Journal Club

‘Adjunct prednisone therapy for patients with community acquired pneumonia’

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To do list

* Do we think it is relevant?
* How it's made (design)
* Well done?
* Who's in?
* Well done?
* Show me the money! (results)
* Well done?
* Say 'yes' (or no, or maybe)

Do we think it's relevant?

Goal/endpoints

Do we think it's relevant?

Primary endpoints

* Time to clinical stability
  * ≤37.8°C, HR ≤ 100/min, RR ≤ 24, systolic BP≥90, mental status, sat ≥90%

Do we think it's relevant?

Secundary endpoints

* Time to discharge
* Recurrence rate
* Re-admission (hospital)
* ICU admission
* Side effects corticosteroids
* Complications
* CAP scores
* Mortality

Do we think it's relevant?

YES

How it's made

* Randomised, double-blind, placebo-controlled
* Multicentre: 7 tertiary hospitals
* Switzerland

Inclusion

* ED or medical ward
* Age > 18 jaar
* CAP
  * New infiltrate CXR

  AND
  * Symptoms (≥1)
    * cough, sputum production, dyspnoea, T ≥38°C, abnormal breathing sounds or rales, WBC > 10000 µL or < 4000 µL

Exclusion

* No informed consent
* Active iv drug use
* Acute burns
* GI bleeding (<3 months)
* Adrenal insufficiency
* Prednisone 0.5mg/kg/day
* Pregnancy, breast feeding
* Severe immunosupression

Randomisation

* Baseline blood samples and nasal swabs
* Antibiotics according guidelines
* Computerized randomisation
  * Prednisone 50mg, 7days
  * Placebo, 7 days

Follow up

* Every 12hrs during admission
* Day 1, 3, 5, 7 and prior to discharge
  * Procalcitonine, CRP, WBC, glucose
* follow-up by telephone on day 30
  * infections, recurrent pneumonia, re-admission, new onset DM or insulin dependence, new onset hypertension

Do we think it's relevant?

YES

Well done?

1. Was the intervention randomised?

Well done?

1. Was the intervention randomised? **YES**

Eligible patients were **randomly assigned (1:1 ratio)** to receive either 50 mg of prednisone or placebo daily for 7 days. Randomisation was done with **variable block sizes of four to six** and patients were stratified at the time of study entry by study centre.

Well done?

2. Includer blinded to randomisation?

How good is good?

2. Includer blinded to randomisation

Yes

‘Patients, treating physicians, investigators, and data assessors were masked to treatment allocation.’

Well done?

3. Were patients and physicians blinded?

Well done?

3. Were patients and physicians blinded?

Yes

Well done?

4. Were the investigators/data assessors blinded?

Well done?

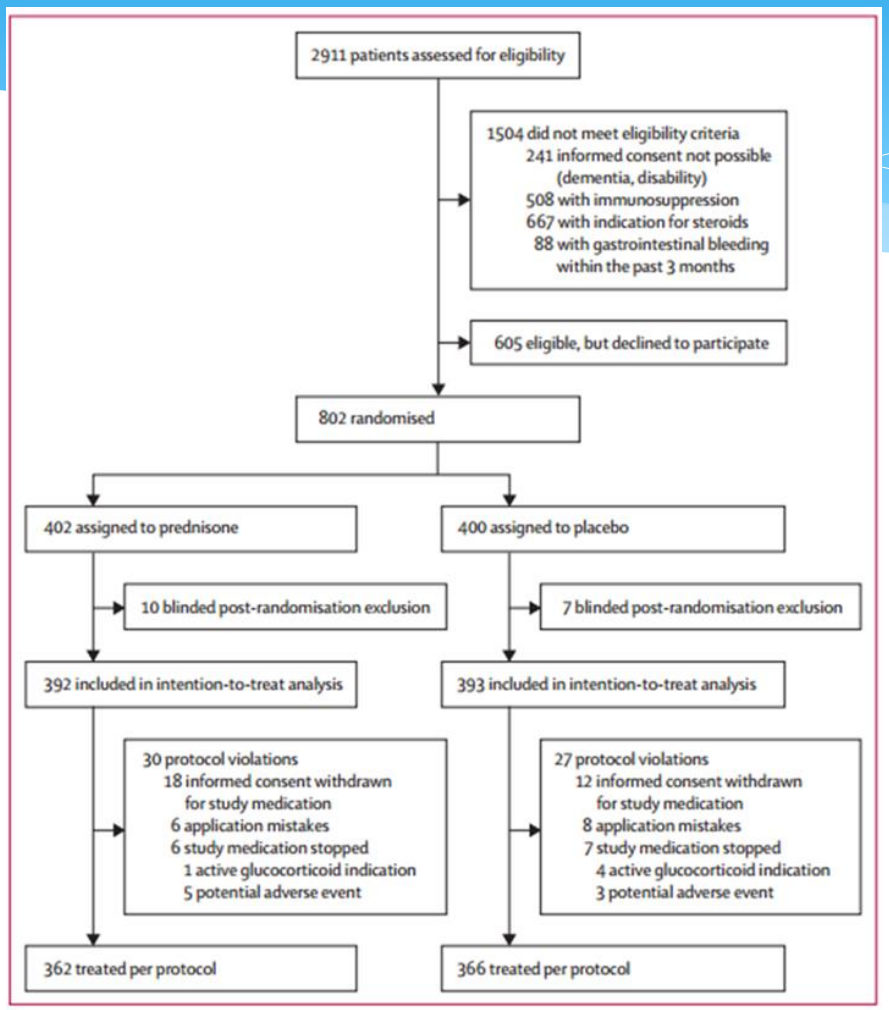
4. Were the investigators/data assessors blinded?

Yes/no

‘Patients, treating physicians, investigators, and data assessors were masked to treatment allocation.’

‘corticosteroid-induced hyperglycaemia might have led to unblinding in some patients.’

Who's in?


2911 patients assessed for eligibility
1504 did not meet eligibility criteria
241 informed consent not possible (dementia, disability)
508 with immunosuppression
667 with indication for steroids
88 with gastrointestinal bleeding within the past 3 months
605 eligible, but declined to participate
802 randomised
402 assigned to prednisone
400 assigned to placebo
10 blinded post-randomisation exclusion
7 blinded post-randomisation exclusion
392 included in intention-to-treat analysis
393 included in intention-to-treat analysis
30 protocol violations
18 informed consent withdrawn for study medication
6 application mistakes
6 study medication stopped
1 active glucocorticoid indication
5 potential adverse event
27 protocol violations
12 informed consent withdrawn for study medication
8 application mistakes
7 study medication stopped
4 active glucocorticoid indication
3 potential adverse event
362 treated per protocol
366 treated per protocol

Who is in?

5. Were the groups balanced?

Who's in?

	Prednisone (n=392)	Placebo (n=393)
General characteristics		
Age, years	74 (61–83)	73 (61–82)
Male sex	241 (61%)	246 (63%)
Clinical variables		
Days with symptoms	4·0 (2·0–7·0)	4·0 (2·0–7·0)
Temperature (°C)	37·6 (37·0–38·2)	37·6 (37·0–38·2)
Systolic blood pressure (mm Hg)	124 (110–140)	123 (110–140)
Heart rate (beats per min)	84 (74–95)	82 (72–96)
Respiratory rate (breaths per min)	20 (18–24)	20 (18–24)
SaO_2 (%)	95 (92–96)	94 (92–97)
Bacteraemia	39 (10%)	48 (12%)
Confusion	22 (6%)	29 (7%)
CAP score (points)*	43 (30–60)	46 (29–63)
Laboratory values		
Procalcitonin (ng/mL)	0·52 (0·18–2·51)	0·50 (0·17–2·63)
C-reactive protein (mg/L)	159 (80·3–245)	164 (79·1–250)
White-blood-cell count (cells per µL)	12 200 (8900–15 800)	11 900 (8700–15 600)
Glucose (fasting morning, mmol/L)	6·3 (5·4–7·8)	6·5 (5·8–7·7)
PSI score†		
PSI class I	47 (12%)	45 (11%)
PSI class II	72 (18%)	69 (18%)
PSI class III	71 (18%)	95 (24%)
PSI class IV	148 (38%)	132 (34%)
PSI class V	54 (14%)	52 (13%)
Total PSI score (points)	93 (63–115)	86 (65–110)
Comorbidities		
Diabetes mellitus (any type)	77 (20%)	78 (20%)
Insulin treatment	44 (11%)	35 (9%)
Chronic obstructive pulmonary disease	73 (19%)	60 (15%)
Heart failure	80 (20%)	62 (16%)
Cerebrovascular disease	38 (10%)	31 (8%)
Renal insufficiency	125 (32%)	126 (32%)
Neoplastic disease	29 (7%)	25 (6%)
Liver disease	17 (4%)	12 (3%)
Co-infections‡	45 (11%)	46 (12%)
Antibiotic pretreatment	84 (21%)	95 (24%)

Who is in?

5. Were the groups balanced?

Yes

‘Baseline characteristics of the two groups were well balanced.’

Show me the money!

	Prednisone (n=392)	Placebo (n=393)	Regression analysis	
			HR, OR, or difference (95% CI)	p value
Primary endpoint				
Intention-to-treat: time to clinical stability, days	3·0 (2·5–3·4)	4·4 (4·0–5·0)	HR 1·33 (1·15 to 1·50)	<0·0001
Per-protocol: time to clinical stability, days	3·0 (2·5–3·2)	4·4 (4·0–5·0)	HR 1·35 (1·16 to 1·56)	<0·0001
Secondary endpoints				
Time to effective hospital discharge, days	6·0 (6·0–7·0)	7·0 (7·0–8·0)	HR 1·19 (1·04 to 1·38)	0·012
Recurrent pneumonia	23 (6%)	18 (5%)	OR 1·30 (0·69 to 2·44)	0·42
Re-admission to hospital	32 (9%)	28 (8%)	OR 1·14 (0·67 to 1·93)	0·64
ICU admission	16 (4%)	22 (6%)	OR 0·72 (0·37 to 1·39)	0·32
Time to ICU admission, days	1 (1–1)	1 (1–1)	HR 0·73 (0·38 to 1·38)	0·33
Time in ICU, days	3 (2–4)	3 (1–12)	Difference –0·2 days (–8·7 to 8·2)	0·96
Death from any cause	16 (4%)	13 (3%)	OR 1·24 (0·59 to 2·62)	0·57
Time to death, days	8·0 (3·0–22·0)	9·0 (2·0–12·0)	HR 1·23 (0·59 to 2·55)	0·59
Total duration of antibiotic treatment, days	9·0 (7·0–11·0)	9·0 (7·0–12·0)	Difference –0·47 days (–1·21 to 0·27 days)	0·22
Intravenous antibiotic treatment, days	4·0 (3·0–6·0)	5·0 (3·0–7·0)	Difference –0·89 days (–1·57 to –0·20) days)	0·011
CAP score* at day 5, points	59 (41–78)	58 (40–74)	Difference 1·00 (–5·23 to 7·23)	0·75
CAP score* at day 30, points	83 (67–88)	84 (72–89)	Difference –1·00 (–4·38 to 2·38)	0·56

	Prednisone (n=392)	Placebo (n=393)	Regression analysis	
			OR (95% CI) or difference (95% CI)	p value
Incidence of pneumonia-associated complications until day 30				
Complications due to community-acquired pneumonia, any	11 (3%)	22 (6%)	0·49 (0·23 to 1·02)	0·056
Acute respiratory distress syndrome	0	1 (<1%)		
Empyema	1 (0·3%)	5 (1%)		
Respiratory failure, intubation	1 (<1%)	6 (2%)		
Persistence of pneumonia	6 (2%)	5 (1%)		
Mortality associated with community-acquired pneumonia*	5 (1%)	7 (2%)		
Incidence of adverse events compatible with corticosteroid use until day 30				
Weight change, kg	−1·0 (−3·0 to 1·0)	−1·0 (−3·0 to 0·4)	Difference 0·34 (−0·56 to 1·25),	0·46
Adverse events, any	96 (24%)	61 (16%)	1·77 (1·24 to 2·52)	0·0020
In-hospital hyperglycaemia needing new insulin treatment	76 (19%)	43 (11%)	1·96 (1·31 to 2·93)	0·0010
New insulin dependence at day 30	5 (1%)	1 (<1%)		
New hypertension at day 30	6 (2%)	2 (1%)		
Delirium	5 (1%)	2 (1%)		
Gastrointestinal bleeding	3 (1%)	4 (1%)		
Nosocomial infections	13 (3%)	14 (4%)		
Other adverse events until day 30				
Any	20 (5%)	34 (9%)	0·57 (0·32 to 1·00)	0·052
Falls with fracture	0	4 (1%)		
Cardiac decompensation	5 (1%)	10 (3%)		
Cardiac event	6 (2%)	3 (1%)		
Acute stroke	2 (1%)	2 (1%)		
Thromboembolic event	0	3 (1%)		
Other	9 (2%)	12 (3%)		

Show me the money!

* Shortens time to clinical stability (1.4 d)
* Earlier discharge (1d)
* Shortens time of iv antibiotics (1d)
* Less complications? (p0.52)

* Adverse events
* Hyperglycaemia

Well done?

6. Loss to follow-up?

Well done?

6. Loss to follow-up?

Yes/No

Well done?

7. Intention to treat analysis?

Yes/No

Well done?

8. Are the groups treated/followed up the same?

Well done?

8. Are the groups treated the same?

Yes

Well done?

9. Publication bias/selective publication excluded?

Well done?

9. Publication bias/selective publication excluded?

Yes?

Well done?

10. Influence of funding excluded

Yes

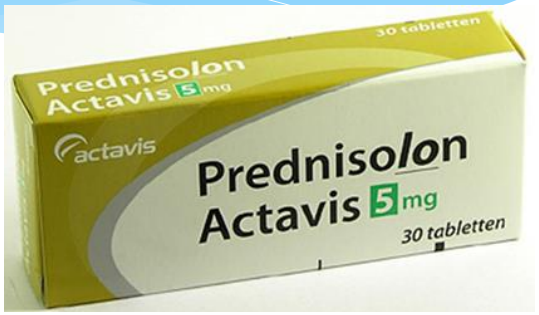
‘The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.’

Discussion

* Primary endpoints
  * Time to stability
  * Influence prednisolon (BP)
* Mortality low (power)
* Insulinetherapy vs 1 d earlier discharge
* Lower severity than previous studies
* Only admitted CAP

Say yes (or no, or maybe)

* Good study
* Some shortcomings
* Consider in case of CAP
* Depend it on risk on hyperglycaemia



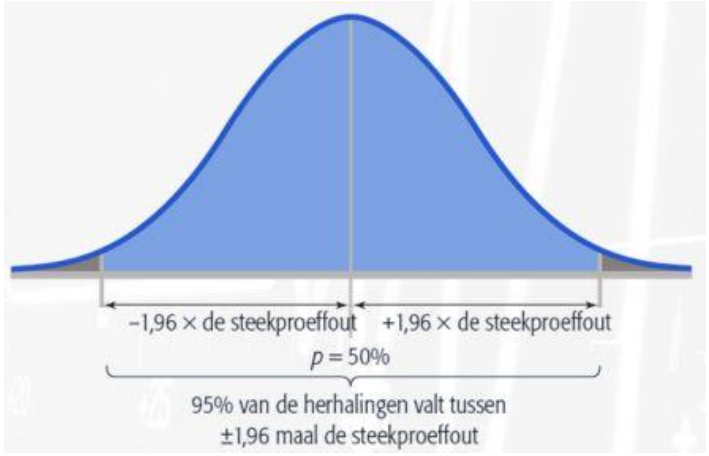
Item	+	–	?
1. Was de toewijzing van de interventie aan de patiënten gerandomiseerd?	●		
2. Degene die patiënten insluit hoort niet op de hoogte te zijn van de randomisatievolgorde. Was dat hier het geval?	●		
3. Waren de patiënten en de behandelaars geblindeerd voor de behandeling?	●		
4. Waren de effectbeoordelaars geblindeerd voor de behandeling?	●		
5. Waren de groepen aan het begin van de trial vergelijkbaar?	●		
Indien nee: is hiervoor in de analyses gecorrigeerd?			
6. Is van een voldoende proportie van alle ingesloten patiënten een volledige follow-up beschikbaar?	●		
Indien nee: selectieve loss-to-follow-up voldoende uitgesloten?			
7. Zijn alle ingesloten patiënten geanalyseerd in de groep waarin ze waren gerandomiseerd?	●		
8 Zijn de groepen, afgezien van de interventie, gelijk behandeld?	●		
9. Is selectieve publicatie van resultaten voldoende uitgesloten?	●		
10. Is ongewenste invloed van sponsoren voldoende uitgesloten?	●		

Statistiek

T-toets (of Student t-toets)

- Twee groepen vergelijken (independent samples t-test)
- 1 groep 2 momenten vergelijken (paired samples t-test)
- 1 groep vergelijken gemiddelde (one sample t-test)

* Nul hypothese
* Betrouwbaarheidsinterval
* Normale verdeelde grootheid



Statistiek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