

SUPPLEMENTARY TABLE 2 Comprehensive summary of published literature about corticosteroids in human Herpes Simplex Virus Encephalitis

| REFERENCE, DESIGN AND SAMPLE SIZE | ANTIVIRAL THERAPY | | | CORTICOSTEROID THERAPY | | | DISEASE ONSET AND COURSE | | | DISEASE OUTCOME | | |
|---|--------------------------|--|------------------|--|-------------------------|----------------------|--|--|---|---|---------------------|--|
| | DRUG AND DOSE | THERAPY ONSET | THERAPY DURATION | DRUG AND DOSE | THERAPY ONSET | THERAPY DURATION | CLINICAL / RADIOLOGICAL | VIRAL MARKERS | INFLAMMATORY/ EEG MARKERS | CLINICAL / RADIOLOGICAL | VIRAL / EEG MARKERS | INFLAMMATORY MARKERS |
| Habel et al 1972 ⁽⁴⁴⁾ 2 cases reported | N/A ^(A) | N/A | N/A | Case 1 Dexamethasone, IV 8 mg. followed by 4 mg Q6H | 3 d after symptom onset | 17 d | 3 d: vomiting, diarrhea. Unconscious, unresponsive, non-focal. Next hours: neck stiffness, left sided convulsions, fixed dilated pupils | Normal CSF EEG: Large-amplitude slow waves over both hemispheres. HSV complement-fixation titer rose from < 1/16 on day 1 to 1/2048 on day 38. | Dramatic effect on pupils. Regained consciousness over 48 h. Focal signs for one more week. 18 months later: walking and talking. Mild residual spasticity. | N/A | | |
| | | | | Case 2 Dexamethasone, IV 2 mg., then IM Q6H | 3 d after admission | 3 d | "Cold sore" on her lip, left-sided jacksonian convulsions for 1 week. Drowsy, irritable. Responded to pain. 3 d after admission: totally unresponsive, decerebrated. | | | | | CSF: Normal pressure, 20 lymphocytes/mm ³ , elevated proteins EEG: widespread synchronous waves, superimposed on irregular large-amplitude slow waves. |
| Upton et al 1971 ⁽⁴⁵⁾ Case report | N/A | N/A | N/A | Dexamethasone | N/A | N/A | N/A | N/A | N/A | Improved outcome. (Authors suggested "as early as possible" use of dexamethasone) | N/A | N/A |
| Kamei et al 2005 ⁽⁴⁶⁾ Case Series 45 patients | Acyclovir, IV 30 mg/kg/d | Day of admission (NR onset of illness) | 14 d | Not used (23 patients) | N/A | N/A | No difference in CT at 24 hrs of admission and MRI at 48 hrs | Positive: PCR, chemiluminescence assay, specific intrathecal HSV antibody synthesis and southern blot hybridization | No difference in EEG (PLEDs) ^(B) at 48 hrs | More patients with poor outcome (moderate, severe sequelae or death) * | N/A | |
| | | | | Dexamethasone or prednisolone (Dosage range: 40 – 96 mg/d) (22 patients) | Day of admission | Range: 2 d – 6 weeks | | | | "Predictor of good outcome" (complete recovery or mild sequelae) * | | |

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| | DRUG AND DOSE | THERAPY ONSET | THERAPY DURATION | DRUG AND DOSE | THERAPY ONSET | THERAPY DURATION | CLINICAL / RADIOLOGICAL | VIRAL MARKERS | INFLAMMATORY/ EEG MARKERS | CLINICAL/ RADIOLOGICAL | VIRAL / EEG MARKERS | INFLAMMATORY MARKERS |
| Nakano et al 2003 ⁽⁴⁷⁾ Case series 5 patients | Acyclovir, IV 1500 mg/d | N/A | N/A | Methylprednisolone, IV 1000 mg/d (3 patients) | 5 d after onset of illness | 3 d | Progressive disturbance of consciousness and other symptoms (tremor, rigidity, seizure) | > 4-fold elevation in anti-HSV antibody titer or neutralization reaction test during clinical course or presence of antiviral Ig M antibodies | N/A | Alert within 24 hrs, neurological symptoms gradually improved | N/A | |
| | | | | Methylprednisolone, IV 1000 mg/d (2 patients) | More than 3 weeks after onset of illness | 3 d | | | N/A | Disturbance of consciousness persisted (Repeated pulse therapy at 2 week intervals resulted in complete recovery) | | |
| Musallam et al 2007 ⁽⁴⁸⁾ Case report | Acyclovir, IV 1500 mg/m ² | Day of admission (NR onset of illness) | 21 d | Methylprednisolone, IV 1g/1.7 m ² | 9 d after admission | 3 d | <ul style="list-style-type: none"> ▪ Admission: focal seizure. ▪ 9th day: Deterioration: lethargy, aphasia, right hemiparesis | <ul style="list-style-type: none"> ▪ Admission: Positive CSF HSV-1 PCR. Viral load: 11,000 copies/mL ▪ 9th day viral load: 750 copies/mL | <ul style="list-style-type: none"> ▪ 9th day MRI: enlargement of edematous foci (parietal and frontal lobes, thalamus) | Became much more alert, started to move her right side, fever subsided. On discharge: fully alert. After 1 month: mild hemiparesis | N/A | |
| Mesker et al 2011 ⁽⁴⁹⁾ Case report | Acyclovir, IV 750 mg x 3 | Day of admission (6 days after onset of illness) | 21 d | Dexamethasone, IV 10 mg x 4 | 5 d after admission | 4 d | <ul style="list-style-type: none"> ▪ CT: hypodense R temporal lesion. ▪ 5th day after admission: fever rose, became drowsy | Positive CSF HSV-1 PCR | 5 th day: CT: hypodense lesion increased with new lesions in L hemisphere and Mesencephalon | Improved, residual deficient spatial orientation | N/A | |
| Lizarraga et al 2013 ⁽²¹⁾ Case report | Acyclovir, IV 10 mg/kg Q8H | Day of admission (3 weeks after onset of illness) | 21 d | Dexamethasone, IV 40 mg daily | 5 d after admission | 5 d | <ul style="list-style-type: none"> • CT: Right temporal hypodensity. • EEG: generalized background delta slowing. • 5th day after admission: no improvement | Positive CSF HSV-1 PCR | 5 th day: Larger, bilateral CT hypodensities. MRI: bilateral compromise of mesial temporal, orbitofrontal, cingular and insular lobes. | 72 hr later: improvement in level of consciousness, able to follow commands and produce sentences | N/A | |

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|--|-------------------------------|---|------|---------------------------------|------------------|-----|--|-----------------------------------|------------------|--|
| Martinez-Torres et al <small>(50)</small> ONGOING Multicenter randomized double-blind placebo-controlled clinical trial 208 – 450 patients | Acyclovir, IV 10 mg/kg Q8h | Day of admission (NR onset of illness) | 14 d | Dexamethasone, IV 40 mg/kg/d | Day of admission | 4 d | ONGOING (Day 0 and day 7 evaluations) | ONGOING (Positive CSF HSV PCR) | ONGOING (MRI) | ONGOING: <ul style="list-style-type: none"> ▪ Seizure (from day 0 to day 30) ▪ 6 months after randomization: neuropsychological testing, MRI ▪ 6 and 12 months after randomization: modified Rankin scale, Glasgow outcome scale, quality of life, seizures, mortality |
| | | | | Placebo | Day of admission | 4 d | | | | |

^A N/A Non-applicable or not reported

^B PLEDs Periodic lateralized epileptiform discharges

* Statistically significant difference (between both marked results)