OFTEN OVERLOOKED: IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

CHRISTOPHER K. ALVORD, MD

PGY-2, HAWAII ISLAND FAMILY MEDICINE RESIDENCY PROGRAM

HPI

- Setting: Primary Care Clinic
- Patient is a 53 year old man with a PMH of HIV presenting for hospital follow-up.
- He was admitted from 20 days for acute hypoxic respiratory failure due to PCP pneumonia which required intubation. His hospital course was complicated by CMV pneumonitis and fungal pneumonia detected with bronchoscopy with bronchial washings. He was treated with voriconazole, valganciclovir, Bactrim, and his Genvoya (HAART) was resumed. He was successfully extubated, however subsequently developed a right-sided pneumothorax after a cough episode. A chest tube was placed, his pneumothorax resolved, and his chest tube was removed. He was discharged on the antibiotic/antiviral/antifungal, and HAART agents mentioned above.

PAST MEDICAL HISTORY

- GERD: sometimes takes Pepcid
- PCP Pneumonia
- CMV Pneumonitis
- HFpEF (Echocardiogram from 06/2023: EF ~45-50%)
- HIV: Stopped Genvoya "sometime during COVID Pandemic." Specific reasons not disclosed.
- No surgical history
- Prior hospitalization as mentioned in HPI
- No allergies

Social: Never smoker, infrequent alcohol use, no recreational drug use

PHYSICAL EXAM

Vitals: T: 99F, HR 128, RR 40, BP 102/60

Pulmonary:

Tachypneic, speaking in complete sentences
Auscultation: clear to auscultation bilaterally with good aeration; No crackles, rhonchi or wheezes

Cardiovascular:

Rate: tachycardic (HR 123), Rhythm: regular rhythm, Heart Sounds: S1 normal and S2 normal

SUBSEQUENTLY…

Patient ambulated 100 feet, O2 saturations decreased to 85%

EKG in clinic: Sinus Tachycardia, 120bpm

Patient escorted to the emergency room for hypoxia and tachypnea.

IN EMERGENCY DEPARTMENT

Vitals: T 99, HR 122, RR 23, BP 88/64, O2 86%, RA; Improved to 96% on 4L NC

Cardiovascular: Regular Rate & Rhythm, Peripheral Pulses Strong and Equal,

Tachycardic, no murmurs, rubs, or gallops

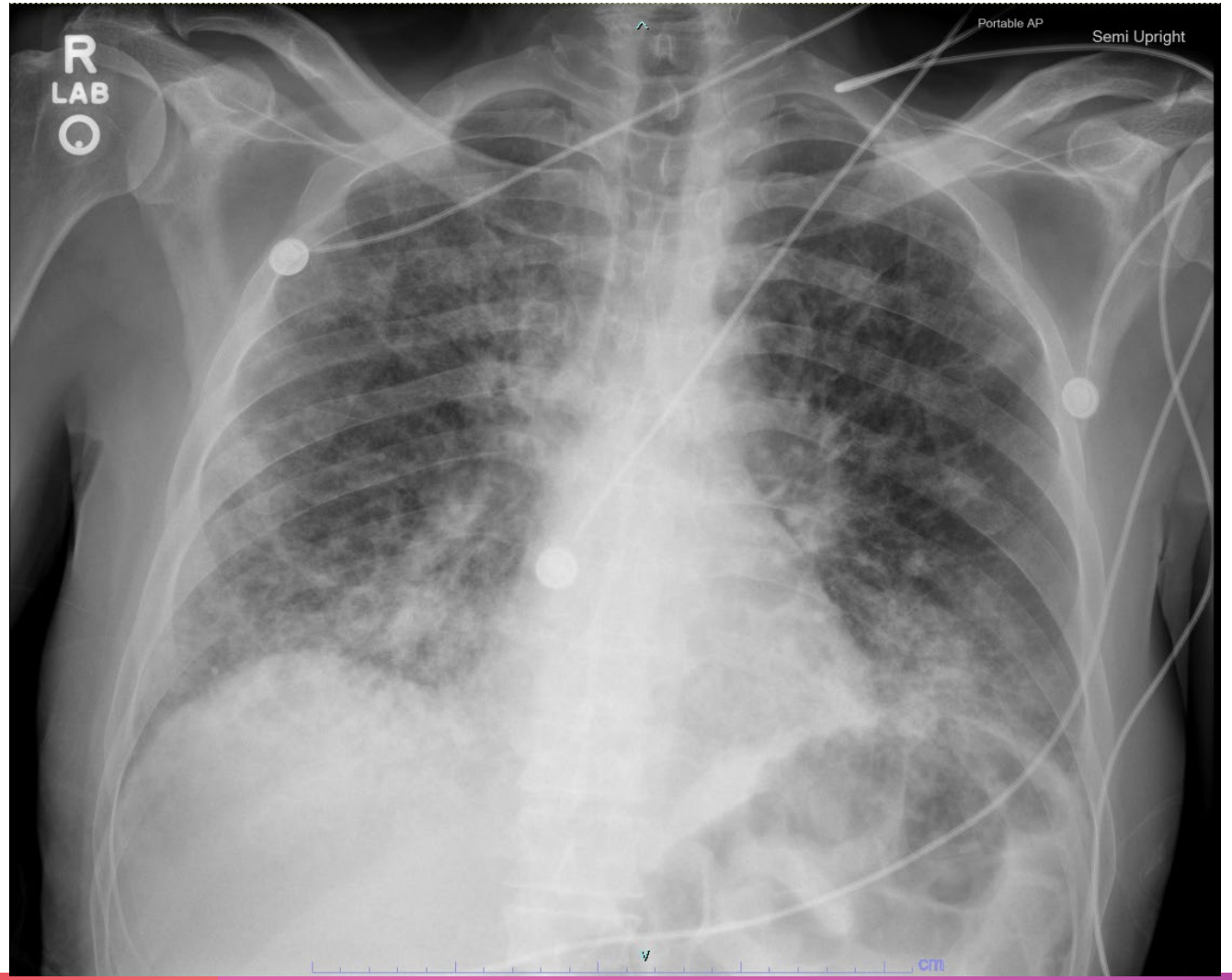
Respiratory: Crackles (crackles at the bases bilaterally and left mid lung field with tachypnea); No Wheezing or Rhonchi

Gastrointestinal: Soft and Normal BS; Not Tender

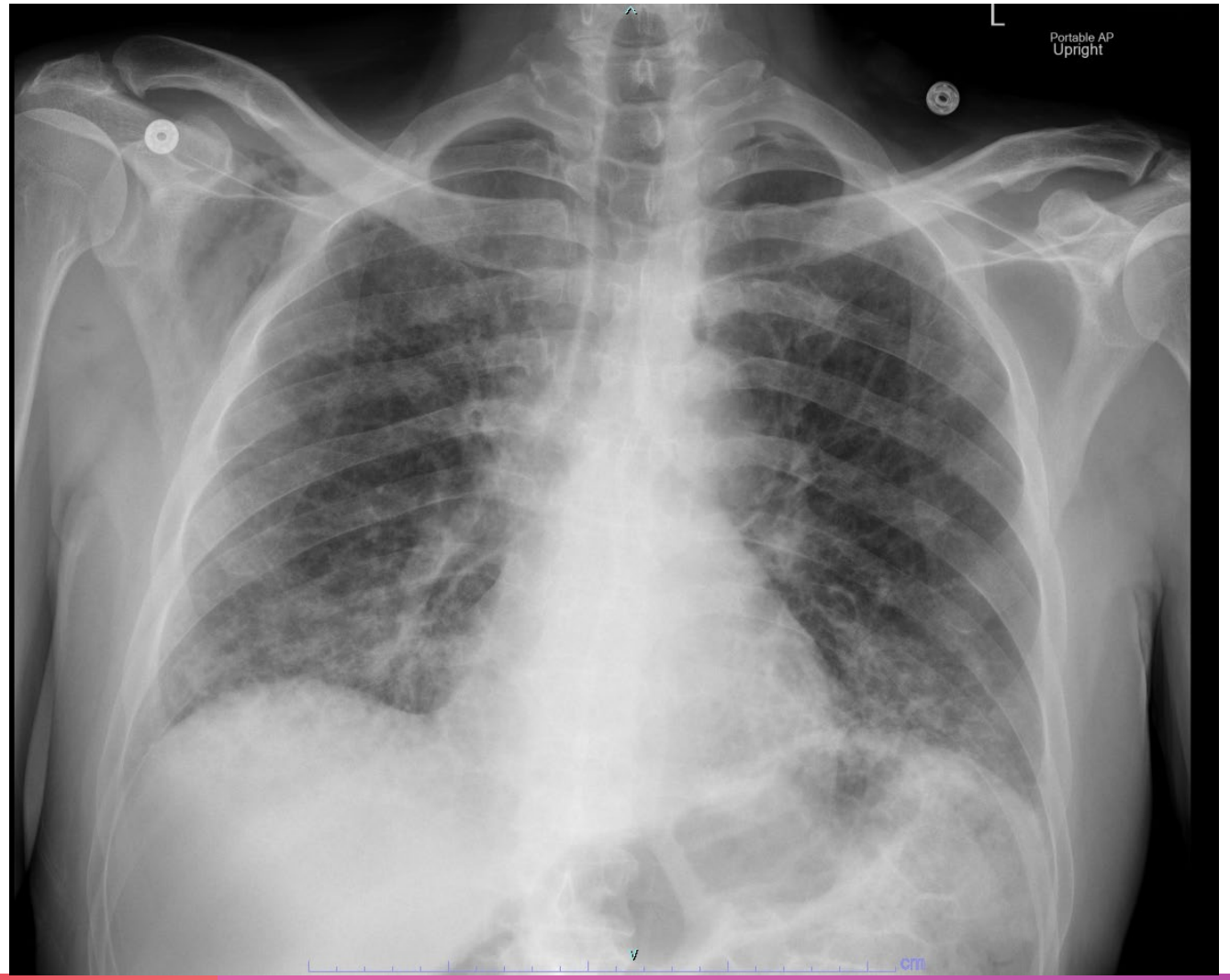
WORKUP

- CBC: Unremarkable
- CMP: Notable for mild AKI (Cr 1.55, baseline 1)
- ABG:
  - PH 7.49, PCO2 19, PO2 65
- Procalcitonin 2.6
- COVID/Flu: Both negative
- Not re-ordered, but of note: Last Absolute CD4 Count from 06/28/23: 7.0

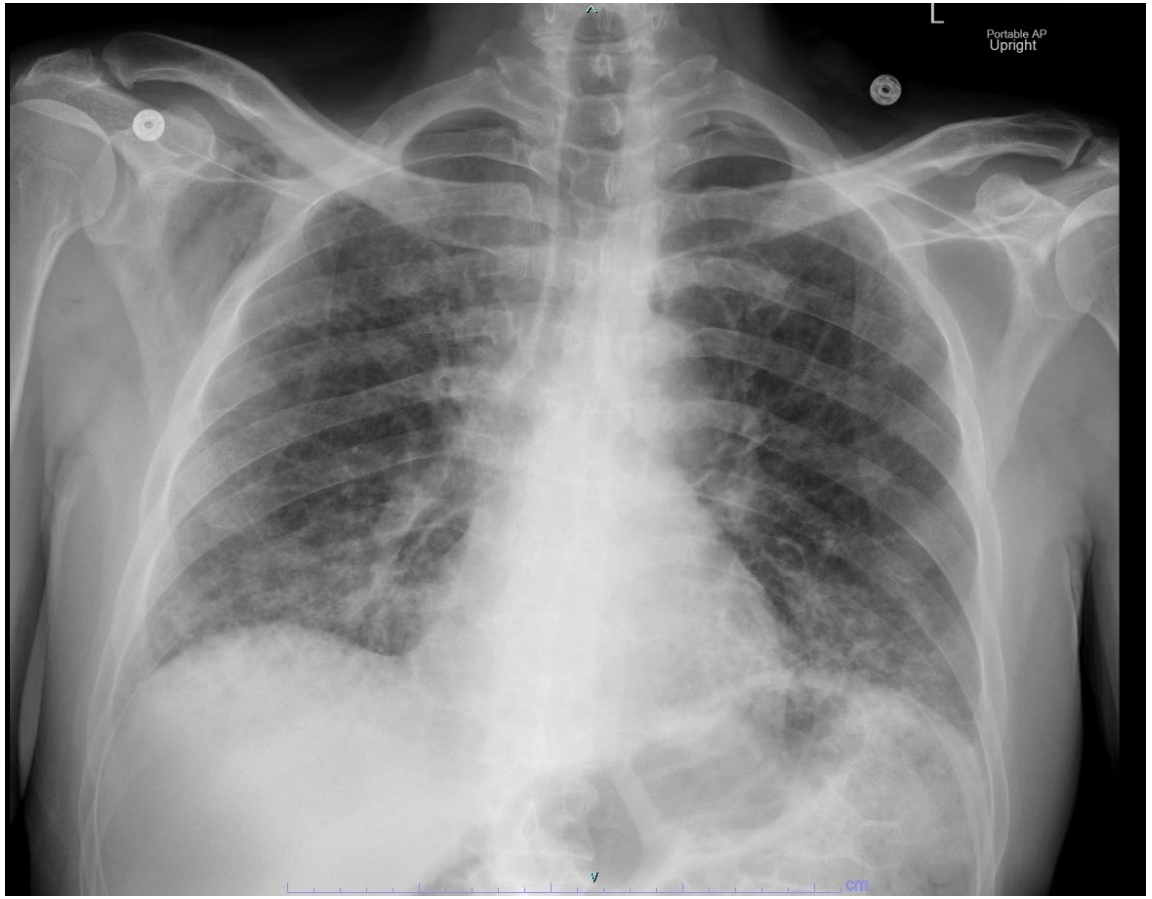
ADMISSION CHEST X-RAY



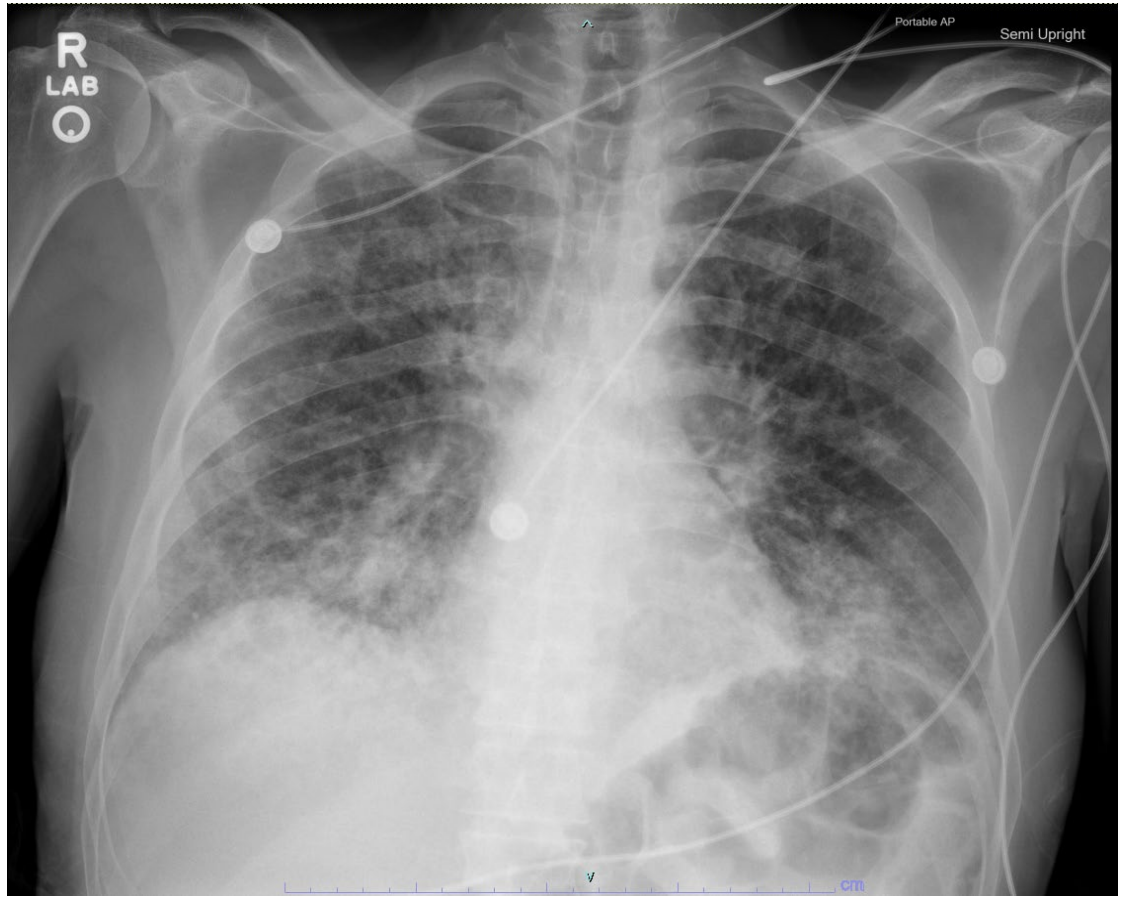
PREVIOUS CHEST X-RAY



CHEST X-RAY COMPARISON



Previous Chest X-ray



Current Chest X-Ray

ED COURSE

Patient met SIRS criteria (Temp, Tachypnea, Tachycardia, WBC <4) patient was given Bactrim IV, cefepime 1 g, vancomycin 1 g, methylprednisolone 40 mg, and 1 L of normal saline, maintained initially on 4L NC

HOSPITAL COURSE

To FMS Team, Patient reported adherence to prescribed medications

FMS consulted Infectious Disease and learned:

- Patient had recently followed up with ID two days prior to admission, had appeared well, disclosed discontinuing Valganciclovir prematurely (unclear why).
- Patient had also been completing prednisone taper; prescription not visible in hospital discharge summary

INFECTIOUS DISEASE RECOMMENDATIONS

Recommendations:

- Continue Bactrim at the PCP treatment dose
- Restart Valcyte 900 mg PO BID. Repeat CMV quantitative PCR again today or tomorrow
- Continue voriconazole 200 mg PO BID
- Continue Genvoya
- Continue vancomycin/cefepime
- Start prednisone 1-2 mg/kg daily for possible IRIS

INFECTIOUS DISEASE RECOMMENDATIONS

"If patient has a fairly rapid improvement over the next 48 hours then that would be clinically consistent with IRIS and it would be OK to stop antibiotics"

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

IRIS DEFINITION

"Immune reconstitution inflammatory syndrome (IRIS) is a state of hyperinflammatory response that usually occurs in the first six months of treatment of HIV/AIDS patients. It is a potential complication of the use of highly active antiretroviral therapy (HAART)."

Thapa S, Shrestha U. Immune Reconstitution Inflammatory Syndrome. [Updated 2023 Jan 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567803/

IRIS, CONTINUED

- Background: First observed in TB and Hansen's Disease patients who showed paradoxical worsening of symptoms after initiating treatment
  - IRIS also observed in:
    - Post-partum period
    - Solid Organ Transplant Patients when finishing Immunosuppression
    - Patients recovering from neutropenia
    - Patients discontinuing TNF-a inhibitors

PREVALENCE AND RISK FACTORS

- Prevalence: Estimated ~15-25% of HIV patients started on HAART experience IRIS
- Risk Factors:
  - 1. Starting HAART treatment at a younger age or in male patients has shown an association with an increased risk of developing IRIS
  - 2. CD4+T cell count less than 100 cells per microliter at the time of initiating HAART.
  - 3. An accelerated rise in CD4 count following treatment with HAART.
  - 4. Rapid HIV RNA viral suppression within ninety days of HAART increases the risk of immune reconstitution syndrome
  - 5. Pre-existing latent opportunistic infection with a high antigenic burden increases the risk and severity of IRIS.
  - 6. Initiating HAART within a short time interval (30 days) after completing treatment for opportunistic infection.

PATHOPHYSIOLOGY

- Mechanism: Imbalance between anti-inflammatory cytokines and pro-inflammatory cytokines that occurs rapidly after the recovery of immune function in HIV patients initiated on HAART.
- Improvement in CD4, CD8 T Cells leads to improvements in cell-mediated and antibody-mediated immunity, resulting in:
  - An excess pathogen-specific cellular immune response.
  - Decrease in the capacity of regulatory T cells to regulate and suppress inflammation.
  - Uncoupling of both innate and acquired immunity.

DIAGNOSTIC CRITERIA

- The patient should be HIV-positive.
- The patient should be receiving HAART with either a decrease in HIV-1 RNA level from baseline or an increase in CD4+ cells from baseline or both.
- Clinical symptoms should be consistent with an inflammatory process.
- Clinical course not consistent with:
  - Expected course of previously diagnosed OI.
  - Expected course of newly diagnosed OI.
  - Drug toxicity or side effects.

DIFFERENTIAL DIAGNOSIS

- Differential Diagnosis:
  - 1. Side effects of HAART therapy or anti-microbial treatment.
  - 2. Resistance to anti-microbial agents and progression of opportunistic infections (OI) as a result.
  - 3. Lack of adherence to anti-microbial agents leading to worsening of existing OI.
  - 4. New untreated opportunistic infections.

PREVENTION

- Screen for latent opportunistic infections in patients started on HAART:
  - PPD, Cryptococcal Antigen Test
- Steroid taper for high risk patients starting HAART

TREATMENT

- Supportive Care (hydrate, correct electrolytes, optimize nutritional status)
- Continue HAART
- Cover for opportunistic Infections
- Steroids for patients with acute hypoxic respiratory failure

- Prognosis: Most cases are mild, self-limiting, but complications may arise from severe CNS or pulmonary involvement.

HOSPITAL COURSE, CONTINUED

- After treating with 80mg prednisone, valganciclovir, voriconazole, Bactrim, continuing HAART:
- Patient weaned off O2 by 07/09/23 (day 2 of hospitalization)
- Ambulated by Respiratory Therapy 500 feet in hallway, O2 sat 92%
- Patient felt much improved, discharged home with plan for close outpatient follow up with Primary Care and Infectious disease

TAKE HOME POINTS

- IRIS is a possible complication of starting or resuming HAART for the management of HIV
- IRIS can resemble acute infection, leading to mis-diagnosis and delays in proper management
- IRIS is driven by immune dysregulation during the initiation of HAART
- Glucocorticoids should be considered in select cases
- Failure to recognize this condition further marginalizes an already marginalized demographic
- A good History and Physical can dramatically affect management decisions

I KA ʻŌLELO NŌ KE OLA,
I KA ʻŌLELO NŌ KA MAKE

IN LANGUAGE THERE IS LIFE,
IN LANGUAGE THERE IS DEATH

REFERENCES

Sansonetti P, Lagrange PH. The immunology of leprosy: speculations on the leprosy spectrum. Rev Infect Dis. 1981 May-Jun;3(3):422-69

Sun HY, Singh N. Immune reconstitution inflammatory syndrome in non-HIV immunocompromised patients. Curr Opin Infect Dis. 2009 Aug;22(4):394-402.

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