# CHAPTER 4.

## Systematic review of 62 cases of adrenal haemorrhage and insufficiency: a potential mechanism of critical illness-associated adrenal dysfunction?

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Submitted

## Abstract

**Background:** The concept of adrenal dysfunction of critical illness remains highly controversial. Adrenal hemorrhage is rare and can develop in the course of surgery, trauma, sepsis and coagulopathy. We wondered whether adrenal hemorrhage may lead to diminished cortisol synthesis, as seen in critical illness-associated adrenal dysfunction and that the latter could thus be sometimes or partly explained by hemorrhages.

**Methods:** A literature search was done. All case reports (n=62 cases in 54 reports) on adrenal hemorrhage in adults diagnosed by imaging and adrenal function tests were extracted.

**Results:** Risk factors were surgery in 79%, anticoagulation in 39%, heparin-induced thrombocytopenia in 27% and sepsis in 15% of patients. Electrolyte disturbances were described in only 31%. Twenty-four % of patients were in the intensive care unit. Adrenal hemorrhages were bilateral in 89%. The mean baseline cortisol was 5.4 (standard deviation 5.1) μg/dL and 16% had a baseline cortisol >10 μg/dL (lower limit of normal). The mean adrenocorticotropic hormone (ACTH), available in 21%, was 505 (627) pg/mL (n 10-60 pg/mL). The cortisol response to ACTH (in 55%) was 0.98 (1.9) μg/dL and was therefore blunted. Reversibility was reported in 18% and irreversibility in 21%.

**Conclusions:** Adrenal hemorrhage following major surgery, anticoagulation, HIT and sepsis, can cause acute primary adrenal insufficiency and this resembles to some extent critical-illness related adrenal dysfunction. This prompts for imaging and function testing in suspected cases with otherwise unexplained hypotension, to further elucidate the role of adrenal hemorrhage in critical illness-associated dysfunction.

## Background

The concept of adrenal dysfunction of critical illness and its treatment with corticosteroids, remain highly controversial. The controversy relates to difficulties in diagnosis by underlying severity of disease causing activation of the pituitary-adrenal axis, by changes in cortisol metabolism and plasma concentrations, and by the controversial validity of the adrenocorticotropic (ACTH) stimulation tests and consensus on its cut-off values. Controversy also relates to the lack of direct evidence for altered adrenal steroidogenesis or injury, in the absence of use of drugs known to inhibit cortisol synthesis, the effects of corticosteroid treatment and the poor predictability hereof by adrenal function parameters [1,2]. When an ACTH test is used to assess adrenal function, adrenal dysfunction is suspected when the plasma cortisol increase upon exogenous ACTH is below 9 $\mu$g/dL (250 nmol/L) [3,4] and/or a random cortisol level is below 10 $\mu$g/dL [5], although the latter may be affected by stress (and endogenous ACTH) and concentrations of cortisol-binding proteins [2-4]. Clinical risk factors for adrenal dysfunction in the critically ill include sepsis, thrombocytopenia and coagulopathy [3,4]. However, an anatomic cause of dysfunction of the adrenals during life has not been documented, but post mortem studies suggest lipid depletion, thrombosis and hemorrhage in 7 critically ill patients with adrenal dysfunction in whom this was evaluated [6]. Conversely, adrenal hemorrhage is a rare but well known entity for decades. It can develop in the course of surgery, trauma, sepsis, coagulopathy, anticoagulation and heparin-induced thrombocytopenia (HIT), which are frequently encountered conditions in the critically ill, [7-12]. The risk factors reported [13] are thus similar to those of the adrenal dysfunction of critical illness [3,4]. Recognition is hard since presenting symptoms of abdominal pain, fever and hypotension are non-specific. The condition may be missed during life and found at autopsy as described in case reports and reviews in the 60's and 70's [7-10,12]. Autopsy studies reported incidences of adrenal hemorrhage between 0.14 and 1.8% [9]. At a high index of suspicion, the diagnosis of adrenal hemorrhage and dysfunction can nowadays be obtained during life by computer tomography (CT) or other imaging techniques and adrenal function tests. Adrenal hemorrhage often lead to acute adrenal insufficiency for which corticosteroid therapy can be life-saving. We wondered whether this could be a mechanism of critical illness-associated adrenal dysfunction and the benefits of corticosteroids in selected patients.

In the hypothesis that adrenal hemorrhage may lead to diminished cortisol synthesis, as seen in critical illness-associated adrenal dysfunction and that, inferentially, the latter entity could be sometimes or partly explained by adrenal hemorrhages, we undertook a systematic search of the literature to summarize the reported risk factors and functional consequences of adrenal hemorrhage. We therefore reviewed cases of adrenal hemorrhage where the diagnosis was obtained by imaging techniques and quantitative results of measurements of plasma cortisol,

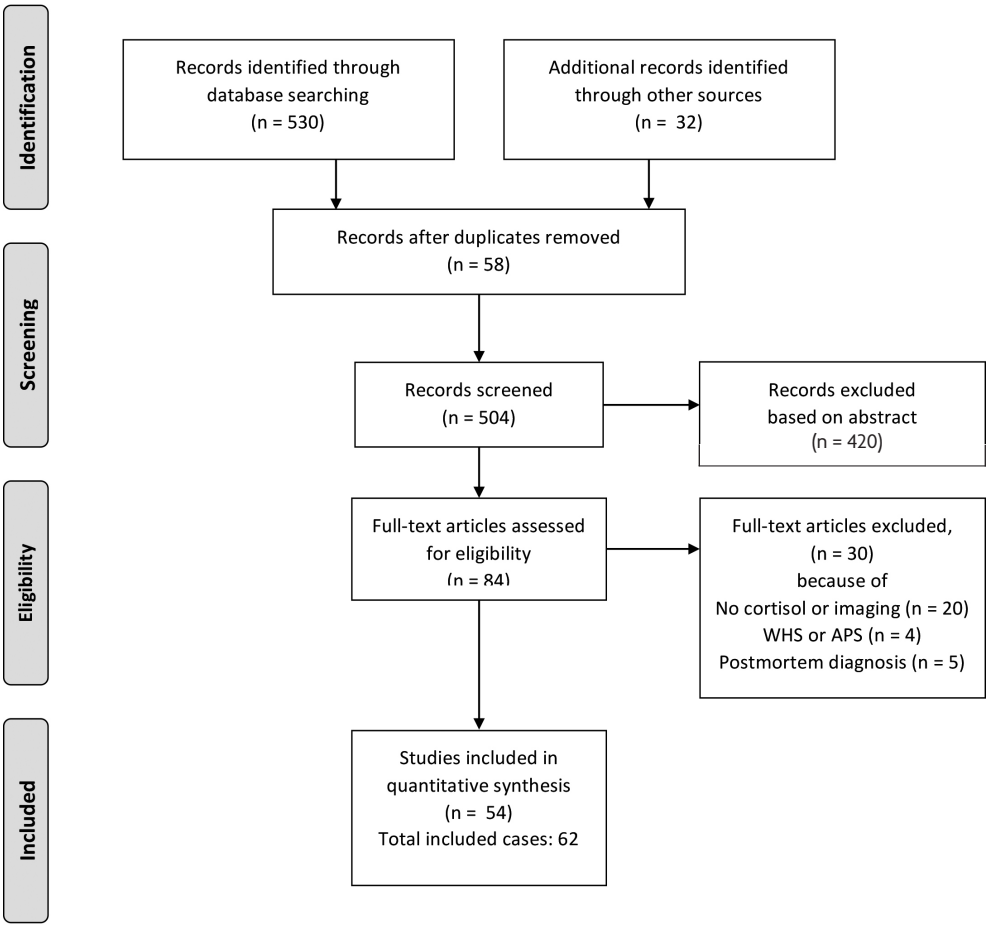
with or without endogenous ACTH levels and with or without exogenous ACTH testing.

## Methods

We performed a systematic search on Medline from 1967 to February 15 2015 to identify papers or correspondence for the functional consequences of adrenal hemorrhage. Major MESH search terms included: adrenal hemorrhage, cortisol, trauma, sepsis, surgery and anticoagulation (adrenal hemorrhage AND sepsis, adrenal hemorrhage AND cortisol AND trauma, adrenal hemorrhage AND cortisol AND surgery, adrenal hemorrhage AND cortisol AND anticoagulation). Additional published reports were identified through a manual search of citations from retrieved articles. The initial literature search yielded 560 papers. There were ultimately 54 papers (Fig. 1) fulfilling our inclusion criteria: English, French, German, Italian or Spanish full papers or correspondence were considered, provided that non-English papers had abstracts in English. Also, the diagnosis must have been established during life with help of imaging techniques and at least one adrenal function test. We excluded papers on the meningococcal or pneumococcal Waterhouse-Friderichsen syndrome (purpura fulminans), a well-known cause of adrenal insufficiency, on the antiphospholipid syndrome, which may result in adrenal hemorrhages, and on adrenal metastatic disease, since these are not typically associated with critical illness. We extracted, by consensus, pertinent data from case description such as age, gender, underlying condition (critical illness) and major perceived contributory factor for adrenal hemorrhage, diagnostic measures, bi- or unilateral hemorrhage, baseline plasma cortisol/ACTH and cortisol increments upon short or long exogenous ACTH testing, reversibility, where available, and summarized the data. We defined adrenal insufficiency when baseline cortisol was <10 μg/dL (276 nmol/L) or, when above 10 μg/dL, was accompanied by an elevated endogenous ACTH or by a diminished response to exogenous ACTH. Normal values for baseline cortisol was determined as ≥10 μg/dL (276 nmol/L), for cortisol increments upon exogenous synthetic ACTH >9 μg/dL (250 nmol/L) and for endogenous ACTH 10-60 pg/mL (2-13 pmol/L), depending on laboratory methods, diurnal variation and level of stress (3-5). Reversibility was judged on the basis of results of ACTH testing weeks to months after the event.

*Statistical analysis*. We summarized the normally distributed continuous data by mean (standard deviation, SD) and percentage as appropriate.

**Figure 1.** Flow diagram of articles selected and reasons for exclusion. WHS: Waterhouse Friderichsen Syndrome, APS: antiphospholipid syndrome




## Results.

Figure 1 represents the search strategy visualized by a PRISMA flow diagram. As indicated in Table 1 (electronic supplementary material), we retrieved 54 papers on 62 cases (11,14-66) and summarized characteristics. Many cases had multiple risk factors so that their relative distribution should be taken with caution (Table 2). Anticoagulation as a risk factor often included heparin prophylaxis (and HIT) and rarely administration of coumadins. Only few cases were 'spontaneous'. Concomitant electrolyte disturbances as hyponatremia and hyperkalemia were rarely described. Fifteen (24%) of patients were reportedly admitted into the ICU.

Cortisol and ACTH. Table 3 describes adrenal function tests. In 84% of patients, cortisol was below ≤10 μg/dL . In 10 (16%) of cases, baseline cortisol was in the normal range (>10.0 μg/dL) and in 8 of these patients adrenal insufficiency was diagnosed by an elevated baseline ACTH or diminished response to exogenous ACTH. Three patients were considered to have normal adrenal function, however in two of them this was only based on baseline cortisol levels since no ACTH concentration or test result was available. Of the four patients who had a baseline cortisol level above 15 μg/dL, two had unilateral adrenal hemorrhage. However, 4 patients with unilateral adrenal hemorrhage (67% of all) had a baseline cortisol <10 μg/dL. Furthermore, the 2 patients with unilateral adrenal hemorrhage in whom an ACTH test was performed were non-responders. In 11 cases, reversible adrenal insufficiency was reported and in 13 irreversibility at follow up after weeks to months.



**Table 2** Patient characteristics (n=62).

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|---|---|
| Age, years | 59.9 (12.9) |
| Sex, m/f/unknown | 35 (56)/ 23 (37)/ 4(6) |
| Risk factors* | |
| Trauma and surgery | 49 (79) |
| Sepsis | 9 (15) |
| Anticoagulation | 24 (39) |
| HIT | 17 (27) |
| Electrolyte disturbances | 19 (31) |
| Adrenal haemorrhage, uni-/bilateral | 6 (10)/ 55 (89) |
| In the ICU | 15 (24) |

Data are expressed as mean (SD) or number (%), where appropriate; HIT: heparin-induced thrombocytopenia; ICU: intensive care unit. *Patients may have more than 1 risk factor.

**Table 3** Cortisol and ACTH values in patients with adrenal haemorrhage

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|---|---|---|
| Cortisol, baseline (μg/dL) | n= 61 | 5.4 (5.1) |
| Cortisol, baseline ≤10 μg/dL | | 51 (84) |
| Normal baseline cortisol | | 10 (16) |
| ACTH (pg/mL) | n=13 | 505 (627) |
| Increment of cortisol (μg/dL) | n= 34 | 0.98 (1.9) |
| Cortisol increment upon ACTH <9 μg/dL | | 34 (100) |
| Cortisol increment <3.6 μg/dL | | 30 (88) |
| Normal adrenal function | | 3 (5) |
| Irreversible/reversible | | 13 (21)/ 11 (18) |

Data are expressed as mean (SD) or number (%), where appropriate. ACTH: adrenocorticotropic hormone.

## Discussion.

The present systematic case series shows that most cases of adrenal hemorrhage in the course of surgery, trauma, sepsis, coagulation disturbances, anticoagulation and HIT are associated with primary acute adrenal insufficiency. The diagnosis of adrenal insufficiency was mostly based on low baseline cortisol values accompanied by a blunted response to the ACTH. In most patients the adrenal hemorrhages were bilateral in some unilateral. Treatment with corticosteroids was considered life-saving in these cases.

Adrenal hemorrhage-related corticosteroid insufficiency may overlap but also differ from the adrenal dysfunction of critical illness. First, very low cortisol and highly elevated ACTH levels are rare in the stressed patient with critical illness [1-4]. Nevertheless, the current series suggests that milder forms of adrenal insufficiency can be encountered in case of adrenal hemorrhage. Sixteen % of the reported patients had a relatively normal baseline cortisol (random total cortisol >10 μg/dL) and some even only slightly elevated ACTH levels, but often showed a poor response to exogenous ACTH, as in critical illness-associated adrenal dysfunction (<9 μg/dL). Hence, adrenal hemorrhage-related corticosteroid insufficiency could in part explain critical illness-associated adrenal dysfunction, a highly controversial disorder for which ACTH testing is even not recommended currently [1,2]. This policy may not be safe in adrenal hemorrhage-related corticosteroid insufficiency. The present study thus argues in favor of both adrenal CT scanning and cortisol/ACTH testing in critically ill patients in whom adrenal hemorrhage is suspected. Another finding of the present study is that adrenal hemorrhage-related corticosteroid insufficiency seems permanent in some cases, at least in as far as repeated testing has been done. Reversibility of insufficiency has been described in other cases [49]. This may agree with critical illness-associated adrenal dysfunction, which is considered to be often reversible [4].

The risk factors for critical illness-associated adrenal dysfunction overlap those of adrenal hemorrhage, i.e. major surgery, sepsis, coagulation disturbances and heparin treatment [3,4,13]. Surgery often involved trauma, abdominal or cardiovascular operations and also major orthopedic operations, a previously reported association with adrenal hemorrhage in the literature [11,62]. Non-HIT thrombocytopenia may be a risk factor for critical illness-associated adrenal dysfunction [3,4] as well as for adrenal hemorrhages [13,23]. Particularly the association between bilateral adrenal hemorrhage and postoperative heparin thromboprophylaxis or HIT has been emphasized in the past [11-13,62]. Hence, recognition of adrenal insufficiency by adrenal hemorrhages in the critically ill is dependent on a high index of suspicion. The high frequency of corticosteroid insufficiency during hemorrhage may have implications for the management of critically ill patients many of them having stressful conditions after surgery/trauma and sepsis, and receiving subcutaneous heparin for

thromboprophylaxis, when signs and symptoms possibly pointing to intercurrent adrenal insufficiency develop over days and raise the suspicion of adrenal hemorrhage.

The signs and symptoms of adrenal hemorrhage commonly include abdominal and flank pain, fever, otherwise unexplained hypotension and, rarely, electrolyte disturbances, developing over days after the insult (Table 1, ref 11,14-66). Symptoms like fever and abdominal pain are non-specific or even obscured because of sedation in critically ill patients and hypotension is often attributed to hypovolemia or sepsis. Indeed, the literature suggests that often a diagnosis of sepsis is considered first and imaging techniques are applied to find a focus. Adrenal enlargement consistent with hemorrhage is then found by coincidence on CT scans, and leads to the correct diagnosis and life-saving treatment with intravenous hydrocortisone if insufficiency is diagnosed. In the past, adrenal hemorrhages have been reported at autopsy of patients with a clinical picture, in retrospect, of adrenal insufficiency [7-10]. Nowadays, CT scanning and in vivo diagnosis with rapid cortisol/ACTH testing thus allow diagnosis during life and lifesaving treatment with corticosteroids.

The pathogenesis of adrenal hemorrhage may be multifactorial. Intravascular coagulation and hyperstimulation by endogenous ACTH may play a role in thrombosis of the central adrenal vein, with subsequent hemorrhages following coagulation disturbances inducing adrenal insufficiency [7]. Subclinical changes to the adrenal gland (not detectable by imaging techniques) or possibly preceding changes to adrenal hemorrhage may also partly explain adrenal insufficiency in patients with an unilateral hemorrhage. We may speculate that, rather than being a distinctly different syndrome, adrenal hemorrhages may constitute the extreme of a continuous spectrum of adrenal dysfunction of critical illness, which is also characterized by activation of the pituitary-adrenal axis.

Our study has several limitations. Most importantly, it is impossible to estimate the incidence of adrenal hemorrhage because of selection by virtue of study design, but underreporting is likely. There are more reports on adrenal hemorrhage (Fig. 1) in which patients were give corticosteroids without prior cortisol/ACTH testing. Furthermore, due to publication bias, it is not known in which proportion of the patients with adrenal hemorrhage corticosteroid insufficiency develops. This would require prospective functional testing in all patients in whom adrenal hemorrhage is diagnosed. A further limitation includes the lack of clarity in many reports whether patients were critically ill or not, but in some reports a patients' stay in the ICU was described. Moreover, definitions of sepsis and diagnostic criteria for HIT also varied between studies. Finally, the various techniques and reported results of ACTH testing and cortisol measurements render comparability of cases limited. On the other hand, our paper represents the largest collection we are aware of, of case histories of adrenal insufficiency following hemorrhage and documented by imaging techniques and cortisol measurements, to raise awareness of the condition in critical illness. Indeed, CT scanning for abdominal sepsis

may miss adrenal hemorrhages, but this requires further study.

## Conclusions.



The present systematic case series analysis shows that adrenal hemorrhage of whatever origin can lead to acute adrenal insufficiency and resembles to some extent the adrenal dysfunction of critical illness. Since adrenal hemorrhages occurred in 24% in the ICU and insufficiency appeared sometimes reversible, our data suggest that the adrenal dysfunction of critical illness can be caused, among others, by adrenal hemorrhage and favors CT imaging of the adrenals and (repeated) ACTH testing with cortisol determinations in suspected cases with abdominal pain, fever and otherwise unexplained hypotension. Recognition may have therapeutic consequences by interrupting heparin anticoagulation and administering corticosteroids.

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**Additional file 1. The selected studies in order of chronology and per year by first letter of first authors name.**

| Ref number First author last name and initials | Cases, signs, symptoms and diagnostics | Cortisol/ACTH | Conclusion |
|---|---|---|---|
| 14<br>Anderson KC. | 59-year old man with peripheral arterial disease on heparin. After leg amputation the patient developed abdominal pain, fever and hypotension. Electrolyte disturbances. CT: BAH. | Baseline cortisol: 1.9 µg/dl.<br>No cortisol response to ACTH. | AAI caused by BAH following anticoagulation. |
| 15<br>Swift DE. | 66-year old man after total hip replacement, put on heparin and warfarin for thrombophlebitis. Developed epigastric pain and weakness. CT scan: bilateral adrenal masses, consistent with haemorrhages. | Baseline cortisol: 8.0 µg/dl.<br>Cortisol after ACTH: 9.2 µg/dl. | AAI caused by anticoagulation-induced BAH. |
| 16<br>Liu L. | 63-year old man on coumarines with incarcerated inguinal hernia. Developed abdominal pain and fever postoperatively. Electrolyte disturbances. CT: BAH. | Baseline cortisol: 3.0 µg/dl.<br>Cortisol after ACTH: 2.0 µg/dl. | AAI due to BAH following anticoagulation and surgery. |
| 17<br>Wheatley T. | 39-year old man presenting with abdominal pain, fever and wound infection after surgery of traumatic injury of the brachial artery. CT: bilateral adrenal enlargement. | Baseline cortisol: 4.4 µg/dl.<br>Cortisol after ACTH: 4.7 µg/dl.<br>ACTH: 270 pg/ml. | AAI following surgery/sepsis-induced BAH. |
| 18<br>Miller EH. | 81-year old woman after aortic aneurysmectomy, developing right flank pain, drowsiness and fever. CT: BAH. | Baseline cortisol: 2 µg/dl.<br>No cortisol response to ACTH. | BAH with AAI after surgery. |
| 19<br>Findling JW. | 42-year old woman on heparin for pulmonary emboli. Developed flank pain, hypotension and fever. Because of thrombocytopenia, heparin was replaced by warfarin. CT: BAH.<br>44-year old man with pulmonary emboli after surgery. Developed heparin-induced thrombocytopenia and signs of adrenal insufficiency over two years. CT: adrenal calcifications and right adrenal enlargement by old haematomas. | Baseline cortisol: 12 µg/dl.<br>Cortisol after ACTH: 15 µg/dl.<br><br>Baseline cortisol: <1 µg/dl.<br>No cortisol response to ACTH.<br>ACTH: 1880 pg/mL. | PAH after BAH following HIT<br><br>AAI after BAH following HIT |
| 20<br>Khardori R. | 42-year old man after coronary bypass surgery. Developed fever, left flank pain, hypotension and electrolyte disturbances. CT: unilateral adrenal enlargement compatible with haemorrhage. | Baseline cortisol: 2.6 µg/dl.<br>ACTH 601 pg/mL. | AAI following UAH after cardiac surgery. |
| 21<br>Ognibene A.J. | 75-year old woman after ankle surgery. Developed C. difficile infection and deep venous thrombosis, for which i.v. heparin and coumadin were given. Developed abdominal pain, fever, hypotension and hyponatraemia. CT: BAH. | Baseline cortisol: 2.6 µg/dl.<br>Cortisol after ACTH: 2.4 µg/dl. | AAI following heparin-induced BAH. |
| 22<br>Rao RH. | 68-year old with severe arterial vascular disease and amputation; on i.v. heparin. Developed abdominal pain, fever and shock; CT: bilateral enlargement with hyperdense areas.<br>47-year old with pulmonary emboli on i.v. heparin and developing abdominal pain, | All 4 cases baseline cortisol <1 µg/dl | All had AAI following BAH caused by coagulation disturbances. |

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| | fever and shock. CT: bilateral enlargement with hyperdense areas.<br>64-year old after laparotomy for sigmoid abscess, developing abdominal pain and fever. Thrombocytopenia and prolonged clotting times due to administered cephalosporin. CT: bilateral adrenal enlargement with hyperdense areas.<br>75-year old after laparotomy for colonic perforation. Developed fever and shock. Thrombocytopenia and prolonged clotting times due to administered cephalosporin. CT: bilateral adrenal enlargement with hyperdense areas. | | |
| 23<br>Dahlberg PJ. | 63-year old woman after trauma, on heparin for pulmonary embolism after surgery. Developed thrombocytopenia, fever and abdominal pain. CT: BAH.<br>41-year old man after partial colectomy. Developed flank pain, hypotension and electrolyte disturbances. CT: bilateral adrenal enlargement. | Baseline cortisol: 1.6 µg/dl. upon ACTH from 12.2 to 11.9 µg/dl.<br><br>Baseline cortisol: 9.3 µg/dl. ACTH: 350 pg/mL | HIT-induced BAH and absolute insufficiency.<br><br>AAI following surgery-induced BAH. |
| 24<br>Siu SCB. | 70-year old man, after cystectomy. Developed fever, hypotension, thrombocytopenia and electrolyte disturbances. CT: bilateral adrenal masses, consistent with haemorrhages.<br>42-year old woman with intracranial masses for evaluation. Developed abdominal pain and thrombocytopenia. CT: bilateral adrenal masses suggestive of haemorrhages. | Baseline cortisol: 6.3 µg/dl. No cortisol response to ACTH ACTH: 240 pg/ml<br><br>Baseline cortisol: 20 µg/dl. No cortisol response to ACTH ACTH 194 pg/ml. | AAI following bilateral adrenal haemorrhage due to coagulation disturbances.<br><br>PAH following bilateral adrenal haemorrhage due to coagulation disturbances. |
| 25<br>Ernest D. | 69-year old woman after hip replacement. On s.c. heparin. Developed fever, hypotension, thrombocytopenia and hyponatraemia. On warfarin for pulmonary emboli. CT scan: BAH. | Baseline cortisol: <1 µg/dl. | AAI following HIT-induced BAH. |
| 26<br>Feuerstein B. | 43-year old man after trauma, developing fever and urosepsis. CT: BAH. | Baseline cortisol: 0.4 µg/dl. Cortisol after ACTH: 4.7 µg/dl | Reversible AAI following trauma-induced BAH. |
| 27<br>Souied F | 63-year old woman after total hip replacement on s.c. heparin. Developed shock, fever, thrombocytopenia and electrolyte disturbances. CT: two enlarged adrenal glands. | Baseline cortisol: 4.8 µg/dl. Cortisol after ACTH: 3.8 µg/dl. | AAI attributed to HIT-induced bilateral adrenal haemorrhagic necrosis. |
| 28<br>Bleasel JF. | 69-year old woman with pulmonary embolism after knee arthroplasty, for which i.v. unfractionated heparin and later low molecular weight heparin was started. Developed fever, shock, thrombocytopenia and hyponatraemia. CT: BAH. | Baseline cortisol 3.6 µg/dl. No cortisol response to ACTH. | AAI caused by HIT-induced BAH. |
| 29<br>Hardwicke MB. | 63-year old woman, developing hypotension and fever after knee surgery, on s.c. heparin. CT: adrenal enlargement consistent with haematomas. | Baseline cortisol 0.6-3.7 µg/dl. Cortisol after ACTH: 2.9 µg/dl. ACTH 181 pg/mL. | AAI due to anticoagulation-induced BAH |

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| 30<br>Hardy K. | 45-year old man, after coronary bypass surgery. On heparin during procedure, later on warfarin. Developed abdominal and flank pain hypotension and electrolyte disturbances. CT: right adrenal haemorrhage. | Baseline cortisol: 7.2 µg/dl.<br>No cortisol response to ACTH. | AAI following anticoagulation-induced UAH. |
| 31<br>Delhumeau A. | 74-year old man on s.c. heparin after hip surgery, developing arterial thrombosis caused by HIT, followed by abdominal pain, fever, shock and hyponatraemia. CT: enlarged adrenals. | Baseline cortisol: 8.0 µg/dl. | AAI due to HIT and BAH. |
| 32<br>Santonastaso M. | 68-year old woman with HIT after osteotomy. Developed hypotension. CT: bilateral haemorrhagic necrosis of adrenal glands. | Baseline cortisol: 2.5-3.9 µg/dl.<br>No cortisol response to ACTH. | AAI following HIT-induced BAH. |
| 33<br>Sheridan RL. | 43-year old man after burn wounds and surgery. Developed a sepsis-like state and electrolyte disturbances. CT abdomen for suspicion of pancreatitis: BAH. | Baseline cortisol: 5.1 µg/dl;<br>Cortisol after ACTH: from 3.8 to 5.2 µg/dl | AAI following burns and surgery-induced BAH. |
| 34<br>Cramer MJM. | 73-year old man after abdominal vascular surgery. Developed flank pain and later hypotension and electrolyte disturbances. CT: bilateral adrenal enlargement. | Baseline cortisol: 3.3 µg/dl.<br>Cortisol after ACTH: 3.6 µg/dl.<br>ACTH 418 pg/mL. | AAI following BAH after vascular surgery. |
| 35<br>LeMense GP. | 55-year old woman on warfarin for thrombosis of left leg. Developed abdominal pain, hypotension. CT: consistent with BAH | Baseline cortisol: 10-13 µg/dl<br>Cortisol after ACTH: 13 µg/dl | Anticoagulation-induced BAH with partial insufficiency. |
| 36<br>Szalados JE. | 65-year old woman with history of left adrenal carcinoma and surgery. Hypotension after left nephrectomy for tumor. CT: suspect for right adrenal haemorrhage. | Baseline cortisol: 7 µg/dl.<br>Cortisol after ACTH: 8 µg/dl | AAI due to postoperative haemorrhage in single, right adrenal. |
| 37<br>Belmore DJ. | 53-year old man after cholecystectomy. Developed abdominal pain, fever, hypotension and electrolyte disturbances. CT: BAH. | Baseline cortisol: 1.4 µg/dl | AAI following surgery-induced BAH. |
| 38<br>Yale SH. | 57-year old woman after liver surgery for metastases. Developed pleural effusions, back pain and fever. CT: BAH | Baseline cortisol: 6.2 µg/dl<br>Cortisol after ACTH: 5.6 µg/dl. | AAI following BAH after surgery. |
| 39<br>Ikekpeazzu N. | 61-year old man with new abdominal complaints after conservative treatment for sigmoid diverticulitis. Anticoagulants for atrial fibrillation discontinued. Developed electrolyte disturbances. CT: BAH | Baseline cortisol: 1.9 µg/dl | AAI following BAH after infection and anticoagulation. |
| 40<br>Gabbay DS. | 67-year old woman with multitrauma and persistent hypotension and fluid/blood requirements. Developed a 'sepsis' like syndrome and abdominal pain over days while receiving s.c. heparin. CT: BAH. | Baseline cortisol: 2.2 µg/dl | AAI following BAH induced by anticoagulation. |
| 41<br>Schmidt J. | 68-year old man after trauma, developing hypertension. CT: right adrenal mass with uptake on scintigraphy. Laparotomy: haematoma. | Baseline cortisol: 1.7 µg/dl | AAI after unilateral adrenal haematoma mimicking pheochromocytoma. |

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| 42<br>Baccot S. | 69-year old man after trauma and surgery. Developed persistent hypotension. CT: suspect for BAH. | Baseline cortisol: 2.5 µg/dl<br>ACTH 23 pg/mL | AAI after traumatic BAH. |
| 43<br>Scheffold N. | 63-year old man on s.c. heparin after hip surgery. Developed thrombocytopenia, abdominal pain and fever. Echo/CT: right adrenal haemorrhage. | Baseline cortisol: 4.8 µg/dl<br>Cortisol after ACTH: 5.0 µg/dl | AAI following HIT-induced UAH. |
| 44<br>Udobi KF. | 50-year old woman after trauma and laparotomy, developing hypotension and hyperkalaemia. CT: BAH. | Baseline cortisol: 10.2 µg/dl<br>Cortisol after ACTH: 11.2 µg/dl | PAH following trauma-induced BAH. |
| 45<br>Weydrich P. | 56-year old man receiving heparin for atrial fibrillation and developing flank pain, thrombocytopenia and hyponatraemia. MRI: BAH. | Baseline cortisol: 4.0 µg/dl<br>ACTH 145 pg/mL | AAI due to HIT-induced BAH |
| 46<br>Runer ER. | 44-year old woman with urinary tract infection developing hypotension and fever. CT: bilateral enlargement of adrenals consistent with haemorrhage. | Baseline cortisol: 1.2 µg/dl<br>ACTH 829 pg/mL | AAI caused by sepsis-induced BAH. |
| 47<br>LaBan MM. | 82-year old woman after knee arthroplasty on s.c. heparin and warfarin. Developed abdominal pain. CT: bilateral adrenal enlargement due to small haemorrhages. | Baseline cortisol: 0.2 µg/dl | AAI following BAH evoked by anticoagulation. |
| 48<br>Guichelaar MMJ. | 60-year old man with multitrauma and persistent haemodynamic instability. CT: BAH. | Baseline cortisol: 6.1 µg/dl<br>Cortisol after ACTH: 12.3 µg/dl | Trauma-induced BAH with transient AAI |
| 49<br>Jahangir-Hekmat M. | 77-year old woman after knee replacement. On warfarin. Developed abdominal complaints. CT: BAH.<br>40-year old man after cardiac surgery. Developed abdominal complaints, hypotension and electrolyte disturbances. CT: enlarged left adrenal and abnormal right adrenal. | Baseline cortisol: 9.2 µg/dl<br>Cortisol after ACTH: 8.1 µg/dl<br><br>Baseline cortisol: 8.6 µg/dl<br>Cortisol after ACTH: 8.9 µg/dl | AAI following anticoagulation-induced BAH.<br><br>Possible surgery-induced BAH causing AAI |
| 50<br>Jublanc C. | 52-year old man with pneumonia developing abdominal complaints and hypotension and bilateral CT adrenal abnormalities suspect for haemorrhage, confirmed by MRI. | Baseline cortisol: 1.6 and <1 µg/dl<br>No response to ACTH.<br>ACTH 64 pg/mL | Partially recovering AAI due to sepsis-induced BAH. |
| 51<br>Gavrilova-Jordan LP. | 20-year old primigravid developing flank pain resulting from a spontaneous UAH as evidenced by echo/MRI, in the third trimester of pregnancy. | Baseline cortisol: 22 µg/dl | Spontaneous UAH with normal function. |
| 52<br>Mongardon N. | 64-year old man after hip surgery on s.c. heparin. Development of thrombocytopenia, shock and fever. CT: bilateral adrenal gland haemorrhagic necrosis. | Baseline cortisol: 1.7 µg/dl<br>Cortisol after ACTH:1.5 µg/dl | AAI caused by BAH in the course of HIT. |
| 53<br>Picolos MK. | 68-year old man on warfarin for heart failure. Presented with low back pain, hypotension. CT/MRI: consistent with BAH. | Baseline cortisol: 5.9 µg/dl<br>Cortisol after ACTH: 12.7 µg/dl | AAI following anticoagulation-induced BAH. |

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| 54<br>Tourrel F. | 73-year old man with septic shock following acute cholecystitis and cholecystectomy. An earlier ileostomy was closed but the patient developed anastomotic leakage and peritonitis. CT scan done in the suspicion of abscesses: BAH. | Baseline cortisol: 3.4 µg/dl<br>Cortisol after ACTH: 5.0 µg/dl | AAI following septic shock-induced BAH. |
| 55<br>Corsini LM. | 63-year old man after colectomy with a 'sepsis' like condition after surgery. CT: bilateral adrenal swelling and active haemorrhage in one. | Baseline cortisol: 10.4 µg/dl<br>Cortisol after ACTH: 12.1 µg/dl | PAH following BAH after surgery. |
| 56 Egan AM. | 81-year old man after hemicolectomy. Postoperative peritonitis and septic shock. CT: BAH. | Cortisol 10.2 and 10.1 µg/dl, at 30 and 60 min after ACTH, respectively. | Sepsis-induced BAH and PAH. |
| 57<br>Rajamanickam A. | 52-year old man after knee surgery on s.c. low molecular weight heparin prophylaxis presenting with abdominal pain. CT: bilateral adrenal enlargement suspect for haemorrhage. | Baseline cortisol described as normal.<br>Increment of cortisol after ACTH: 0.8 µg/dl. | PAH due to anticoagulation-induced BAH |
| 11<br>Rosenberger LH. | 69-year old man after gastrectomy on s.c. heparin. Developed HIT, later followed by abdominal pain and hypotension. CT: BAH. | Baseline cortisol: 6.1 µg/dl<br>Cortisol after ACTH: 6.3 µg/dl | PAH due to HIT-induced BAH. |
| 58<br>Chow VW. | 44-year old man after knee surgery on prophylactic i.v. heparin. Heparin-induced thrombocytopenia was followed by shock, hyponatraemia and CT-confirmed BAH. | Baseline cortisol: 3 µg/dl | AAI caused by BAH following HIT. |
| 59<br>Thota R. | 68-year old man after knee arthroplasty on s.c. heparin. Developed abdominal pain, fever, thrombocytopenia and hyponatraemia. CT: bilateral adrenal enlargement and haemorrhages. | Baseline cortisol: 0.9 µg/dl | AAI caused by HIT-induced BAH. |
| 60<br>Best M. | 75-year old woman developing respiratory insufficiency due to pneumonia and pulmonary embolism after hip replacement. Received dabigatran and thrombolysis. Remained hypotensive. CT: bilateral adrenal haemorrhage. | Baseline cortisol: 0 µg/dl<br>Cortisol after ACTH: 0.14 µg/dl | AAI following BAH due to anticoagulation. |
| 61<br>Mandanas S. | 52-year old woman after hip arthroplasty on s.c. heparin. Developed hypotension, abdominal pain, hyponatraemia and hyperkalaemia. CT/MRI suspect for bilateral adrenal haemorrhage. HIT not proven. | Baseline cortisol: 1.5 µg/dl<br>No cortisol response to ACTH. ACTH 1763 pg/mL | AAI caused by heparin-induced BAH. |
| 62<br>Ogino J. | 54-year old woman with sudden abdominal and left back pain. CT: bilateral adrenal enlargement and haemorrhage. | Baseline cortisol: 10.7 µg/dl<br>ACTH 26.5 pg/mL | Idiopathic BAH with normal adrenal function. |
| 63<br>Chronopoulos E. | 73-year old man on subcutaneous heparin after knee arthroplasty, developing fever and abdominal pain. CT: high-density mass in left adrenal suggestive for haematoma. | Baseline cortisol: 16 µg/dl | Anticoagulation-induced UAH with normal adrenal function. |
| 64<br>McNicol RE. | 67-year old man, vague abdominal pain and hyponatraemia after rectal surgery, followed by wound infection and anastomotic leakage. CT: suspect for adrenal haematomas. | Baseline cortisol: 2.5 µg/dl<br>Described: 'Blunted' response to ACTH. | AAI due to postoperative and sepsis-induced BAH. |

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| 65<br>Leong M. | 57-year old man with traumatic brain injury. Develops hypotension over days and renal tenderness. CT: adrenal enlargement suspect for BAH. | Baseline cortisol: 4.2 µg/dl µg/dl | AAI due to BAH following traumatic brain injury. |

Abbreviations: BAH, bilateral adrenal haemorrhage; UAH, unilateral adrenal haemorrhage; AAI, absolute adrenal insufficiency; PAH, partial adrenal insufficiency; CT, computer tomography; MRI, magnetic resonance imaging; ACTH, adrenocorticotropic hormone; HIT, heparin-induced thrombocytopenia; s.c., subcutaneous; i.v., intravenous. Cortisol : 1 µg/dl = 27.6 nmol/L.