USE OF STEROIDS IN SEPSIS A TALE OF TWO TRIALS

Dr Jamie Hornsby
ST7 Respiratory, General and Intensive Care Medicine

STORY SO FAR…..

- First double-blind, multicentre trial in use of hydrocortisone in the management of severe infections reported in 1963
- 1980 – Randomised controlled trials showed high dose methylprednisolone (30mg/kg) was associated with higher morbidity and mortality
- 2002 and 2008 (CORTICUS) – 2 RCTs showed earlier reversal of shock but conflicting evidence with regards to mortality
- 2015 – Cochrane review of 33 RCT's accounting for 4268 patient with sepsis Corticosteroids reduced 28 day mortality RR 0.87 (CI) 0.76-1.00 (low quality of evidence)

STORY SO FAR…..

- 2015 – Systematic review of 35 trials randomising 4682 patients – no statistically significant effect was found for any dose of steroids vs placebo/no intervention RR 0.89 CI 0.74-1.08
- **Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016**
  - 'We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).'

THE TWO TRIALS

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Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

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- Trail Design: Investigator initiated, pragmatic, double blind, parallel-group randomised controlled trial
- Participating centres: 69 medical/surgical ITUs: Australia (45),UK (12), New Zealand (8), Saudi Arabia(3), Denmark (1)
- Intervention: Intravenous infusions of hydrocortisone with matched placebo in patients with septic shock undergoing mechanical ventilation
- Inclusion criteria:
  - Adults (≥18 years)
  - documented or strong clinical suspicion of infection
  - fulfilled two or more criteria of the systemic inflammatory response syndrome
  - Undergoing mechanical ventilation
  - Treated with vasopressors or inotropic agents for a minimum of 4 hours up to and at time of randomisation

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- Exclusion criteria:
  - Likely to receive treatment with a systemic glucocorticoid for indication other than septic shock
  - Received etomidate
  - Considered likely to die from a pre-existing disease within 90 days of randomisation
  - Treatment limitations in place
  - Met inclusion criteria for more than 24 hours prior to consideration
- Randomisation
  - Minimisation algorithm stratified according to participating centre and according to medical or surgical admission

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- Primary Outcomes:
  - Death from any cause 90 days after randomisation
- Secondary Outcomes:
  - Death from any cause 28 days after randomisation
  - Time to resolution of shock
  - Recurrence of shock
  - Length of ICU and Hospital Stay
  - Frequency and Duration of mechanical ventilation
  - Frequency and Duration of treatment with renal replacement therapy
  - Incidence of new onset bacteraemia or fungemia between 2 and 14 days after randomisation
  - Receipt of blood transfusion in the ICU

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- Power calculation
  - 3800 patients provide trial with 90% power to detect absolute difference in all-cause mortality from an estimated baseline mortality of 33% at alpha level of 0.05

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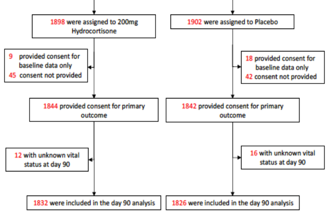

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Hydrocortisone (N=1853)	Placebo (N=1860)
Age — yr	62.3±14.9	62.7±15.2
Male sex — no./total no. (%)	1119/1853 (60.4)	1140/1860 (61.3)
Weight — kg	85.8±26.6	85.6±26.3
Admission type — no./total no. (%)†		
Medical	1273/1849 (68.8)	1266/1857 (68.2)
Surgical	576/1849 (31.2)	591/1857 (31.8)
APACHE II score‡		
Median	24.0	23.0
Interquartile range	19.0–29.0	18.0–29.0
Therapy at baseline — no./total no. (%)§		
Mechanical ventilation	1845/1849 (99.8)	1855/1857 (99.9)
Inotropes or vasopressors	1843/1853 (99.5)	[illegible]/1860 (99.7)
Norepinephrine	[illegible]	[illegible]
Vasopressin	280/1853 (15.1)	321/1860 (17.3)
Epinephrine	134/1853 (7.2)	113/1860 (6.1)
Other	157/1853 (8.5)	173/1860 (9.3)
Antimicrobial agent	1817/1848 (98.3)	1821/1857 (98.1)
Renal-replacement therapy	228/1849 (12.3)	242/1857 (13.0)
Physiological variables¶		
Heart rate — beats/min	96.0±21.6	95.0±20.9
Mean arterial pressure — mm Hg	72.5±8.2	72.2±8.3
Central venous pressure — mm Hg	12.0±5.2	12.1±5.3
Lowest mean arterial pressure — mm Hg	57.3±8.5	57.1±9.1
Highest lactate level — mg/dl	34.2±29.1	34.5±28.2
Highest bilirubin level — mg/dl	1.7±2.4	1.7±2.4
Highest creatinine level — mg/dl	2.2±2.0	2.1±1.7
Lowest $Pa_{O_2}:Fi_{O_2}$	164.6±91.3	166.4±91.9
Highest white-cell count — cells ×10^{-9}/liter	17.4±11.4	17.8±14.7
Primary site of infection — no./total no. (%)		
Pulmonary	623/1844 (33.8)	677/1854 (36.5)
Abdominal	477/1844 (25.9)	467/1854 (25.2)
Blood	316/1844 (17.1)	325/1854 (17.5)
Skin or soft tissue	137/1844 (7.4)	116/1854 (6.3)
Urinary	146/1844 (7.9)	133/1854 (7.2)
Other	145/1844 (7.9)	136/1854 (7.3)
Time from ICU admission to randomization — hr	26.1±70.7	28.9±72.8
Time from shock onset to randomization — hr	20.9±91.9	21.2±83.4
According to subgroup — no./total no. (%)		
Catecholamine dose >15 μg/min	981/1834 (53.5)	1013/1832 (55.3)
Pulmonary sepsis	805/1853 (43.4)	840/1860 (45.2)

Table 1. (Continued.)

Characteristic	Hydrocortisone (N=1853)	Placebo (N=1860)
APACHE II score ≥25	[illegible] (45.9)	800/1856 (43.1)
Time from shock onset to randomization		
<6 hr	357/1842 (19.4)	349/1851 (18.9)
6 to <12 hr	516/1842 (28.0)	495/1851 (26.7)
12 to <18 hr	441/1842 (23.9)	427/1851 (23.1)
18 to 24 hr	528/1842 (28.7)	580/1851 (31.3)

No significant differences between groups

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- Primary Outcome
  - No difference in mortality at 90 days
    - Hydrocortisone group 511 of 1832 (27.9%)
    - Placebo group 526 of 1828 (28.8%)
    - OR 0.95 95%CI 0.82 – 1.10 P=0.50

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- Secondary Outcome
  - Time to resolution of shock shorter in hydrocortisone group
    - HCT median 3days IQR 2 – 5 vs Placebo median 10 days IQR 5 - 30 (HR 1.32; 95% CI, 1.23 to 1.41; P<0.001)
  - Time to discharge from ICU less in hydrocortisone group
    - HCT median 10 days IQR 5 -30 vs Placebo median 12 days IQR 6 – 42 (HR 1.14; 95% CI, 1.06 to 1.23;)

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- Secondary Outcome
  - Fewer patients in the Hydrocortisone group received a blood transfusion (37.0% vs 41.7% odd ratio, 0.82; 95% CI, 0.72 – 0.94; P=0.004)
  - No Significant difference between groups:
    - Rate of recurrence of shock
    - Rate of development of new-onset bacteraemia or fungemia

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- Adverse Outcomes:

Table 3. Adverse Events.*

Adverse Event	Hydrocortisone (N=1835)	Placebo (N=1829)
No. of patients with event	21	6
No. of events		
Total adverse events	27	6
Hyperglycemia	6	3
Hypernatremia	3	0
Hyperchloremia	1	0
Hypertension	3	0
Bleeding	2	1†
Encephalopathy	3	0
Leukocytosis	2	0
Myopathy‡	3†	0
Septic arthritis	1	0
Ischemic bowel	1†	0
Abdominal-wound dehiscence	0	1†
Circulatory shock	1†	0
Thrombocytopenia	1	0
Miscellaneous	0	1

B Subgroup Analysis of Death at 90 Days

Subgroup	Hydrocortisone no. of patients with event/total no. of patients (%)	Placebo	Odds Ratio (95% CI)	P Value for Interaction
Sex				0.53
Male	312/1106 (28.2)	336/1122 (29.9)	0.92 (0.76–1.10)	
Female	199/726 (27.4)	190/704 (27.0)	1.01 (0.80–1.28)	
Admission type				0.73
Surgical	125/568 (22.0)	138/580 (23.8)	0.91 (0.69–1.21)	
Medical	386/1264 (30.5)	388/1245 (31.2)	0.97 (0.81–1.15)	
Catecholamine dose				0.25
≤15 μg/min	224/968 (23.1)	228/995 (22.9)	1.02 (0.82–1.26)	
>15 μg/min	281/849 (33.1)	291/805 (36.1)	0.86 (0.70–1.05)	
Site of sepsis				0.63
Pulmonary	243/799 (30.4)	250/828 (30.2)	0.99 (0.80–1.23)	
Other	268/1033 (25.9)	276/998 (27.7)	0.92 (0.76–1.12)	
APACHE II score				0.17
≥25	326/840 (38.8)	297/785 (37.8)	1.01 (0.83–1.24)	
<25	184/990 (18.6)	229/1039 (22.0)	0.82 (0.66–1.02)	
Time from shock onset to randomization				0.08
<6 hr	110/352 (31.2)	96/344 (27.9)	1.16 (0.83–1.61)	
6 to <12 hr	127/511 (24.9)	153/486 (31.5)	0.71 (0.54–0.94)	
12 to <18 hr	119/437 (27.2)	106/423 (25.1)	1.13 (0.83–1.54)	
≥18 hr	154/525 (29.3)	167/566 (29.5)	0.99 (0.76–1.29)	

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- Authors Conclusions:
  - Steroids did not reduce the 90 day mortality
  - Observed a more rapid resolution of shock and lower incidence of blood transfusion (hypothesis generating)
  - More adverse events in hydrocortisone group but did not affect patient centred outcomes
  - Central randomisation process that was blinded and independently verified
  - Population with a substantial risk of death
  - Intervention was successfully administered in both groups

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- Authors Conclusions:
  - Adverse events were not standardised and judged by the treating clinicians to be related to the trial
  - Did not collect data on all possible secondary infections
  - Did not assess long term neuromuscular weakness

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Highest bilirubin level — mg/dl	1.7±2.4	1.7±2.4
Highest creatinine level — mg/dl	2.2±2.0	2.1±1.7
Lowest Pa_{O_2}:Fi_{O_2}	164.6±91.3	166.4±91.9
Highest white-cell count — cells $\times 10^{-9}$/liter	17.4±11.4	17.8±14.7


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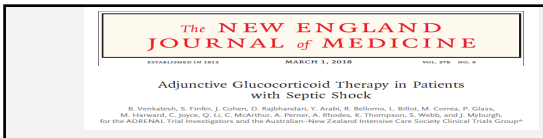
1. Did the trial address a clearly focused issue? *Yes*
2. Was the assignment of patient to treatments randomised? *Yes*
3. Were all if the patients who entered the trial properly accounted for at it's conclusion? *Yes*
4. Were patients, health workers and study personnel 'blind' to the treatment? *Yes*
5. Were the groups similar at the start of the trial? *Yes*
6. Aside from the experimental intervention, were the groups treated equally? *Can't tell*
7. How large was the treatment effect? *Treatment effect w.r.t time to shock resolution was significant*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8. How precise was the estimate of the treatment effect? *For time to shock resolution quite precise*
9. Can the results be applied to the local population, or in your context? *Yes, a pragmatic trial in a population that is generalisable to our unit*
10. Were all clinically important outcomes considered? *No more attention could have been applied to standardising treatment and adverse events*
11. Are the benefits worth the harms and costs? *Can't tell, a negative trial for mortality and most other end points other than shock resolution and ICU stay.Adverse events are more in the intervention group which may suggest potential harm might outweigh the benefit*


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ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

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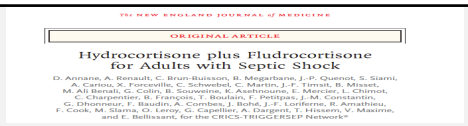
- Trail Design: Investigator initiated, placebo controlled trial with four parallel groups organised in a 2x2 factorial design.
- Participating centres: 34 Intensive Care Units in France
- Intervention:
  - 50mg Hydrocortisone (HCT) IV 6 hourly and Fludrocortisone (FCT) 50µg daily via NG tube
  - Drotrecogin alfa (activated) (DAA)
  - Both
  - Placebo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- Inclusion criteria:
- Adults
- Admitted to ICU < 7 days
- Indisputable or probable septic shock for <24 hours
  - Clinically or microbiologically documented infection
  - SOFA score >=3 for >=2 organs >=6hours
  - Treatment for >=6 hours with catecholamine's to maintain MAP >=65mmHg


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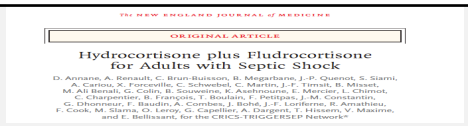
- Exclusion criteria (DAA Specific):
  - Surgical Procedure <= 7days
  - Gastrointestinal bleeding <=6 weeks
  - Chronic Liver disease
  - Trauma <= 3months
  - Any Intracranial mass
  - Stroke or head injury in last 3 months
  - Thrombocytopenia
  - Formal anticoagulation necessary
  - Any other increased risk of bleeding
  - Known hypersensitivity to DAA
- Exclusion criteria (General):
  - Pregnancy or breast feeding
  - Patients with palliative goals
  - Underlying fatal (<=1month) condition
  - Patients already taking cotricosteriods (30mg Prednisolone eq. >1month)
  - No affiliation to social security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- Randomisation: Randomization was centralized, through a secured Web site, and stratified according to centre, using permutation blocks of 8 to receive HCT&FCT, DAA, combination of all 3 drugs, Placebo
- Power calculation:
  - Anticipated 90 days mortality of 45% with patients with septic shock.
  - 2x2 factorial design with a two sided formulation 320 patient were needed in each group (1280 in total)
  - Absolute difference in 90 day mortality of 10% with an alpha 0.05 and power 95%

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- Primary Outcome:
  - 90 day all-cause mortality
- Secondary Outcomes:
  - All cause mortality at ICU discharge
  - Hospital Discharge at day 28 or day 180
  - Percentage of patient in whom care was withheld or withdrawn
  - Percentage of patients weaned from vasopressors at day 28 or day 90
  - Time to weaning of vasopressors
  - Number of days patients were alive and free of vasopressors up to day 28 or 90

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- Secondary Outcomes:
  - Percentage of patient weaned from mechanical ventilation at day 28 and day 90
  - Percentage of patients with a total SOFA score below 6 at day 28 and day 90
  - Percentage of patients discharged from ICU or hospital up to day 28 or 90
  - Time to discharge from the ICU and hospital
  - ICU-free and hospital free days up to day 28 and day 90
- Safety outcomes
  - Superinfection up to day 180
  - GI bleeding up to day 28
  - Hyperglycaemia up to day 7
  - Neurological sequelae (cognitive impairment and muscle weakness) ICU and Hospital discharge

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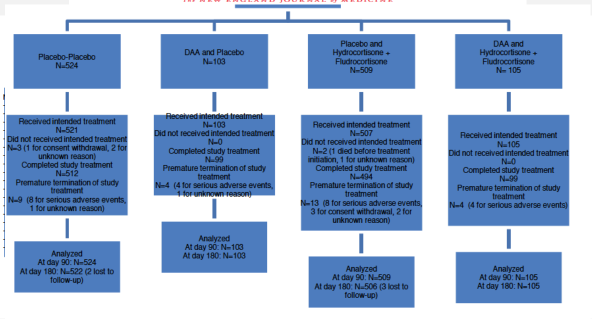

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N=627)	Hydrocortisone plus Fludrocortisone (N=614)	All Patients (N=1241)
Male sex — no./total no. (%)	424/626 (67.7)	402/614 (65.5)	826/1240 (66.6)
Age — yr†	66±15	66±14	66±14
Admission from a medical ward — no./total no. (%)	499/616 (81.0)	495/601 (82.4)	994/1217 (81.7)
SAPS II‡	56±19	56±19	56±19
SOFA score§	11±3	12±3	12±3
Community-acquired infection — no./total no. (%)	459/608 (75.5)	468/602 (77.7)	927/1210 (76.6)
Site of infection — no./total no. (%)¶			
Unknown	18/626 (2.9)	11/614 (1.8)	29/1240 (2.3)
Lung	363/626 (58.0)	373/614 (60.7)	736/1240 (59.4)
Abdomen	68/626 (10.9)	[illegible]	142/1240 (11.5)
Urinary tract	[illegible]	[illegible]	[illegible]
Positive blood culture — no./total no. (%)	229/626 (36.6)	225/614 (36.6)	454/1240 (36.6)
Documented pathogen — no./total no. (%)	441/626 (70.4)	450/614 (73.3)	891/1240 (71.9)
Gram-positive bacteria — no./total no. (%)	228/626 (36.4)	235/614 (38.3)	463/1240 (37.3)
Gram-negative bacteria — no./total no. (%)	264/626 (42.2)	261/614 (42.5)	525/1240 (42.3)
Adequate antimicrobial therapy — no./total no. (%)	602/626 (96.2)	595/614 (96.9)	1197/1240 (96.5)
Vasopressor administration			
Epinephrine			
No. of patients	58	53	111
Dose — μg/kg/min	1.74±2.41	2.31±6.62	2.01±4.88
Norepinephrine			
No. of patients	552	534	1086
Dose — μg/kg/min	1.14±1.66	1.02±1.61	1.08±1.63
Mechanical ventilation — no./total no. (%)	569/623 (91.3)	567/614 (92.3)	1136/1237 (91.8)
Renal-replacement therapy — no./total no. (%)	168/598 (28.1)	161/596 (27.0)	329/1194 (27.6)

No significant differences between groups

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- Trial was stopped twice:
  - Once when Xigris was withdrawn from the market (Oct 25th 2011 – May 12 2012)
  - Second time at the request of data and safety monitoring board (July 22nd 2014 - Oct 7,2014) to check quality of trial agents and the distribution of serious adverse events

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- Primary Outcome (All cause mortality at day 90):
  - Hydrocortisone-Fludrocortisone group 264 of 614 patients died
    - (43.0%; 95% CI 39 – 47%)
  - Placebo group 308 of 627 patients
    - (49.1%; 95% CI, 45.1 to 53.)
  - Relative Risk of death 0.88 (95% CI, 0.78 to 0.99) in favour of intervention
  - Fragility Index = 3

Table 2. Trial Outcomes.*

Outcome	Placebo (N=627)	Hydrocortisone plus Fludrocortisone (N=614)	All Patients (N=1241)	Relative Risk (95% CI)†	P Value
Primary outcome: death from any cause at day 90 — no. (%)	308 (49.1)	264 (43.0)	572 (46.1)	0.88 (0.78–0.99)	0.03
Secondary outcomes					
Death from any cause					
At day 28 — no. (%)	244 (38.9)	207 (33.7)	451 (36.3)	0.87 (0.75–1.01)	0.06
At ICU discharge — no./total no. (%)	257/627 (41.0)	217/613 (35.4)	474/1240 (38.2)	0.86 (0.75–0.99)	0.04
At hospital discharge — no./total no. (%)	284/627 (45.3)	239/613 (39.0)	523/1240 (42.2)	0.86 (0.76–0.98)	0.02
At day 180 — no./total no. (%)	328/625 (52.5)	285/611 (46.6)	613/1236 (49.6)	0.89 (0.79–0.99)	0.04
Decision to withhold or withdraw active treatment by day 90 — no./total no. (%)	61/626 (9.7)	64/614 (10.4)	125/1240 (10.1)	1.07 (0.77–1.49)	0.69
Vasopressor-free days to day 28‡					
Mean	15±11	17±11	16±11	—	<0.001
Median (IQR)	19 (1–26)	23 (5–26)	21 (2–26)		
Ventilator-free days to day 28‡					
Mean	10±11	11±11	11±11	—	0.07
Median (IQR)	4 (0–21)	10 (0–22)	8 (0–21)		
Organ-failure–free days to day 28‡					
Mean	12±11	14±11	13±11	—	0.003
Median (IQR)	12 (0–24)	19 (0–25)	15 (0–24)		

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Shown is the relative risk for hydrocortisone plus fludrocortisone versus placebo.
‡ Patients who died before day 28 were assigned zero free days.

Table 3. Adverse Events.*

Event	Placebo (N=627)	Hydrocortisone plus Fludrocortisone (N=614)	Relative Risk (95% CI)†	P Value
≥1 Serious event by day 180 — no./total no. (%)	363/626 (58.0)	326/614 (53.1)	0.92 (0.83–1.01)	0.08
≥1 Serious bleeding event by day 28 — no./total no. (%)	119/626 (19.0)	127/614 (20.7)	1.09 (0.87–1.36)	0.46
Gastroduodenal bleeding — no./total no. (%)	45/626 (7.2)	39/614 (6.4)	0.88 (0.58–1.34)	0.56
≥1 Episode of superinfection by day 180 — no./total no. (%)	178/626 (28.4)	191/614 (31.1)	1.09 (0.92–1.30)	0.30
Site of superinfection — no./total no. (%)				
Lung	116/626 (18.5)	127/614 (20.7)	1.12 (0.89–1.40)	0.34
Blood	48/626 (7.7)	49/614 (8.0)	1.04 (0.71–1.53)	0.84
Catheter-related	37/626 (5.9)	40/614 (6.5)	1.10 (0.71–1.70)	0.66
Urinary tract	33/626 (5.3)	40/614 (6.5)	1.24 (0.79–1.93)	0.35
Other	57/626 (9.1)	70/614 (11.4)	1.25 (0.90–1.74)	0.18
New sepsis — no./total no. (%)	122/626 (19.5)	134/614 (21.8)	1.12 (0.90–1.39)	0.31
New septic shock — no./total no. (%)	103/626 (16.5)	109/614 (17.8)	1.08 (0.84–1.38)	0.54
Hyperglycemia				
≥1 Episode of blood glucose levels ≥150 mg/dl by day 7 — no./total no. (%)	520/626 (83.1)	547/614 (89.1)	1.07 (1.03–1.12)	0.002
No. of days with ≥1 episode of blood glucose levels ≥150 mg/dl by day 7				
Mean	3.4±2.5	4.3±2.5	—	<0.001
Median (IQR)	3 (1–6)	5 (2–6)		
Neurologic sequelae by day 28 — no./total no. (%)‡				
Last MDRS score >1	130/626 (20.8)	153/614 (24.9)	1.20 (0.98–1.47)	0.08
Last MDRS score >3	92/626 (14.7)	108/614 (17.6)	1.20 (0.93–1.54)	0.17
Last MDRS score =5	65/626 (10.4)	73/614 (11.9)	1.15 (0.84–1.57)	0.40

* Plus–minus values are means ±SD.
† Shown is the relative risk for hydrocortisone plus fludrocortisone versus placebo.
‡ Neurologic sequelae were assessed according to the score on the Muscular Disability Rating Scale (MDRS), with a score of 1 indicating no deficit, 2 minor deficit with no functional disability, 3 distal motor deficit, 4 mild-to-moderate proximal motor deficit, and 5 severe proximal motor deficit.

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Authors Conclusions'

- Improvement in mortality at day 90 and 180 compared with placebo
- Duration in weaning from vasopressors (28days) and mechanical ventilation (90 days) and time improvement in SOFA score was shorted in intervention group
- Risk of secondary infections, GI bleeding and neurological sequelae was not increased by intervention
- Increase in hyperglycamia with intervention
- Imbalance between pathogens between two groups (more viral pathogens in intervention group)

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Authors Conclusions'

- Results in keeping with Cochrane review
- CORTICUS and HYPRESS did not include Fludrocortisone
- HYPRESS was not powered to address effects of hydrocortisone and excluded septic shock
- Patients in this trial were 'sicker' compared with CORTICUS
- Mortality rate in the placebo arm of the trial was close to that reported by the Sepsis-3 task force

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My comments:

- Effect of drotrecogin alpha can not be ignored and groups should not have been 'lumped together'
- Mortality rate of 49% in the placebo group at 90 days is high
- Majority of patient were admitted from a medical ward
- Standardised the complications using MEDRA classification of serious adverse events

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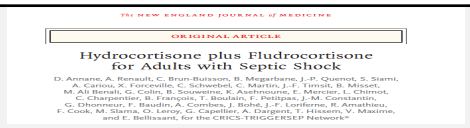
1. Did the trial address a clearly focused issue? *Yes*
2. Was the assignment of patient to treatments randomised? *Yes*
3. Were all if the patients who entered the trial properly accounted for at it's conclusion? *Can't tell – I am unclear what happened after with withdrawal of drotrecogin alpha*
4. Were patients, health workers and study personnel 'blind' to the treatment? *Yes (I think)*
5. Were the groups similar at the start of the trial? *Yes*
6. Aside from the experimental intervention, were the groups treated equally? *Can't tell ('treatment harmonized according to 2008 Surviving Sepsis Guidelines')*
7. How large was the treatment effect? *Appeared significant*



8. How precise was the estimate of the treatment effect? *Confidence intervals of primary outcome were close to limits and fragility index was 3*
9. Can the results be applied to the local population, or in your context? *Can't tell, mortality rate is quite high in the placebo population*
10. Were all clinically important outcomes considered? *No, although the adverse events were well recorded there was no consideration of the effect of drotrecogin alpha*
11. Are the benefits worth the harms and costs? *Yes perhaps; if concerns regarding high baseline mortality are resolved*

CONCLUSIONS

- Two large multicentre trials with conflicting results
- Problems identified with study showing benefit in intervention with Hydrocortisone-Fludrocortisone
- Possible harm to patients for intervention that has not been proven to benefit mortality
- It would be interesting to add these studies to the current systematic reviews
- I will probably continue to give low dose corticosteroids (with or without Fludrocortisone) in sepsis that is refractory to vasopressors