41.9%). Multiorgan microvascular thrombosis and hemorrhagic diathesis were recurrent findings across multiple reports, supporting a systemic septic-coagulopathic process.

Additional histological findings variably included leukocytoclastic vasculitis, septic emboli, hemophagocytosis, and inflammatory infiltrates depending on pathogen and clinical context. Overall, histopathology reinforced the concept of WFS as a systemic pathological process rather than an isolated adrenal lesion.

Predisposing factors

Predisposing conditions were variably reported across the included cases. Splenic dysfunction, either anatomical or

Table 1 Overview of included autopsy-confirmed fatal WFS cases

Author, Year (Ref.)	Country	Age/Sex	Pathogen identified	Key autopsy findings	Predisposing factors
Abouzahir et al., 2020 [8]	Morocco	4 F	<i>Neisseria meningitidis</i> (serogroup B)	Massive bilateral adrenal hemorrhage; multiorgan congestion	NR
Angelski et al., 2011 [9]	Canada	8 months F	<i>Streptococcus pneumoniae</i>	Bilateral cortical adrenal hemorrhage; pulmonary edema; serous effusions	Functional hyposplenism (trisomy 21)
Beach et al., 1979 [10]	UK	9 months F	<i>Haemophilus influenzae</i> type b	Bilateral hemorrhagic adrenal infarction; systemic congestion	NR
Beltrán et al., 2014 [11]	Spain	51 F	<i>Neisseria meningitidis</i>	Bilateral adrenal hemorrhage; visceral congestion; shock liver	NR
Berlot et al., 2023 [12]	Italy	53 F	Probable <i>Capnocytophaga canimorsus</i>	Bilateral adrenal hemorrhagic necrosis; multiorgan involvement	Anatomical asplenia (previous splenectomy); other risk factor (dog bite exposure)
Bramley et al., 1989 [13]	UK	56 F	<i>Streptococcus pneumoniae</i>	Bilateral adrenal hemorrhage; ovarian hemorrhage	NR
Cooper et al., 2015 [14]	USA	53 M	<i>Capnocytophaga canimorsus</i>	Bilateral adrenal hemorrhage; widespread organ hemorrhages	Other risk factor (dog bite exposure)
Danciger, 1940 [15]	USA	3 M	<i>Neisseria meningitidis</i>	Massive bilateral adrenal hemorrhage	NR
de Almeida Araújo et al., 2009 [16]	Brazil	15 F	Group A β -hemolytic <i>Streptococcus</i>	Extensive bilateral adrenal hemorrhage; systemic bleeding	Other risk factor (post-partum condition)
Emori et al., 2016 [17]	Japan	50 M	<i>Streptococcus pneumoniae</i>	Bilateral adrenal hemorrhage; hypoplastic spleen	Functional hyposplenism (hypoplastic spleen)
Ferrara et al., 1977 [18]	Italy	44 M	<i>Acinetobacter calcoaceticus</i> (formerly <i>Mima polymorpha</i>)	Massive bilateral adrenal hemorrhage; purulent leptomeningitis; pulmonary edema; diffuse serosal petechiae	NR
Fort et al., 2025 [19]	France	27 M	<i>Capnocytophaga canimorsus</i>	Bilateral adrenal hemorrhage; multiorgan congestion	NR
Gertner et al., 1992 [20]	USA	7 months F	Group A β -hemolytic <i>Streptococcus</i>	Bilateral adrenal hemorrhage; brain edema; skin hemorrhages	NR
Rodriguez Gomez et al., 1998 – Case 1 [21]	Germany	56 F	<i>Streptococcus pneumoniae</i>	Hemorrhagic bilateral adrenal necrosis; pulmonary edema; generalized shock-organ changes	Anatomical asplenia (previous splenectomy – traumatic rupture); other risk factor (chronic hepatitis C); unvaccinated against pneumococcus
Rodriguez Gomez et al., 1998 – Case 2 [21]	Germany	28 M	<i>Streptococcus pneumoniae</i>	Massive bilateral adrenal hemorrhagic necrosis; multiorgan congestion; pulmonary edema	Anatomical asplenia (previous splenectomy – sports trauma); prior hepatitis B infection; unvaccinated against pneumococcus
Grant et al., 1970 [22]	USA	54 F	<i>Streptococcus pneumoniae</i> (type 22)	Bilateral adrenal cortical hemorrhagic necrosis; serosal hemorrhages; small infarcted spleen	Functional hyposplenism (splenic infarction)
Grellner & Madea, 1999 [23]	Germany	26 F	Viridans streptococci (possible post-mortem contaminant)	Bilateral adrenal hemorrhage; purulent meningitis; myocardial involvement	NR
Hale et al., 2016 [24]	USA	36 F	Presumed <i>Streptococcus pneumoniae</i>	Bilateral adrenal hemorrhage	Anatomical asplenia (previous splenectomy – ITP)
Hamilton et al., 2004 – Case 1 [25]	UK	4 M	Group A β -hemolytic <i>Streptococcus</i>	Acute adrenal hemorrhage (right predominance); bronchopneumonia; DIC-compatible pattern	NR
Hamilton et al., 2004 – Case 2 [25]	UK	64 M	<i>Streptococcus pneumoniae</i>	Massive bilateral adrenal hemorrhage; pulmonary congestion; cerebral congestion	Anatomical asplenia (previous splenectomy); immunosuppression (methotrexate therapy for rheumatoid arthritis)

Table 1 (continued)

Author, Year (Ref.)	Country	Age/Sex	Pathogen identified	Key autopsy findings	Predisposing factors
Hamilton et al., 2004 – Case 3 [25]	UK	65 M	<i>Streptococcus pneumoniae</i>	Bilateral adrenal hemorrhage; metastatic gastric carcinoma; septic liver abscess	Immunosuppression (advanced metastatic gastric carcinoma)
Hata et al., 2015 [4]	Japan	56 M	<i>Streptococcus pneumoniae</i>	Massive bilateral adrenal hemorrhage	Possible functional hyposplenism
Holmes et al., 1981 – Case 1 [26]	USA	17 F	<i>Neisseria meningitidis</i> (serogroup W135)	Bilateral adrenal hemorrhage; purulent meningitis; pulmonary hemorrhage	Anatomical asplenia (post-traumatic splenectomy); splenosis
Holmes et al., 1981 – Case 2 [26]	USA	27 F	<i>Neisseria meningitidis</i> (serogroup C)	Bilateral adrenal hemorrhagic necrosis; multiorgan hemorrhages; meningitis	Anatomical asplenia (post-traumatic splenectomy); splenosis
Horita et al., 2022 – Case 1 [27]	Japan	M (50s)	<i>Streptococcus pneumoniae</i>	Severe bilateral adrenal hemorrhage; systemic hemorrhagic shock pattern	Anatomical asplenia (previous splenectomy)
Horita et al., 2022 – Case 2 [27]	Japan	M (40s)	<i>Streptococcus pneumoniae</i>	Bilateral adrenal hemorrhagic necrosis; DIC-related microthrombosis	Functional hyposplenism (hypoplastic spleen)
Horita et al., 2022 – Case 3 [27]	Japan	F (60s)	<i>Streptococcus oralis</i>	Massive bilateral adrenal hemorrhage; diffuse visceral bleeding	Anatomical asplenia (previous splenectomy); immunosuppression (chronic steroid therapy for systemic lupus erythematosus)
Horvatic et al., 2010 [28]	Croatia	2.5 F	<i>Neisseria meningitidis</i>	Massive bilateral adrenal hemorrhage; pulmonary edema; pulmonary hemorrhage; brain edema	Other risk factor (recent varicella infection)
Jochum et al., 2008 [29]	Germany	52 F	<i>Streptococcus pneumoniae</i>	Bilateral adrenal hemorrhage; multiorgan failure; marked hyposplenism	Functional hyposplenism (hypoplastic spleen)
Karakousis et al., 2001 [30]	USA	32 M	Group A β -hemolytic <i>Streptococcus</i>	Bilateral adrenal congestion and hemorrhage	NR
Kitamura et al., 1992 [31]	Japan	52 F	Infection associated with otic meningitis (pathogen not identified)	Massive bilateral adrenal cortical hemorrhagic necrosis; systemic hemorrhagic findings	NR
Levinson, 1939 [32]	USA	11 months M	<i>Neisseria meningitidis</i>	Massive bilateral adrenal hemorrhage; meningitis; diffuse visceral congestion	NR
Mascolo et al., 2021 [33]	Italy	2 M	<i>Neisseria meningitidis</i> (serogroup B)	Bilateral adrenal hemorrhagic necrosis; pulmonary edema; cerebral edema; generalized congestion	NR
Mirza et al., 2000 [34]	USA	47 F	<i>Capnocytophaga canimorsus</i>	Bilateral adrenal hemorrhage; serous effusions; multiorgan hemorrhagic involvement	Other risk factor (dog exposure)
Morrison et al., 1985 [35]	Ireland	5 months F	<i>Haemophilus influenzae</i> type b	Bilateral adrenal hemorrhage; no external skin hemorrhages	Other risk factor (prematurity)
Mularski et al., 2019 [36]	Poland	2 M	<i>Neisseria meningitidis</i>	Bilateral adrenal hemorrhage; multiorgan petechiae; visceral congestion	NR
Neff et al., 1973 [37]	USA	10 months F	Meningococcemia (clinical–pathological diagnosis)	Massive bilateral adrenal hemorrhage; near-complete cortical destruction	Functional hyposplenism (hypoplastic spleen)
Rizzo et al., 2004 [38]	Italy	52 M	Pathogen not identified	Bilateral acute adrenal hemorrhagic necrosis	Anatomical asplenia (previous splenectomy)
Roberts et al., 1974 [39]	Canada	31 M	<i>Streptococcus pneumoniae</i> ; concomitant influenza A viremia	Bilateral adrenal hemorrhage; near-total cortical destruction	Anatomical asplenia (previous splenectomy – hereditary spherocytosis)
Romanova et al., 2023 [40]	Russia	58 M	SARS-CoV-2 infection; secondary bacterial infection	Bilateral adrenal hemorrhage; cortical necrosis	Other risk factor (severe COVID-19–associated coagulopathy)

Table 1 (continued)

Author, Year (Ref.)	Country	Age/Sex	Pathogen identified	Key autopsy findings	Predisposing factors
Santunione et al., 2025 [41]	Italy	62 M	<i>Streptococcus pneumoniae</i> (serotype 23B)	Massive bilateral adrenal hemorrhage; multiorgan congestion; fulminant septic shock pattern	Anatomical asplenia (previous splenectomy – post-traumatic); vaccinated against <i>S. pneumoniae</i> (non-covered serotype)
Satoh et al., 2023 [42]	Japan	16 days F	Group A <i>Streptococcus pyogenes</i>	Diffuse bilateral adrenal cortical hemorrhage; DIC; multiorgan septic emboli	NR
Schuler et al., 2022 [43]	Germany	61 F	<i>Capnocytophaga canimorsus</i> (terminal <i>Candida</i> superinfection)	Bilateral hemorrhagic necrosis of adrenal cortex	Anatomical asplenia (previous splenectomy); other risk factor (dog bite exposure)
Shah et al., 2008 [44]	USA	42 F	<i>Neisseria meningitidis</i>	Bilateral adrenal hemorrhages	Functional hyposplenism (inflammatory bowel disease-associated)
Slater et al., 1981 – Case 1 [45]	UK	47 F	<i>Streptococcus pneumoniae</i>	Massive bilateral adrenal intracortical hemorrhage; fibrin thrombi; pneumonia	NR
Slater et al., 1981 – Case 2 [45]	UK	69 M	<i>Staphylococcus pyogenes</i>	Bilateral adrenal hemorrhage; bronchopneumonia; DIC pattern	NR
Slater et al., 1981 – Case 3 [45]	UK	89 M	<i>Haemophilus influenzae</i>	Massive bilateral adrenal hemorrhage; bronchopneumonia	NR
Stiegler et al., 2010 [46]	Australia	40 M	<i>Capnocytophaga canimorsus</i>	Bilateral diffuse adrenal hemorrhage; dark red discoloration	Anatomical asplenia (previous splenectomy); other risk factor (dog bite exposure)
Stojanović et al., 2013 [47]	Serbia	20 M	No pathogen identified (meningococcal infection suspected)	Bilateral adrenal hemorrhage; widespread multiorgan hemorrhages	NR
Strick, 1944 – Case 1 [48]	USA	2 M	<i>Neisseria meningitidis</i>	Massive bilateral adrenal hemorrhage	NR
Strick, 1944 – Case 2 [48]	USA	2 F	<i>Neisseria meningitidis</i>	Bilateral adrenal hemorrhage; purulent meningitis; purpura fulminans	NR
Strick, 1944 – Case 3 [48]	USA	2.5 M	Presumed <i>Neisseria meningitidis</i>	Extensive bilateral adrenal hemorrhage; acute leptomeningitis	NR
Swierczewski et al., 1969 [49]	USA	3 months F	<i>Neisseria gonorrhoeae</i>	Soft dark hemorrhagic adrenal glands	NR
Tanaka et al., 2025 [50]	Japan	27 F	<i>Escherichia coli</i>	Bilateral adrenal hemorrhage; focal necrosis (left predominance)	Immunosuppression (chronic corticosteroid therapy)
Tattoli et al., 2015 [51]	Italy	43 M	<i>Neisseria meningitidis</i>	Bilateral adrenal hemorrhage; purpura fulminans; multiorgan hemorrhagic shock	NR
Tormos et al., 2013 – Case 1 [3]	USA	34 M	<i>Staphylococcus aureus</i>	Bilateral adrenal hemorrhage; necrotizing pneumonia; sepsis	NR
Tormos et al., 2013 – Case 2 [3]	USA	48 M	<i>Streptococcus pneumoniae</i>	Bilateral adrenal hemorrhage; severe pulmonary edema; septic shock	NR
Tormos et al., 2013 – Case 3 [3]	USA	26 M	Yeast+coagulase-negative staphylococci (possible contaminants)	Microscopic adrenal medullary hemorrhage; necrotizing pneumonia	NR
Tormos et al., 2013 – Case 4 [3]	USA	2 M	<i>Pseudomonas aeruginosa</i>	Bilateral adrenal hemorrhage; burn-related sepsis	Other risk factor (extensive burns)
Tormos et al., 2013 – Case 5 [3]	USA	2 M	MRSA (<i>Staphylococcus aureus</i>)	Bilateral adrenal hemorrhage; necrotizing pneumonia	NR
Tsokos, 2002 – Case 1 [52]	Germany	35 F	Not identified (bacterial meningitis pattern)	Bilateral adrenal hemorrhage; purulent meningitis; DIC changes	NR
Tsokos, 2002 – Case 2 [52]	Germany	74 F	Not identified (bacterial meningitis pattern)	Bilateral adrenal hemorrhage; septic spleen; purpura; microthrombi	NR

Table 1 (continued)

Author, Year (Ref.)	Country	Age/Sex	Pathogen identified	Key autopsy findings	Predisposing factors
Tsokos, 2003 [53]	Germany	74 F	<i>Ewingella americana</i>	Diffuse bilateral adrenal hemorrhage; brain edema; lung edema; septic spleen changes	NR
Urata et al., 1990 [54]	Japan	26 M	<i>Streptococcus pneumoniae</i>	Bilateral acute adrenal hemorrhagic necrosis; systemic hemorrhagic diathesis; multiorgan involvement	Anatomical asplenia (previous splenectomy); immunodeficiency (IgG3 subclass deficiency)
Ventura Spagnolo et al., 2019 [55]	Italy	40 M	<i>Proteus mirabilis</i>	Bilateral adrenal hemorrhagic infiltration; cortico-medullary apoplexy	Other risk factor (recent facial trauma)
Verzeletti et al., 2017 [56]	Italy	64 M	<i>Streptococcus pneumoniae</i>	Extensive bilateral adrenal hemorrhage; no clear primary infection focus	Anatomical asplenia (previous splenectomy)
Vincintelli et al., 2009 [57]	USA	67 F	<i>Streptococcus pneumoniae</i>	Massive bilateral adrenal cortical hemorrhagic necrosis; systemic hemorrhagic manifestations	Anatomical asplenia (congenital)
Wan Razali et al., 2024 [58]	Malaysia	3 months M	Dengue virus (bacterial cultures negative)	Bilateral adrenal hemorrhage; multiorgan congestion; diffuse hemorrhagic lesions	NR
Wenk & Dutta, 1975 [59]	USA	71 F	<i>Streptococcus pneumoniae</i>	Massive bilateral adrenal hemorrhage; diffuse visceral petechiae; ecchymoses	Anatomical asplenia (previous splenectomy)
Ventura et al., 2013 [60]	Italy	2 M	Co-infection: <i>Neisseria meningitidis</i> (sero-group C) + <i>Streptococcus pneumoniae</i>	Bilateral adrenal hemorrhagic infiltration	NR
Aegerter, 1936 [61]	USA	Infant (pediatric case)	Presumed <i>Neisseria meningitidis</i>	Massive bilateral adrenal hemorrhage; fulminant purpura; meningitic presentation	NR
Monfort et al., 1940 [62]	USA	18 months M	Not identified	Massive bilateral adrenal cortical hemorrhage; diffuse purpura fulminans	NR
Newman, 1944 – Case 1 [63]	USA	24 F	<i>Neisseria meningitidis</i>	Diffuse bilateral adrenal hemorrhage; fulminant purpura; multiorgan vascular injury	NR
Newman, 1944 – Case 2 [63]	USA	21 M	<i>Neisseria meningitidis</i>	Complete bilateral adrenal destruction by hemorrhage; visceral hemorrhages	NR
Newman, 1944 – Case 3 [63]	USA	26 F	<i>Neisseria meningitidis</i>	Massive bilateral adrenal hemorrhage; systemic purpura; shock organs	NR
Doherty, 2001 [64]	Australia	28 F	<i>Streptococcus pneumoniae</i>	Extensive bilateral adrenal cortical and medullary hemorrhage	NR
Hughes, 1940 [65]	UK	10 weeks F	Gram-negative diplococci compatible with <i>Neisseria meningitidis</i>	Bilateral adrenal hemorrhage	NR
Park et al., 1953 [66]	South Korea	Pediatric case	<i>Neisseria meningitidis</i> (clinical diagnosis)	Bilateral adrenal hemorrhage; systemic visceral congestion; multiorgan involvement	NR
Polayes et al., 1953 [67]	USA	34 F (pregnant)	<i>Neisseria meningitidis</i> (gram-negative diplococci)	Massive bilateral adrenal hemorrhage; cortical and medullary destruction	Other risk factor (pregnancy with pre-eclamptic toxemia)
Tudosa et al., 2017 – Case 1 [68]	Romania	5 months M	<i>Neisseria meningitidis</i>	Bilateral adrenal hemorrhage; cerebral edema; fulminant septic shock pattern	NR
Tudosa et al., 2017 – Case 2 [68]	Romania	8 months F	Not identified	Bilateral adrenal hemorrhage; purpura fulminans; multiorgan congestion	NR
Tudosa et al., 2017 – Case 3 [68]	Romania	1 M	Not identified	Massive bilateral adrenal hemorrhage; cerebral edema; interstitial pneumonia	NR
Tudosa et al., 2017 – Case 4 [68]	Romania	1.5 M	Not identified	Bilateral adrenal hemorrhage; diffuse purpuric rash; shock-organ changes	NR
Tudosa et al., 2017 – Case 5 [68]	Romania	2 F	Not identified	Bilateral adrenal hemorrhage; systemic hemorrhagic syndrome; DIC pattern	NR
Vecilla et al., 2023 [69]	Spain	55 F	<i>Capnocytophaga canimorsus</i> (serovar B)	Bilateral adrenal hemorrhage	Other risk factor (dog bite exposure)
Jensen et al., 2025 [70]	Norway	Male, 70s	<i>Capnocytophaga canimorsus</i>	Bilateral adrenal hemorrhagic infarction	Other risk factor (dog exposure)

Abbreviations: COVID-19=coronavirus disease 2019; CSF=cerebrospinal fluid; DIC=disseminated intravascular coagulation; ICU=intensive care unit; NR=not reported; OPSI=overwhelming post-splenectomy infection; PCR=polymerase chain reaction

Table 2 Semi-quantitative synthesis of autopsy-confirmed fatal WFS cases (N=86)

Domain	Variable	Cases, n/N (%)
Demographic characteristics	Male	42/86 (48.8%)
	Female	41/86 (47.7%)
	Sex not reported	3/86 (3.5%)
	Pediatric (< 18 years)	29/86 (33.7%)
	Adult (≥ 18 years)	54/86 (62.8%)
	Age not reported	3/86 (3.5%)
	Mean age±SD	31.7±25.4 years*
Microbiological etiology	<i>Neisseria meningitidis</i>	23/86 (26.7%)
	<i>Streptococcus pneumoniae</i>	23/86 (26.7%)
	<i>Capnocytophaga canimorsus</i>	8/86 (9.3%)
	Group A <i>Streptococcus</i>	6/86 (7.0%)
	<i>Haemophilus influenzae</i>	3/86 (3.5%)
	Other identified pathogens	13/86 (15.1%)
	No pathogen identified	10/86 (11.6%)
Cutaneous manifestations	Any hemorrhagic skin manifestation	67/86 (77.9%)
	Purpura/purpuric lesions	43/86 (50.0%)
	Petechiae (with or without purpura)	30/86 (34.9%)
	Purpura fulminans	4/86 (4.7%)
	Skin necrosis	4/86 (4.7%)
Histopathological findings	DIC-related changes†	36/86 (41.9%)
	Hemophagocytosis	4/86 (4.7%)
	Leukocytoclastic vasculitis	2/86 (2.3%)
Predisposing factors	Anatomical asplenia	15/86 (17.4%)
	Functional hyposplenism	8/86 (9.3%)
	Any splenic dysfunction	23/86 (26.7%)
	Immunosuppression	5/86 (5.8%)
	Dog bite/exposure	7/86 (8.1%)
	Pregnancy/post-partum state	2/86 (2.3%)
	No reported predisposing factor	49/86 (57.0%)
	Ante-mortem blood culture performed	28/86 (32.6%)
Microbiological investigations	Post-mortem culture performed	24/86 (27.9%)
	PCR-based methods performed	11/86 (12.8%)
	Combined multi-modal microbiological investigation‡	43/86 (50.0%)
	Microbiology-negative cases	6/86 (7.0%)

* Age available for 83/86 cases

† DIC-related changes included disseminated intravascular coagulation, fibrin thrombi, microvascular thrombosis, thrombotic microangiopathy, vascular thrombosis, or equivalent histopathological findings compatible with systemic coagulation activation

‡ Combination of two or more microbiological approaches, including culture, PCR, antigen testing, MALDI-TOF identification, immuno-histochemistry, Gram staining, or histopathological bacterial detection

functional, represented the most frequently reported predisposing condition (23/86, 26.7%). Other recurrent conditions included immunosuppression, recent infections, pregnancy or postpartum status, and additional factors associated with increased susceptibility to overwhelming infection. Nevertheless, a substantial proportion of cases occurred in previously healthy individuals without clearly documented predisposing factors.

Synthesis of forensic-pathological patterns

Qualitative synthesis of the included cases identified recurring forensic-pathological patterns characterized by bilateral adrenal hemorrhage or hemorrhagic necrosis, systemic evidence of sepsis and DIC, multiorgan hemorrhagic or congestive changes, and variable but supportive microbiological evidence. These recurring elements consistently emerged across heterogeneous reports and formed the evidentiary basis for the interpretative frameworks proposed in this study.

Discussion

The semi-quantitative synthesis performed in the present review highlights several recurrent patterns across otherwise heterogeneous reports. In particular, hemorrhagic cutaneous manifestations, DIC-related histopathological changes, and splenic dysfunction emerged as the most frequently reported forensic-pathological features. Moreover, although *Neisseria meningitidis* and *Streptococcus pneumoniae* remained the predominant etiological agents, a substantial proportion of cases involved less common pathogens, particularly *Capnocytophaga canimorsus*, emphasizing the need for a broad microbiological differential diagnosis in suspected WFS.

Autopsy and histopathological findings

Across historical and contemporary reports, bilateral adrenal hemorrhage consistently appeared within recurring systemic pathological patterns rather than as an isolated autopsy finding [3, 4, 43]. Gross examination frequently demonstrated pulmonary edema, visceral congestion, serosal petechiae, and multiorgan hemorrhagic manifestations, reflecting a common background of fulminant septic circulatory collapse.

Histopathological examination reinforced this interpretation, with recurrent findings including adrenal hemorrhagic necrosis, fibrin microthrombi, and variable DIC-related changes [23, 55]. Classical external signs such as purpura fulminans or overt DIC morphology were inconsistently present, indicating that their absence does not exclude WFS.

Figure 2 translates the forensic reasoning process into a practical autopsy algorithm for suspected WFS. This

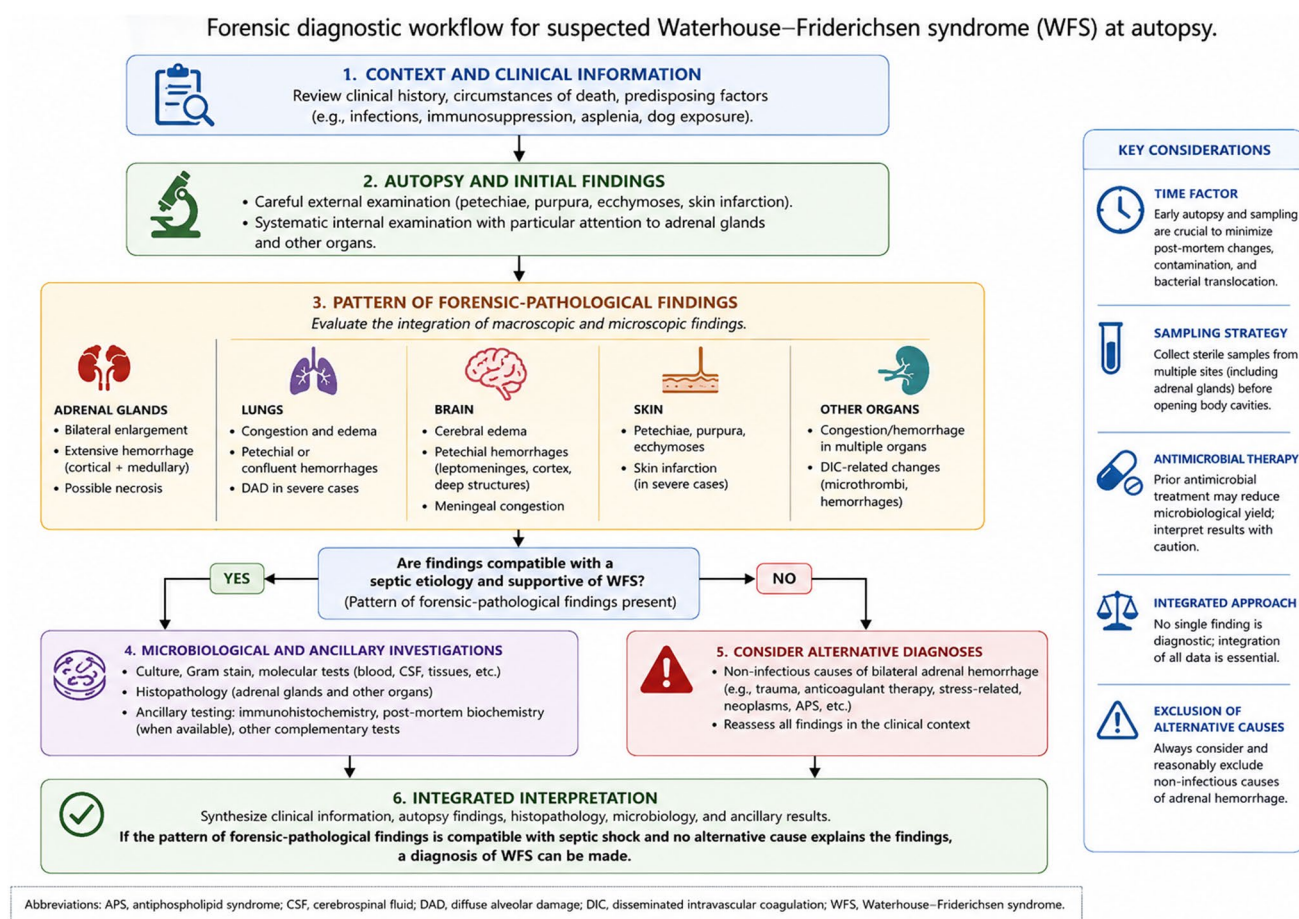


Fig. 2 Forensic diagnostic workflow for suspected WFS at autopsy. This algorithm represents an evidence-informed interpretative tool derived from qualitative synthesis of the included cases and is intended

algorithm is intended to support forensic interpretation by organizing recurrent forensic-pathological findings rather than to define rigid diagnostic criteria. Starting from the recognition of bilateral adrenal hemorrhage, the pathway progresses through successive interpretative checkpoints, including evaluation of systemic septic morphology, histopathological support, microbiological findings, and exclusion of major alternative causes. This sequence reflects the way diagnostic confidence is progressively built during medico-legal examination. The algorithm emphasizes that interpretation does not rely on a single defining lesion but on the integration of multiple lines of evidence, ultimately supporting a pattern of findings consistent with WFS when the overall pathological context is coherent.

Microbiology and operational sampling: limits and practical implications

Microbiological investigation represented one of the most heterogeneous aspects of the reviewed literature. Cases included positive ante-mortem cultures, post-mortem

to support forensic diagnostic reasoning rather than to provide validated diagnostic criteria

cultures, molecular identification, and situations in which microbiological analyses remained negative despite strong pathological evidence of sepsis [43, 56, 69]. Similar variability has been described in contemporary forensic literature, where post-mortem diagnosis of infectious deaths frequently depends on integration of clinical history, autopsy findings, histology, and microbiology rather than on a single diagnostic element [71, 72].

A distinction should be made between ante-mortem and post-mortem microbiological findings. Ante-mortem cultures generally provide stronger evidence of active infection, whereas post-mortem microbiological results require cautious interpretation because of potential contamination, post-mortem bacterial translocation, the influence of post-mortem interval, prior antimicrobial therapy, and methodological differences between culture-based and molecular approaches [5–7]. Consequently, microbiological findings should always be interpreted in conjunction with autopsy, histopathological, and circumstantial evidence.

Because the interpretative value of microbiology depends largely on how and when samples are obtained, inadequate

or delayed sampling may reduce diagnostic reliability and increase the risk of misleading interpretations [73].

Figure 3 summarizes a practical post-mortem sampling scheme aimed at maximizing diagnostic reliability in suspected WFS. The proposed workflow integrates pre-autopsy assessment, coordinated microbiological sampling, histopathology, post-mortem biochemistry, and ancillary investigations through a structured approach emphasizing early sterile collection, targeted tissue selection, and parallel acquisition of material for complementary analyses. In addition to microbiological and histopathological investigations, collection of specimens suitable for post-mortem biochemical analyses should be considered when available, as these may provide complementary information in the evaluation of suspected septic deaths. Beyond a purely technical recommendation, the figure reflects the operational reality of medico-legal autopsy, where sampling strategy directly influences the strength of microbiological interpretation and reduces the risk of conclusions biased by contamination or post-mortem artefacts.

This integrative approach is increasingly reflected in contemporary forensic literature, where microbiological, histopathological, molecular, biochemical, and ancillary investigations are interpreted together to improve diagnostic

reliability in infectious deaths and to support standardized post-mortem sampling strategies [74–79].

Differential diagnosis and practical forensic framework

A major challenge emerging from the reviewed literature concerns differential diagnostic scenarios in which bilateral adrenal hemorrhage may mimic WFS. Non-infectious causes include catastrophic coagulopathies, thrombotic microangiopathies, severe trauma, hemorrhagic shock, anticoagulant-related bleeding, and metastatic adrenal disease [3, 23, 55].

Figure 4 summarizes the principal forensic differential diagnoses of bilateral adrenal hemorrhage by contrasting infectious contexts compatible with WFS against non-infectious mimics frequently encountered in medico-legal practice. The figure emphasizes a key interpretative principle emerging from the reviewed evidence: bilateral adrenal hemorrhage, when considered in isolation, lacks diagnostic specificity and should be interpreted within the overall pattern of forensic-pathological findings. The framework is intended as a practical aid to differential diagnostic reasoning, adaptable to the variability of real-world medico-legal

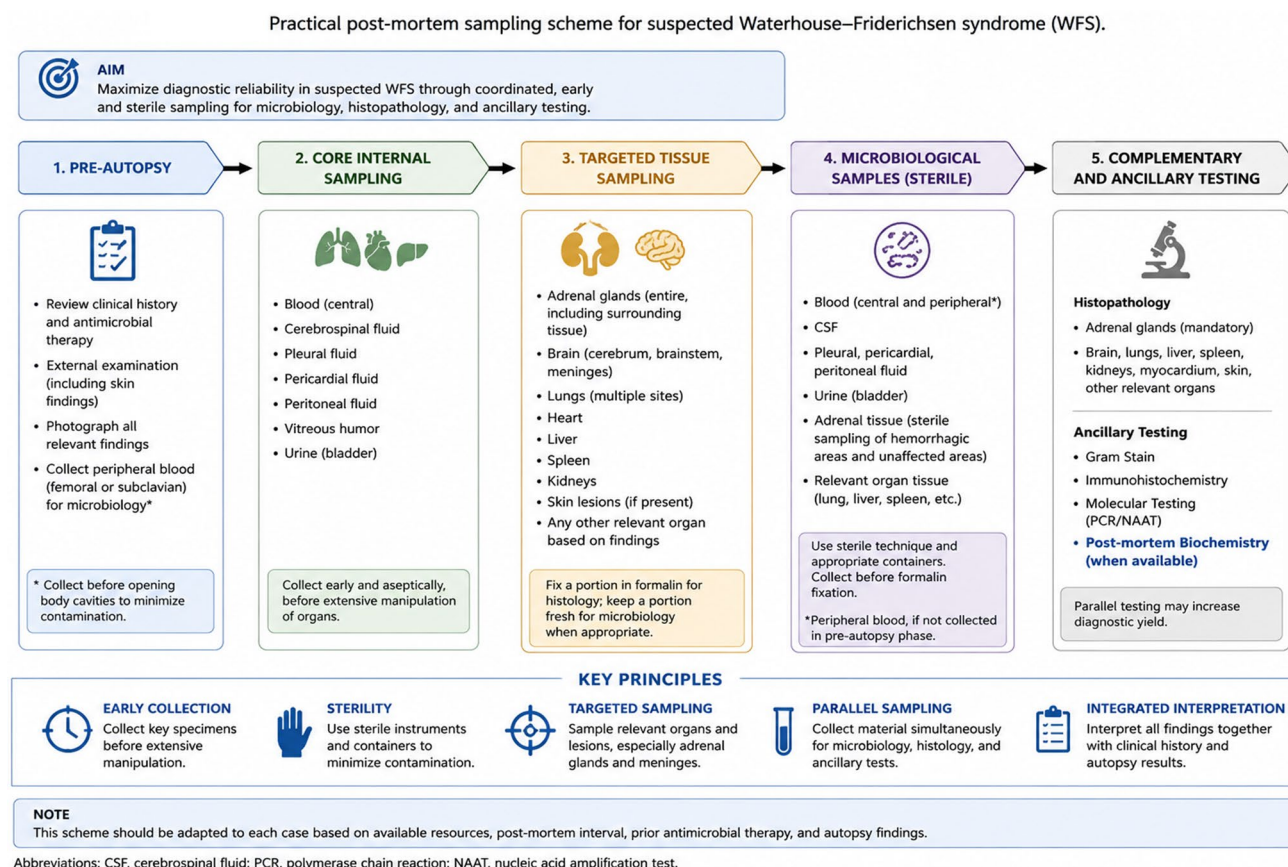


Fig. 3 Practical post-mortem sampling scheme for suspected WFS. The proposed workflow integrates microbiology, histopathology, post-mortem biochemistry, and ancillary investigations through coordinated

sampling. This framework represents an evidence-informed interpretative tool and is not intended as a validated diagnostic protocol

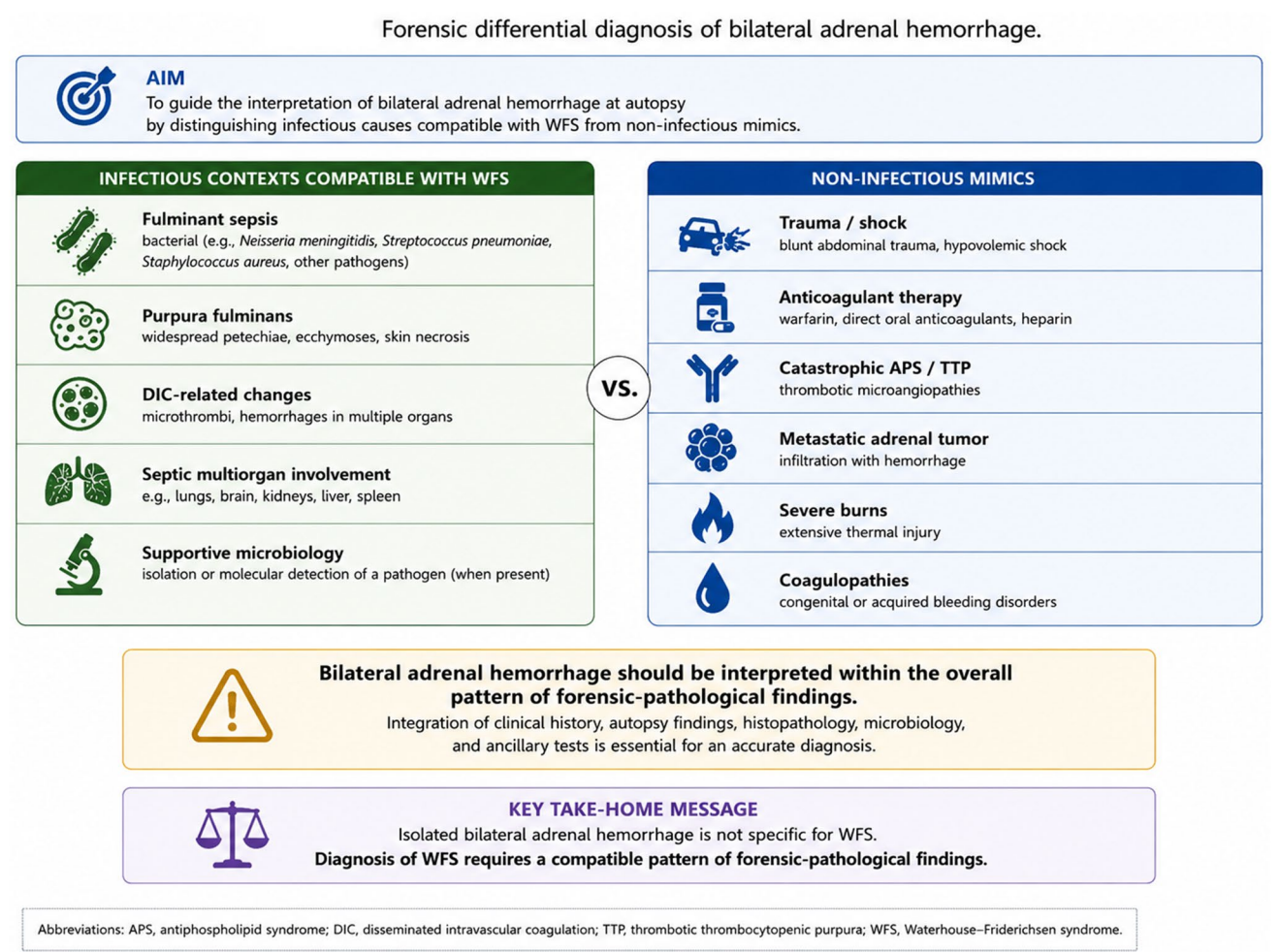


Fig. 4 Forensic differential diagnosis of bilateral adrenal hemorrhage. The framework summarizes infectious contexts compatible with WFS and major non-infectious mimics encountered in forensic practice. It

represents an evidence-informed interpretative tool intended to support differential diagnostic reasoning rather than validated diagnostic criteria

scenarios and supportive of a structured assessment of findings consistent with WFS.

Across the included cases, bilateral adrenal hemorrhage acquired diagnostic significance when accompanied by systemic septic morphology, supportive histopathological evidence, and microbiological or circumstantial findings consistent with fulminant infection. Conversely, the absence of this broader pattern of findings required careful consideration of alternative non-infectious causes.

The proposed algorithm, sampling strategy, and differential diagnosis framework should be interpreted within the methodological limitations of the available evidence. They were derived from qualitative synthesis of recurrent patterns identified across published cases and supplemented by forensic-pathological expert interpretation. Consequently, they are intended as practical evidence-informed tools to support autopsy investigation and diagnostic reasoning in suspected WFS, rather than as formally validated diagnostic criteria.

Limitations

Several limitations should be acknowledged. First, the available evidence is largely derived from isolated case reports and small case series, making publication bias unavoidable and potentially favoring unusual or particularly severe presentations. Second, substantial heterogeneity existed in autopsy protocols, histopathological reporting, microbiological investigations, and case documentation across studies, limiting direct comparability. The generally high level of reporting completeness among the included studies facilitated the identification of recurring forensic-pathological patterns. Nevertheless, findings derived from reports with incomplete clinical, histopathological, or microbiological documentation were interpreted with greater caution and were not considered in isolation when developing the proposed forensic frameworks. Third, interpretation of post-mortem microbiological findings remains inherently challenging because of potential

contamination, post-mortem bacterial translocation, variability in post-mortem intervals, prior antimicrobial therapy, and differences in sampling procedures and laboratory methods. Furthermore, negative microbiological results do not necessarily exclude infection, particularly when antimicrobial treatment was administered before death or when sample quality is suboptimal.

An additional limitation relates to the inability to retrieve 34 reports identified during screening. Although multiple retrieval strategies were employed, several studies were historical publications or articles with limited electronic accessibility, particularly those published in languages other than English. Their exclusion may have introduced selection bias and may have resulted in underrepresentation of uncommon pathogens, clinical contexts, or pathological findings. In addition, Embase was not included among the searched databases, which may have reduced the comprehensiveness of literature retrieval.

Conclusions

WFS should be interpreted in forensic practice as a syndrome characterized by a recurrent pattern of septic and forensic-pathological findings rather than as a diagnosis based solely on bilateral adrenal hemorrhage. The integration of autopsy findings, histopathology, microbiology, and structured sampling strategies improves diagnostic consistency and reduces the risk of misinterpretation in sudden septic deaths. By translating dispersed case-level evidence into structured forensic reasoning tools, this review may facilitate more consistent and reproducible interpretation.

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Declarations

Clinical trial number Not applicable.

Ethical approval This study is a systematic review of published literature and did not involve new human participants or biological samples. Therefore, approval from an institutional review board or ethics committee was not required.

Human ethics and consent to participate declaration Not applicable.

Competing interests The authors declare no competing interests. One of the included studies is a previously published case report authored by members of the research team.

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