# Management of Children with Severe Influenza (H5N1, H1N1)


**By**

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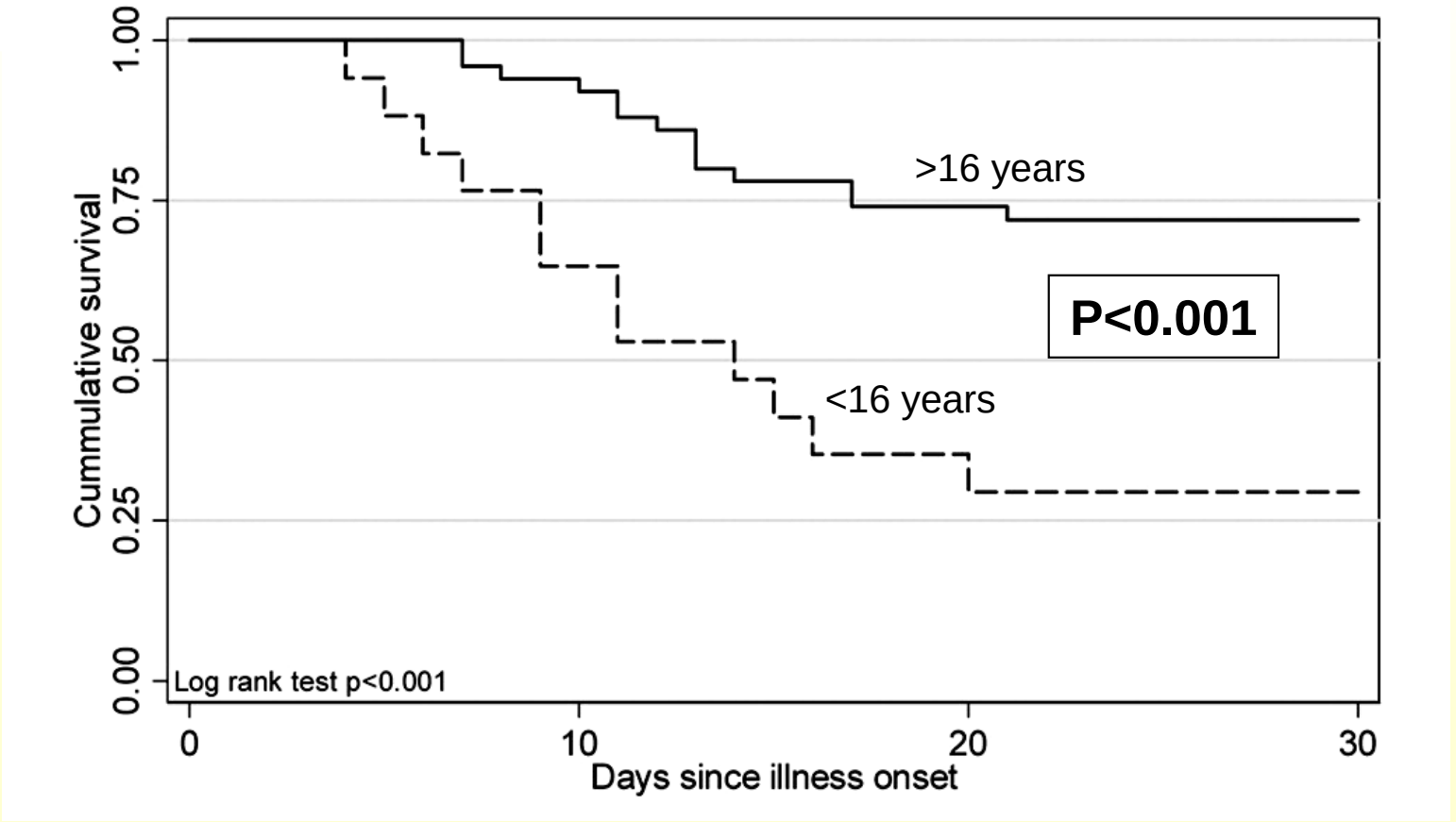
# What is the matter with influenza in children?

- Children acquire infection easily from day-care, school, and a also good spreader
- Young children handle infection less well
  - Higher incidence of pneumonia in children < 1 year of age
  - Children has less background immunity
- Children have higher potential of recovery and less underlying diseases
- H5N1: Children have similar severity but less mortality
- H1N1 (2009): Children has higher rate of illness and hospitalization but less ICU admission / mortality

# How a Child got Avian Influenza

# Clinical Features of Human Influenza A (H5N1) Infection in Vietnam: 2004–2006




**Survival plot for cases involving patients aged <16 years *(dashed line)*, compared with cases involving patients aged >16 years *(solid line)*, by duration since onset of illness.**

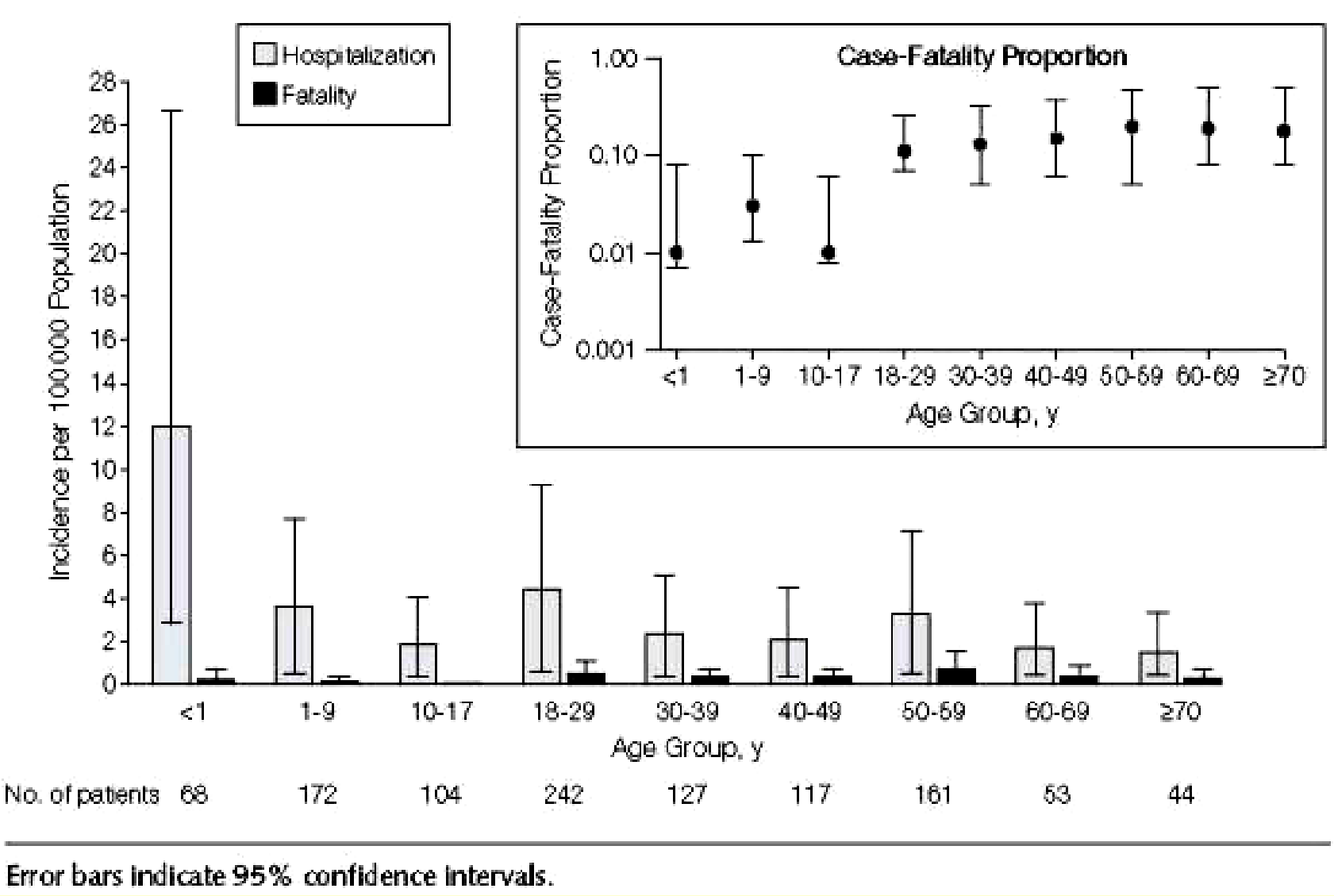
*Liem NT. CID 2009;48:1639-46.*

# Clinical Course of 642 Patients with Confirmed Novel Swine-Origin Influenza A (H1N1) Virus in Humans

| Hospitalization — no./total no. (%) | |
|---|---|
| Total | 36/399 (9) |
| Had infiltrate on chest radiograph | 11/22 (50) |
| Admitted to intensive care unit | 8/22 (36) |
| Had respiratory failure requiring mechanical ventilation | 4/22 (18) |
| Treated with oseltamivir | 14/19 (74) |
| Had full recovery | 18/22 (82) |
| Vaccinated with influenza vaccine during 2008–2009 season | 3/19 (16) |
| Died | 2/36 (6) |

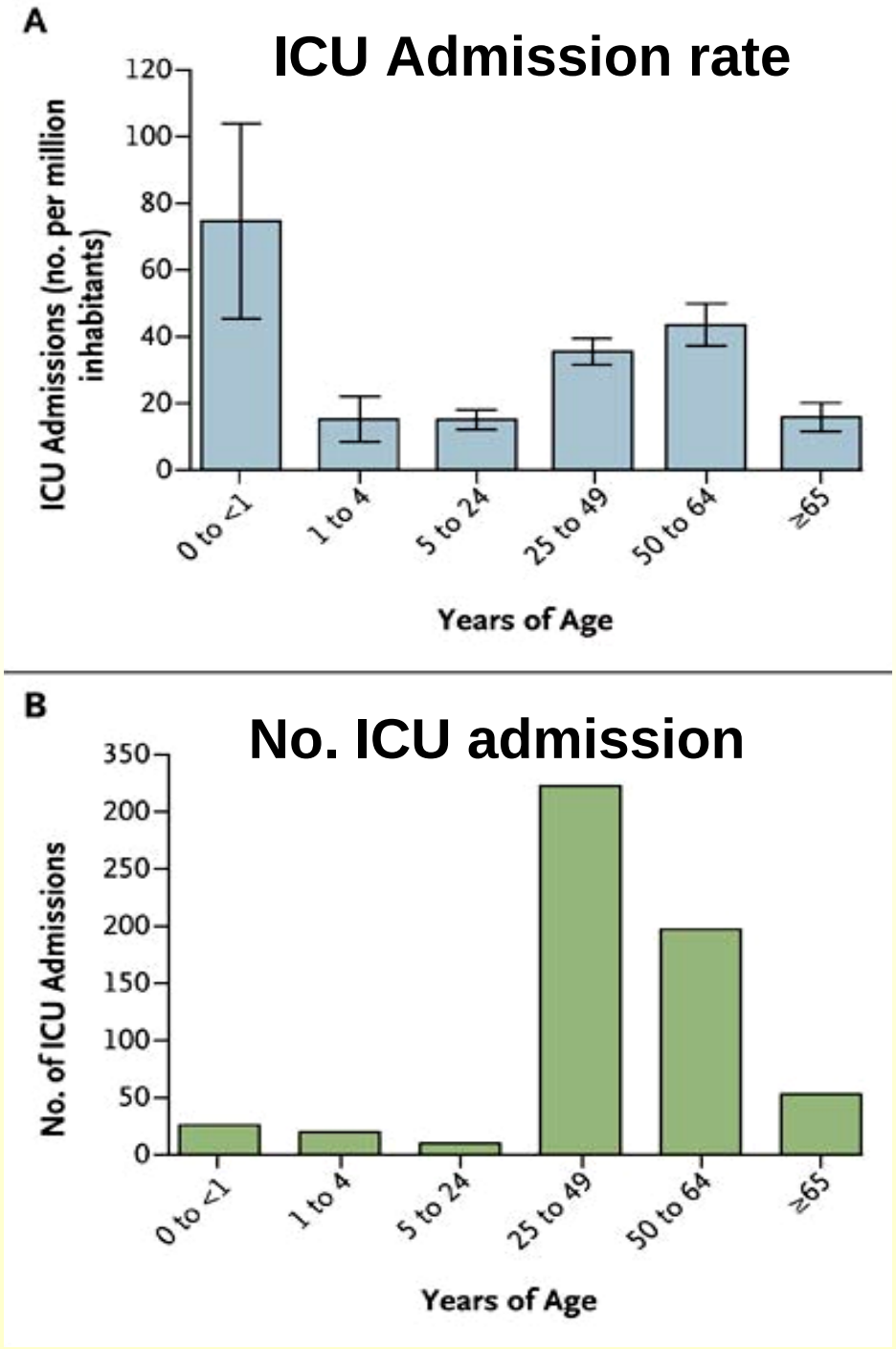
*Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. NEJM 2009;360:2605-15.*

# Death or Hospitalization Due to Pandemic 2009 Influenza A(H1N1) Infection in California




Error bars indicate 95% confidence intervals.

*Louie JK. JAMA 2009;302:1896-1902.*




# Critical Care Services and 2009 H1N1 Influenza in Australia and New Zealand

- **Risk of ICU admission include: pregnancy, ULD, BMI >35, indigenous AUS, NZ**
- **1/3 had no risk factors**
- **Risk of death increased with age**

*ANZIC Influenza Investigators. NEJM 2009;361:1925-34.*

# Management of Suspected / Confirmed Cases of H5N1 or Severe Influenza A (H1N1) 2009

# Respiratory Rate is the Best Marker for Severe Influenza

## 2009-2010 Influenza Season Triage Algorithm for Children (≤18 years) With Influenza-Like Illness

| Age | Respiratory rate |
|---|---|
| Birth up to 3months | > 60/min |
| 3 months up to 1 year | > 50/min |
| 1 to < 3 years | > 40/min |
| 3 to < 6 years | > 35/min |
| 6 to <12 years | > 30/min |
| 12 to 18 years | > 20/min |

**ALWAYS TAKE CXR IN THESE CHILDREN**

*CDC.2009-2010 Influenza Season Triage Algorithm for Children (≤18 years) With Influenza-Like Illness. http://www.cdc.gov/h1n1flu/clinicians/pdf/childalgorithm.pdf*

# Management of Suspected / Confirmed Cases of H5N1 or Severe Influenza A (H1N1) 2009 -1

- **Start oseltamivir as soon as possible**
  - **Zanamivir can be used in children > 7 yo, and able to use disk haler**
- **Supportive care. Give bronchodilator as needed.**
  - **Use MDI via spacer if possible**
- **Check for bacterial infection, start ATB as required**
- **Avoid salicylate**
- ***Should not use steroid in general case, but may consider in severe cases with ARDS***

# Management of Suspected / Confirmed Cases of H5N1 or Severe Influenza A (H1N1) 2009 -2

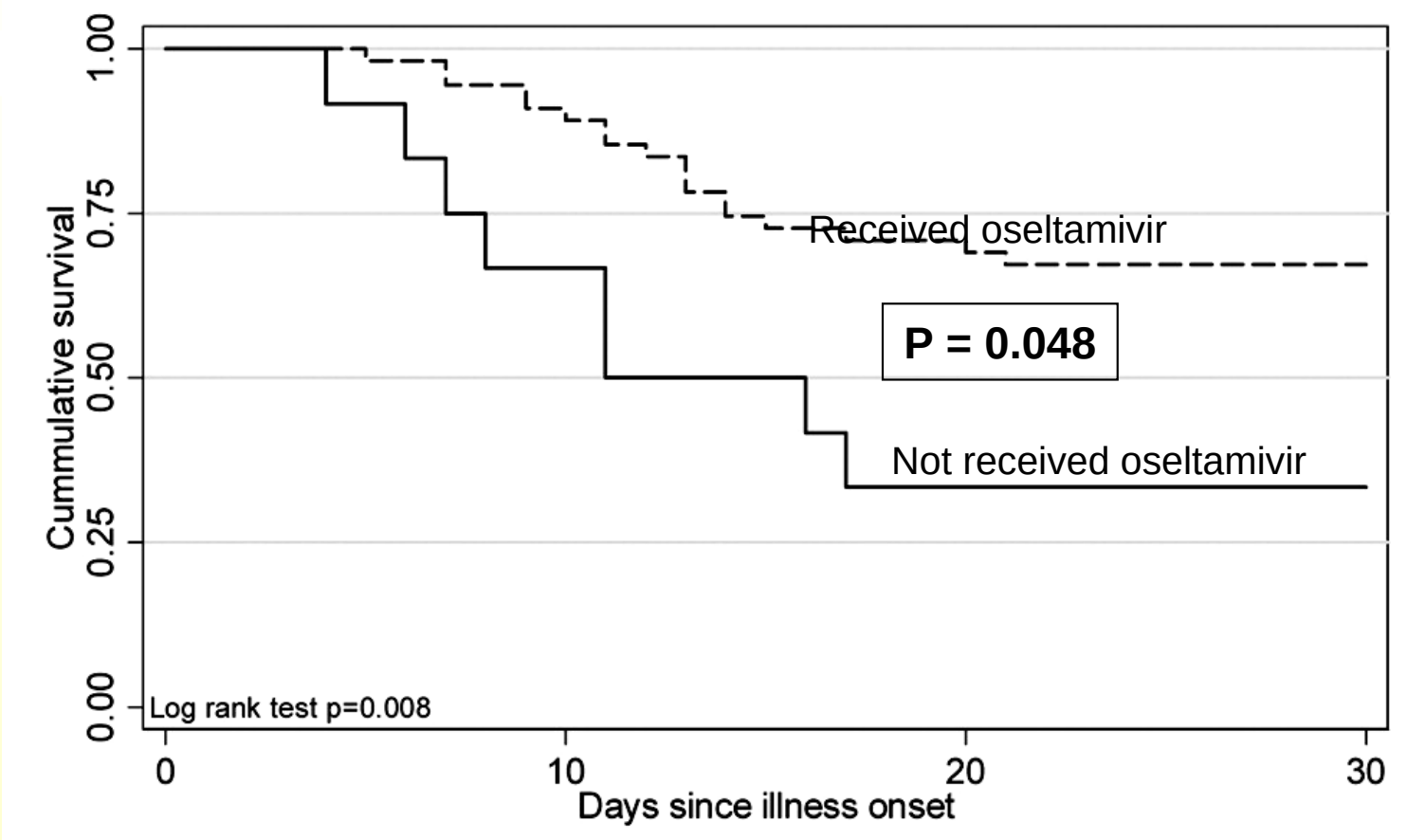
- Careful fluid intake and output. Avoid over- hydration.
- Keep $SpO_2 \geq 95\%$
- Intubation in cases of:
  - $SpO_2 < 95\%$ with partial rebreathing mask $\geq$ 10 LPM
  - Excessive use of accessory muscle

# Management of Suspected / Confirmed Cases of H5N1 or Severe Influenza A (H1N1) 2009 -3

- Ventilator settings:
  - Use pressure-controlled CMV
  - Watch out for air leak, pneumothorax
  - In case that need airway pressure > 30 cmH2O, consider to increase inspiratory time instead of increasing peak airway pressure.
  - Use PEEP when needed, starting from 8-10 cmH2O
  - May need high frequency ventilator
  - Decrease oxygen as tolerate
- Avoid transporting the unstable patients

# TAMIFLU

# Clinical Features of Human Influenza A (H5N1) Infection in Vietnam: 2004–2006




**Survival plot for cases in which patients received oseltamivir *(dashed line)*, compared with cases in which patients did not receive oseltamivir *(solid line)*, by duration since onset of illness (censored at day 30, because all deaths had occurred by day 21 after illness onset).**

*Liem NT. CID 2009;48:1639-46.*

# Hospitalized Patients with 2009 H1N1 Influenza in the United States, April-June 2009.

| Characteristic | Patients Who Were Not Admitted to an ICU and Survived (N=205) | Patients Who Were Admitted to an ICU or Died (N=67) |
|---|---|---|
| Age | | |
| Median — yr (range) | 19 (21–80) | 29 (1–86) |
| <18 Yr — no. (%) | 98 (48) | 24 (36) |
| Shortness of breath — no. (%) | 104 (51) | 58 (87) |
| Neurocognitive disorder — no. (%) | 11 (5) | 9 (13) |
| Neuromuscular disorder — no. (%) | 10 (5) | 9 (13) |
| Pneumonia seen on chest radiography on admission — no./total no. (%) | 51/182 (28) | 49/67 (73) |
| Antiviral treatment — no./total no. (%) | | |
| Any — no./total no. (%) | 144/203 (71) | 56/65 (86) |
| ≤2 Days after onset of symptoms — no./total no. (%) | 62/139 (45) | 13/56 (23) |
| Days from onset of symptoms to initiation — no. (range) | 3 (0–29) | 5 (0–24) |
| Antibiotic treatment — no./total no. (%) | 144/195 (74) | 62/65 (95) |
| Corticosteroid treatment — no./total no. (%) | 57/183 (31) | 29/56 (52) |

**All had P<0.05**

*Jain S. NEJM 2009; 361:1-10. http://content.nejm.org/cgi/content/abstract/NEJMoa0906695v1*

# Dosing of Oseltamivir in Children

- >40 kg — 75 mg bid
- >23-40 kg — 60 mg bid
- >15-23 kg — 45 mg bid
- If > 1 yo, and < 15 kg — 30 mg bid
- In < 1 yo:
  - 6-11 months — 25 mg bid
  - 3-5 months — 20 mg bid
  - < 3 months — 12 mg bid

**If Ccr 10-30 ml/min, reduce to OD**

**If Ccr < 10 ml/min, no data**

# What could be the antiviral therapy in critical cases who:……

- May not be able to take or absorb Oseltamivir
- Could be infected by resistant strain (rare in H1N1 2009, but common in seasonal H1N1)
- Cannot inhale disk-haler of Zanamivir

# The Emergency Use Authorization of Peramivir for Treatment of 2009 H1N1 Influenza

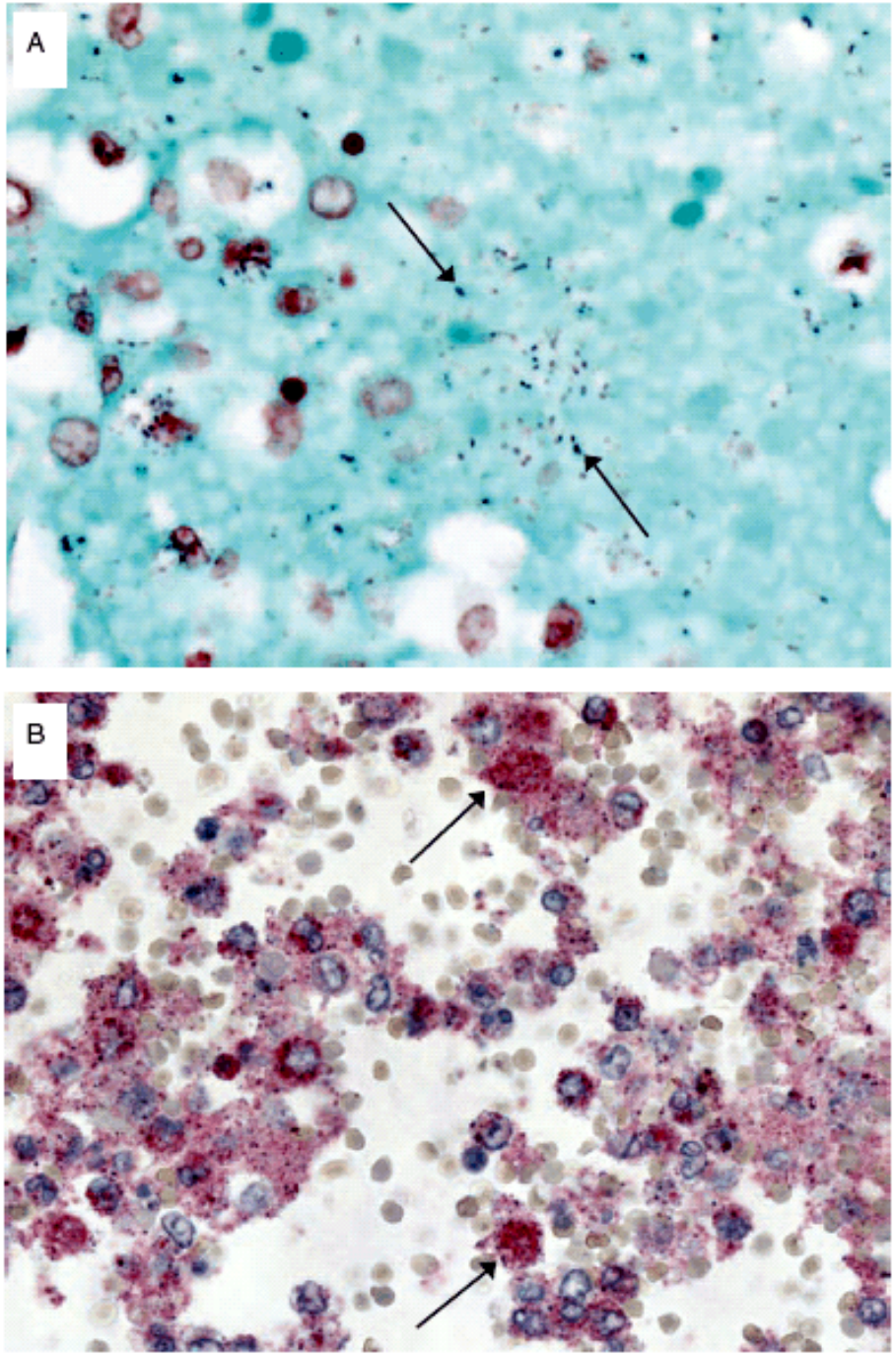
- It was “reasonable to believe” that Peramivir may be effective
  - Improved symptoms 1 day sooner in uncomplicated seasonal influenza
  - No data in comparison with oseltamivir
  - No efficacy information for novel H1N1
  - No data in children
- It should be considered in patients with hospitalized severe influenza that may benefit from this i.v. drug
- Dose: 600 mg OD 5-10 days
- Common AE: vomiting, diarrhea, nausea, neutropenia

*Birnkrant D. NEJM 2009 Nov 3. [Epub ahead of print]*
*http://content.nejm.org/cgi/content/full/NEJMp0910479*

# In Vitro Neuraminidase Inhibition of Seasonal Influenza

| Influenza virus strain | No. of isolates | $IC_{50}$, median nmol/L (range) | | |
|---|---|---|---|---|
| | | Peramivir | Oseltamivir carboxylate | Zanamivir |
| A(H1N1) | 5 | 0.34 (0.26–0.43) | 0.45 (0.45–0.60) | 0.95 (0.73–1.05) |
| A(H3N2) | 6 | 0.60 (0.47–0.87) | 0.37 (0.27–0.45) | 2.34 (1.85–3.13) |
| B | 8 | 1.36 (1.08–1.95) | 8.50 (5.33–18.33) | 2.70 (2.00–3.10) |

*Hayden F. CID 2009;48 (Sup1):S3-13.*




# Bacterial Coinfections in Lung Tissue Specimens from Fatal Cases of 2009 Pandemic Influenza A (H1N1) --- United States, May--August 2009

**Concurrent bacterial infection was found in specimens from 22 (29%) of the 77 patients**

**(A) Detection of Gram-positive cocci (arrows) with use of Lillie- Twort Gram stain of lung tissue (original magnification ×63). (B) Immunohistochemical staining of multiple S. pneumoniae (arrows) with use of immunoalkaline phosphatase with naphthol-fast red and hematoxylin counterstain**

*CDC. MMER September 29, 2009 / 58(Early Release);1-4*

*http://www.cdc.gov/mmwr/preview/mmwrhtml/mm58e0929a1.htm*

# Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: Autopsy of cases died in 1918-1919 “Spanish Flu”

| | Pleural fluid (1245) | Blood (1887) | High quality lung (3074) |
|---|---|---|---|
| | No (%) | No (%) | No (%) |
| *S.Pneumoniae* | 263 (21.1) | 509 (27) | 712 (23.2) |
| *S.Pyogenes* | 539 (43.3) | 377 (20) | 553 (18.0) |
| *S.aureus* | 59 (4.7) | 68 (3.6) | 238 (7.7) |
| *N.Meningitidis* | 0 | 5 (0.3) | 21 (0.7) |
| Mixed | 74 (5.9) | 28 (1.5) | 828 (26.9) |
| *H.Influenzae* | 21 (1.7) | 61 (3.2) | 144 (4.7) |
| Others | 45 (3.6) | 278 (14.7) | 353 (11.5) |
| No growth | 244 (19.6) | 561 (29.7) | 225 (7.3) |

*Morens DM. JID 2008;198:962-70.*


# Risk Factors for Poor Outcomes in Children

# Factors Associated With Death or Hospitalization Due to Pandemic 2009 Influenza A(H1N1) Infection in California

| | Cases Aged 0-17 Years | | Cases Aged ≥18 Years | |
|---|---|---|---|---|
| | Fatal (n=8) | Nonfatal (n=336) | Fatal (n=110) | Nonfatal (n=634) |
| Other chronic comorbid illness | 25 | 13 | 63 | 40 |
| Obesity | 0 | 19 | 66 | 52 |
| BMI 30-34.9 | 0 | 0 | 24 | 40 |
| BMI 35-39.9 | 0 | 0 | 26 | 20 |
| BMI ≥40 | 0 | 0 | 50 | 40 |
| Gastrointestinal tract | 25 | 9 | 11 | 10 |
| GERD | 13 | 2 | 4 | 4 |
| Other/unknown | 13 | 7 | 7 | 7 |
| Hyperlipidemia | 0 | 0 | 2 | 5 |
| Hypertension | 0 | <1 | 25 | 23 |

*Louie JK. JAMA 2009;302:1896-1902.*

# Factors Associated With Death or Hospitalization Due to Pandemic 2009 Influenza A(H1N1) Infection in California

| | Cases Aged 0-17 Years | | Cases Aged ≥18 Years | |
|---|---|---|---|---|
| | Fatal (n=8) | Nonfatal (n=336) | Fatal (n=110) | Nonfatal (n=634) |
| Male, No. (%) | 38 | 60 | 51 | 43 |
| Age, median (range), y | <1-14 | <1-17 | 18-85 | 18-92 |
| Clinical finding and course, No. (%) | | | | |
| Positive rapid test result | 83 | 85 | 44 | 59 |
| Infilltrates on chest radiograph | 80 | 60 | 97 | 62 |
| Admitted to intensive care unit | 75 | 25 | 80 | 26 |
| Mechanical ventilation | 88 | 10 | 93 | 19 |
| Secondary bacterial infections | 13 | 2 | 14 | 4 |
| Antiviral treatment | 63 | 77 | 73 | 82 |
| Received <48 h after symptom onset | 20 | 57 | 26 | 52 |

*Louie JK. JAMA 2009;302:1896-1902.*

# AAP Reaffirms Children at High Risk for Serious Outcomes from H1N1

- **Neurological disorders and neuromuscular conditions**
- **Chronic respiratory diseases with impaired pulmonary function and/or difficulty handling lung secretions**
- **Moderate to profound intellectual disability (mental retardation) or developmental delay**
- **Immune deficiency or immune system conditions that require medications or treatments**
- **Cardiovascular disease including congenital heart disease**
- **Significant metabolic (e.g., mitochondrial) or endocrine disorders**
- **Renal, hepatic, hematological (including sickle cell disease) disorders**
- **Receiving chronic aspirin therapy**
- **Pregnancy or up to 2 weeks post-partum regardless of how the pregnancy ended**

*Red Book Online News & Features – November 4, 2009*

# Cases Scenarios

# A 6 year-old boy from Kanchanaburi

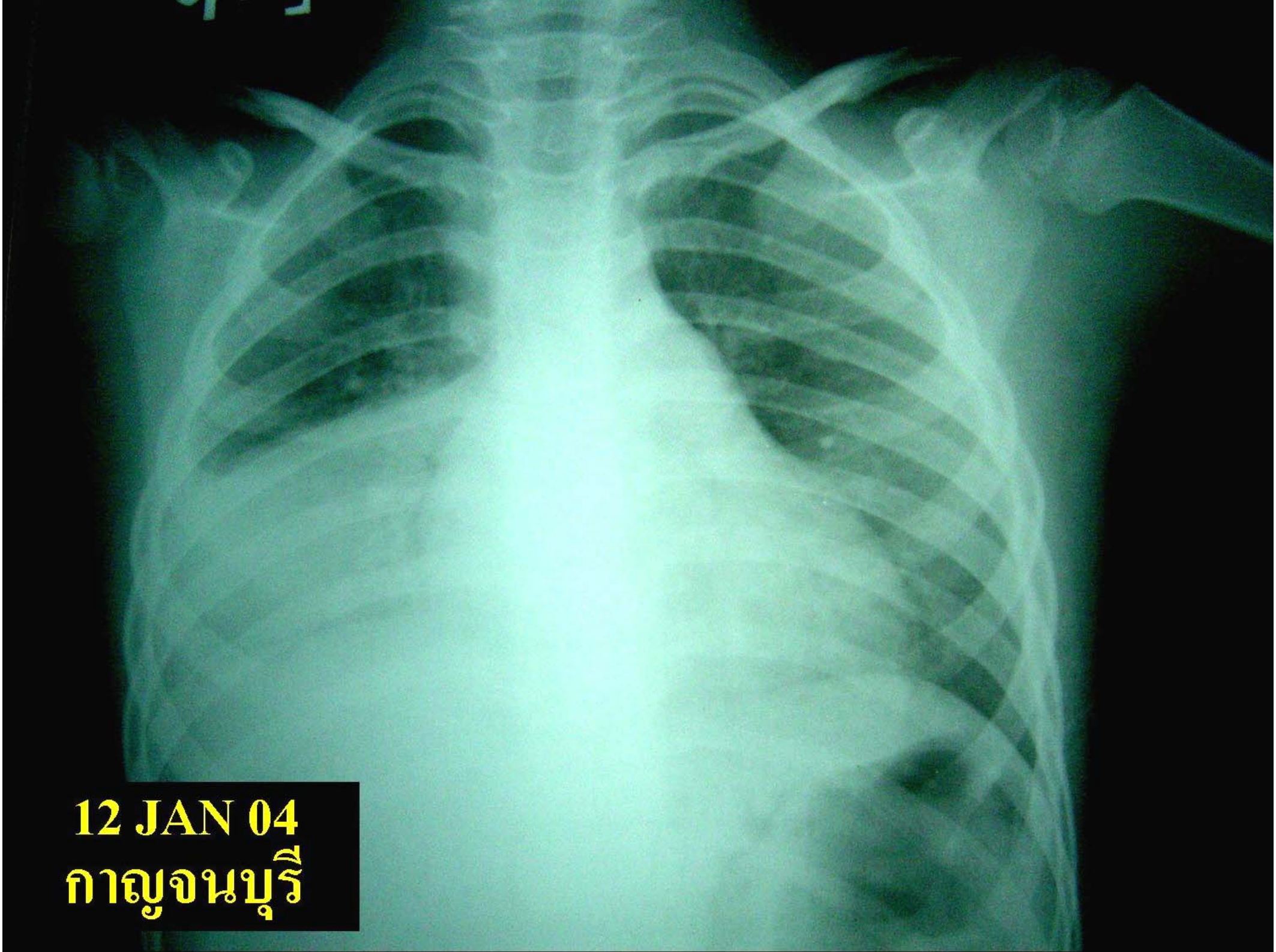
Presenting symptoms : Fever and shortness of breath for 5 day

History : 9 days prior to admission ( on Jan 4, 2004 ), he started to have low grade fever, productive cough, no running nose.

5 days later, he had high fever, more severe productive cough, poor appetite. Got ceftriaxone 50 mg. IV x 3 days, CXR revealed patchy infiltration RLL. He was put on imipenem, but the clinical condition was worse.

CBC on Jan 13, 2004: Hct. 33%, WBC1,200/mm3( N44%, L52%, E2%, M2% ) Plt. 89,000/mm3.

Family Hx: Raised chicken at home. Pt contacted sick chicken.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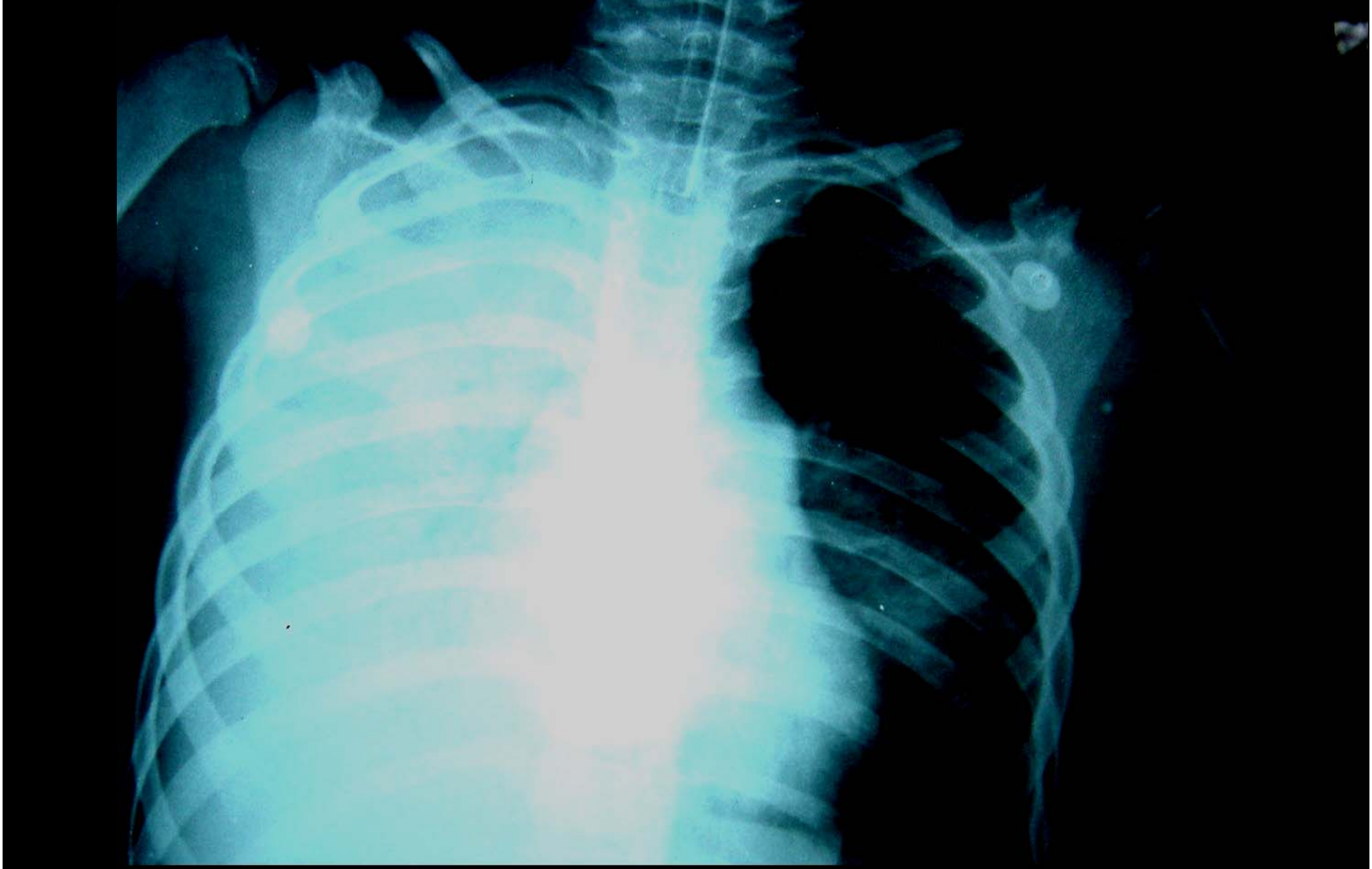
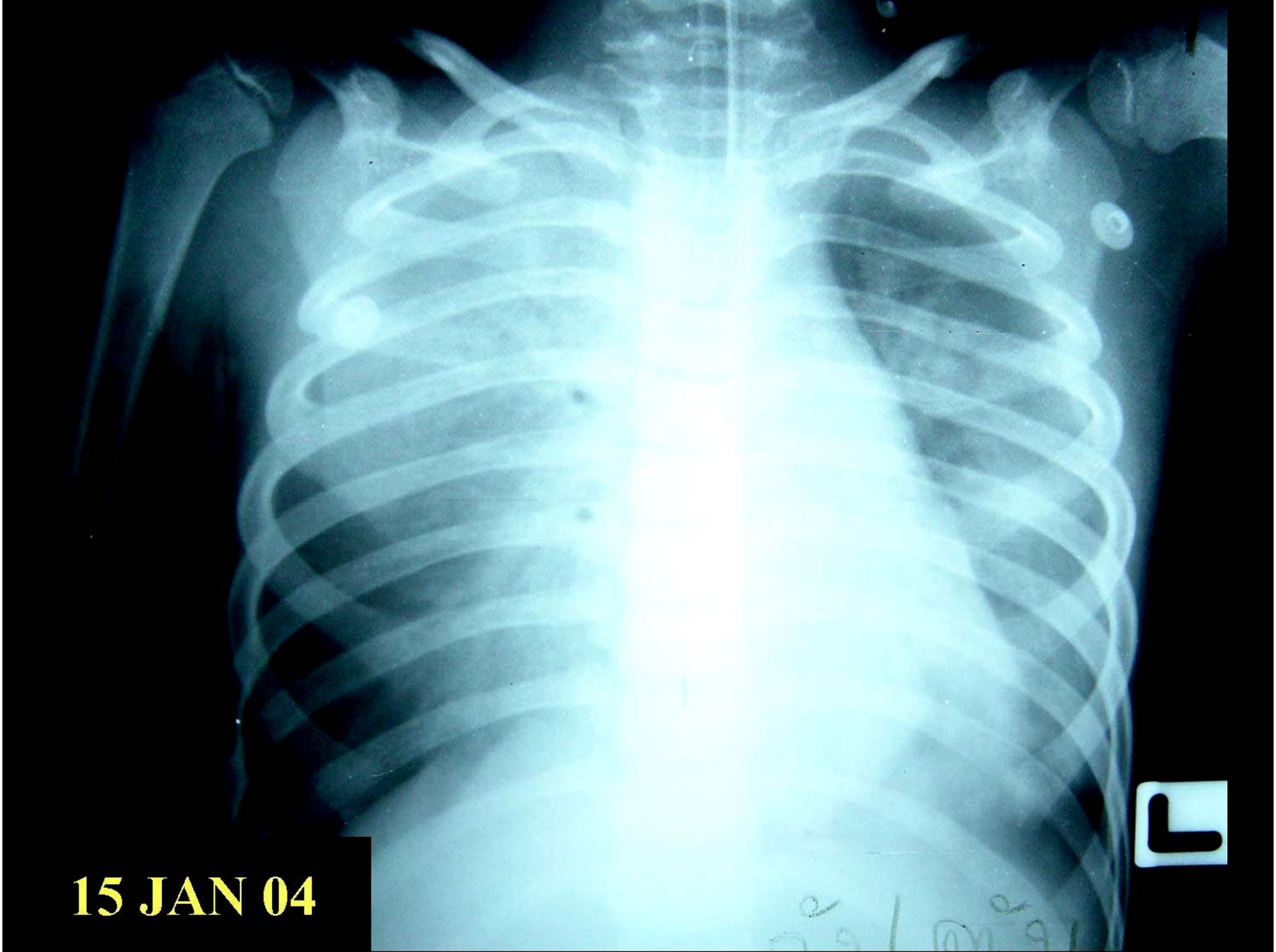


14 JAN 04 9 hr. after admission

Respiratory failure → intubation and tranfer to ICU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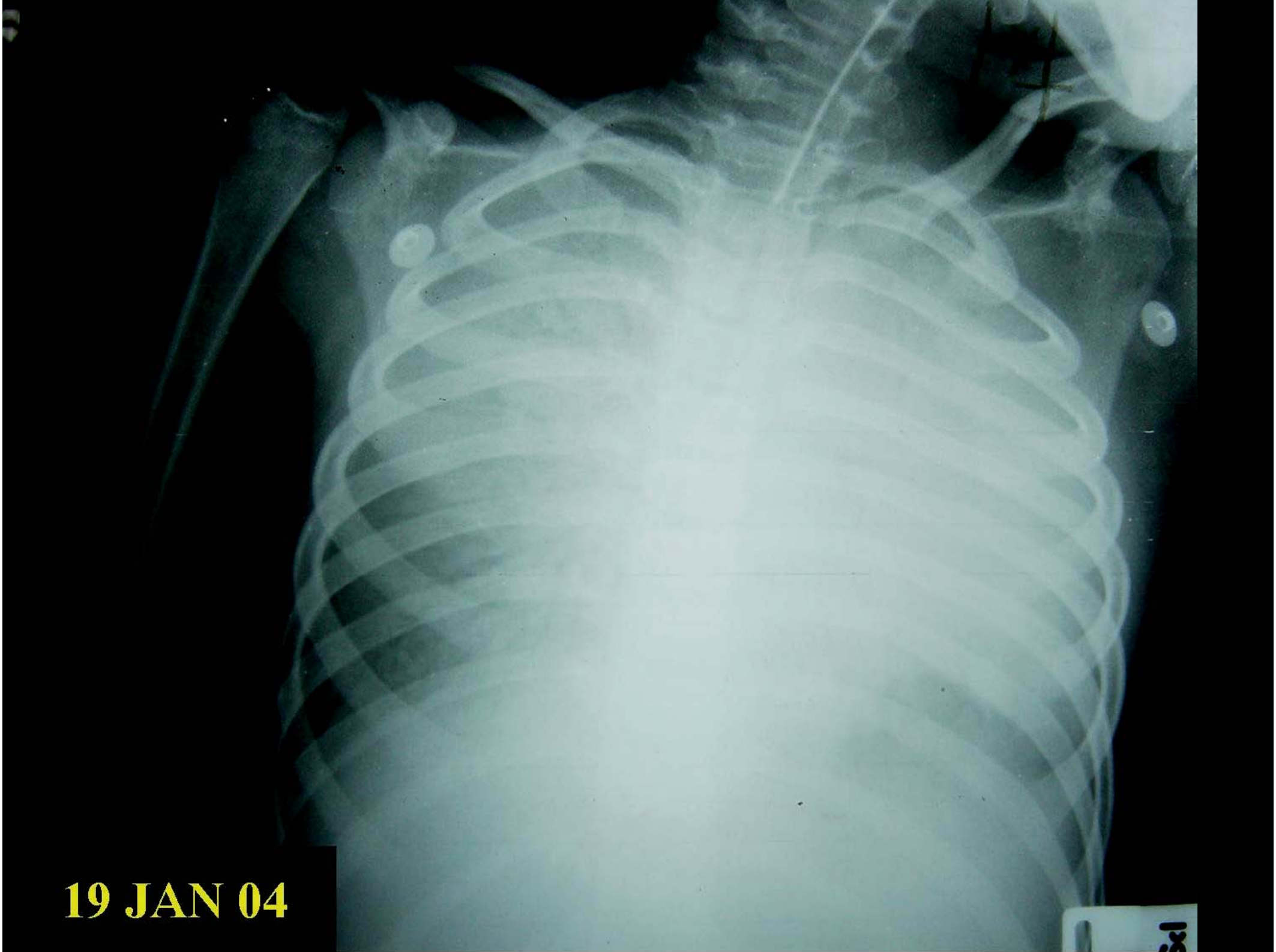
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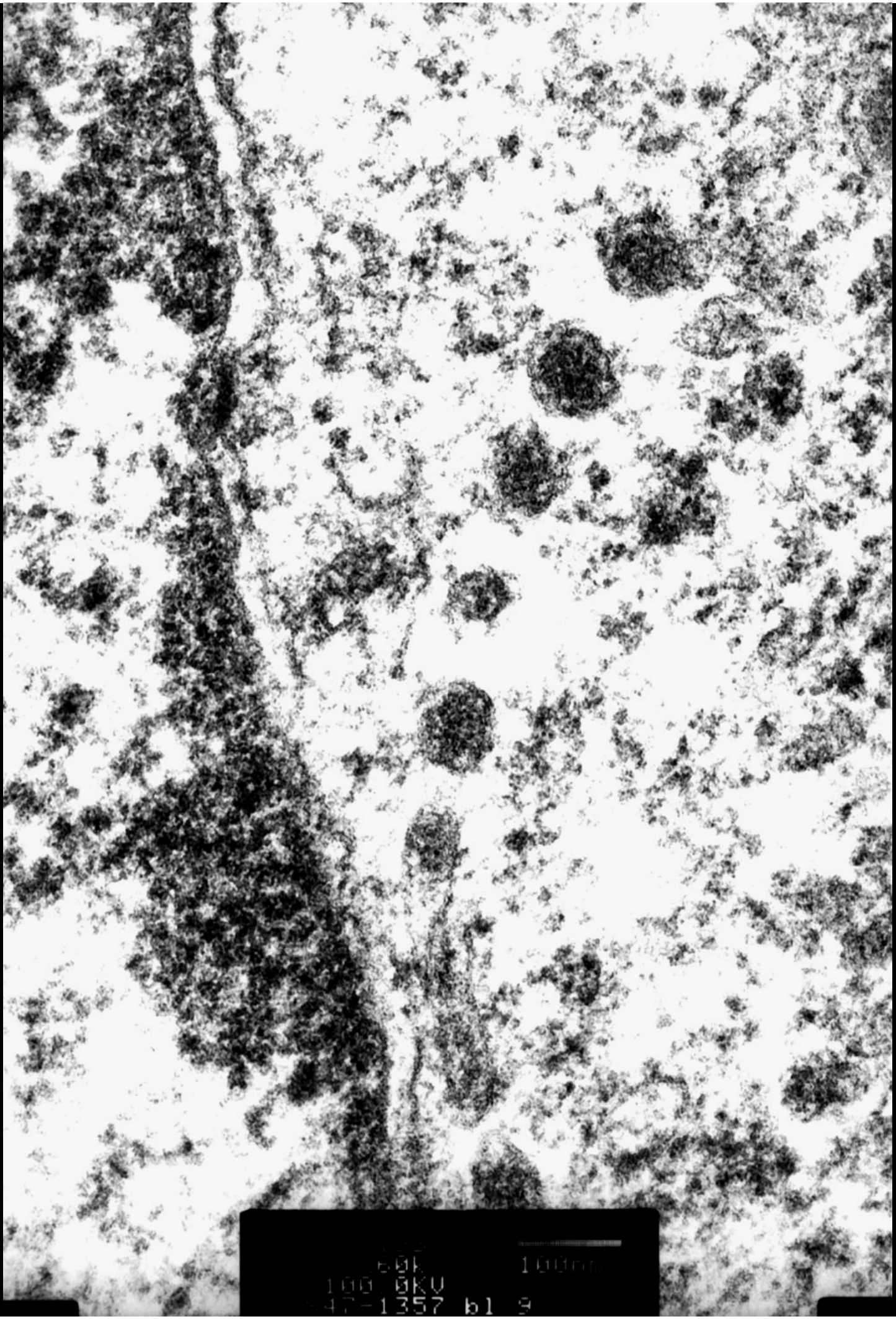
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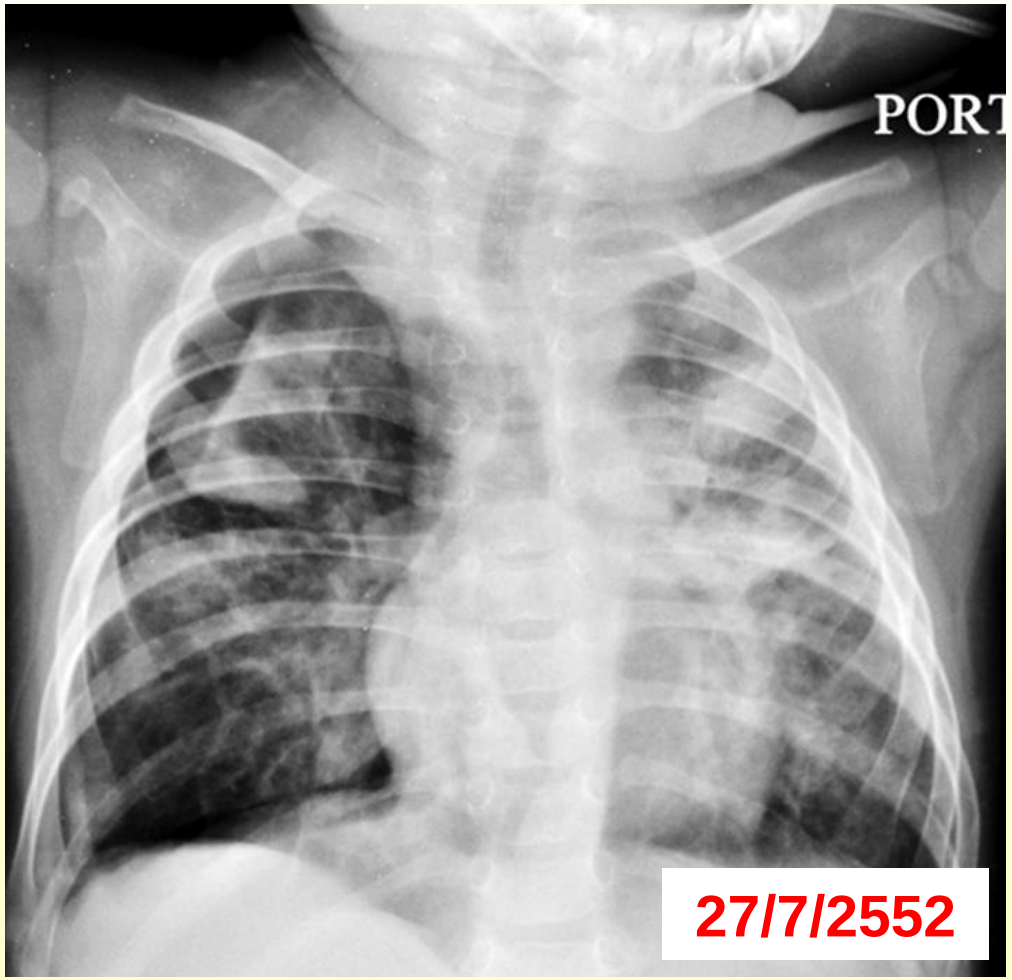
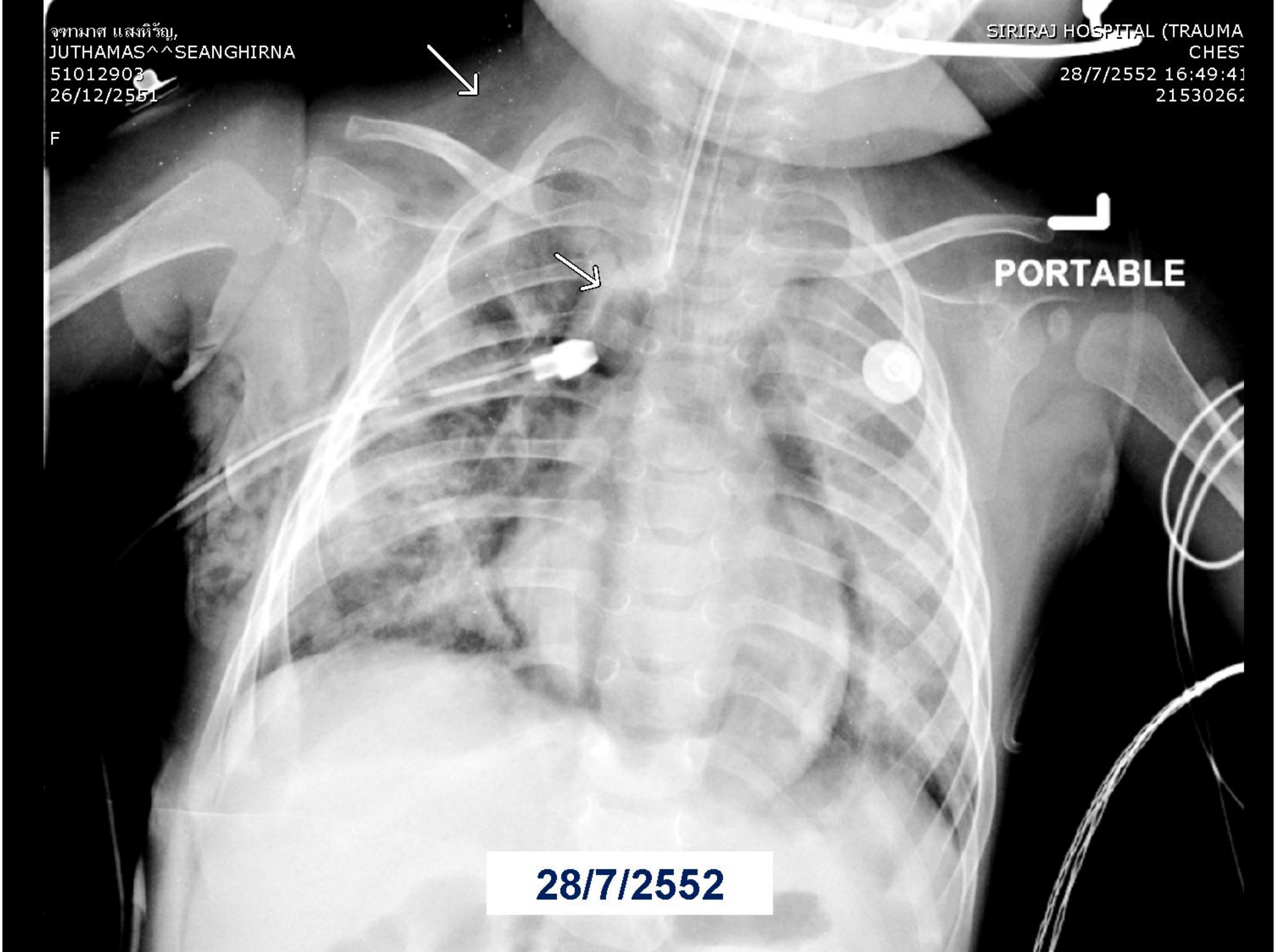
# 7 month-old-girl with H1N1 (2009)

- Underlying : Hemangioma at Lt. eyelid  On prednisolone 1 MKD
- Admission for propranolol titration
- During admission on day 19, she developed abrupt onset of high fever, rhinorrhea, and dyspnea
- T 38.8°C, P 150/min, RR 70/min, BP 108/57mmHg, SpO2 88-90% (room air), tachypnea, dyspnea
  - RS : flaring ala nasi, subcostal retraction, crepitation both lungs decrease breath sound at Rt. lung

# Investigations

- **CBC: Hct 42%, Hb 15 g/dl**
  **WBC 9,690 (N 51%,L 43%,**
  **M5%), platelets 489,000**
- **CBG while on oxygen mask**
  **with bag 8 LPM**
  **pH 7.38**
  **pCo2 44**
  **pO2 52**
  **HCO3 24.4**
  **BE 0.5**
  **O2 sat 86.2**

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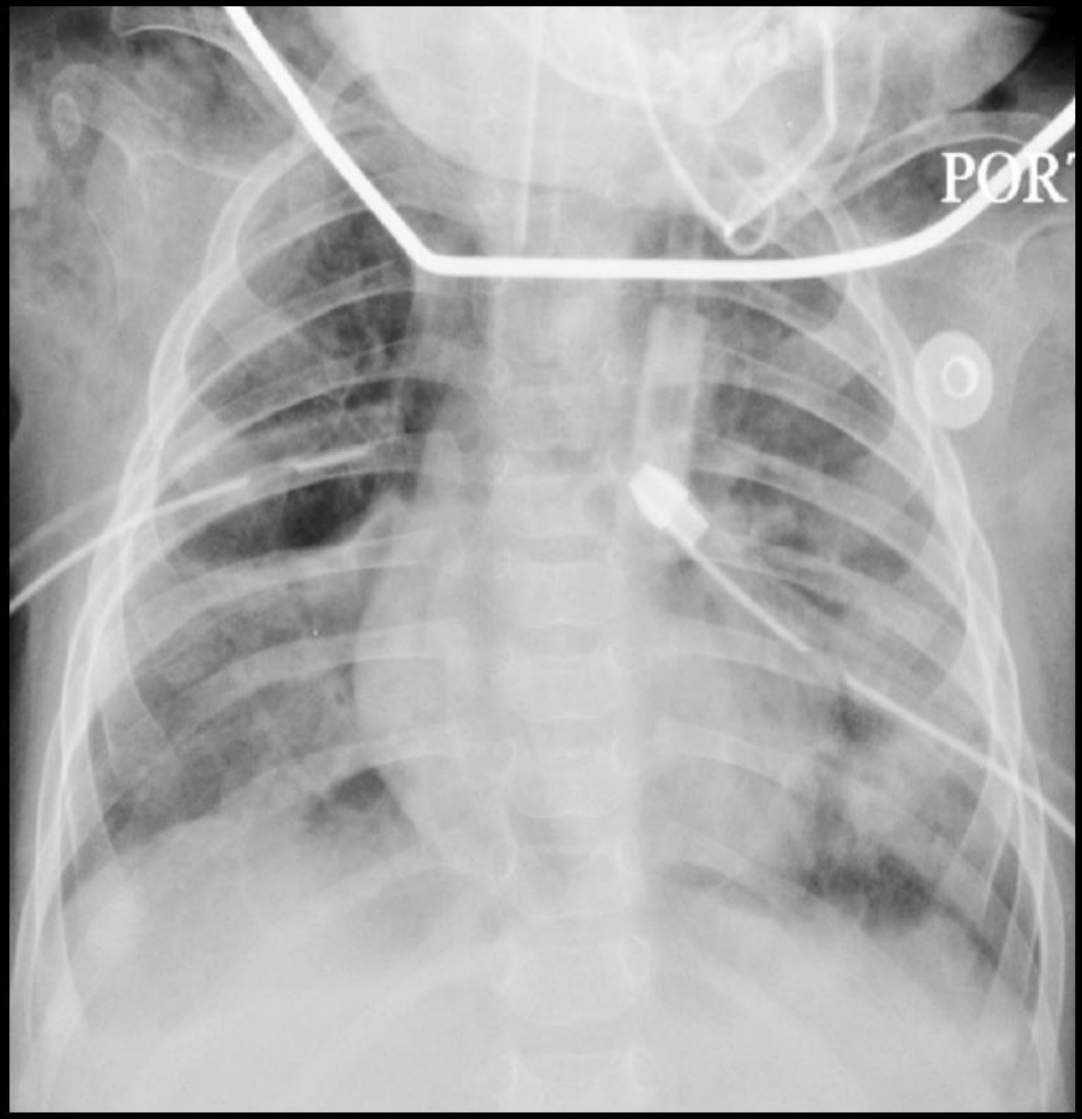
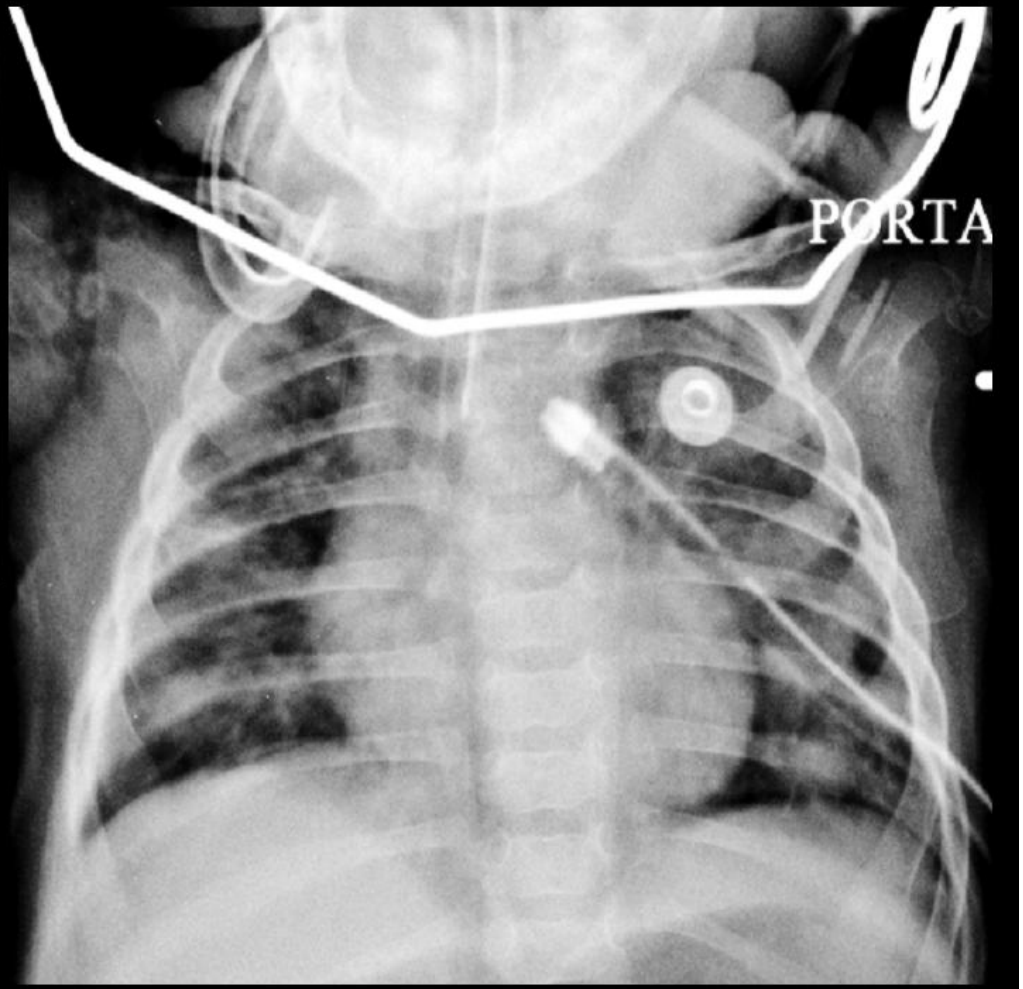
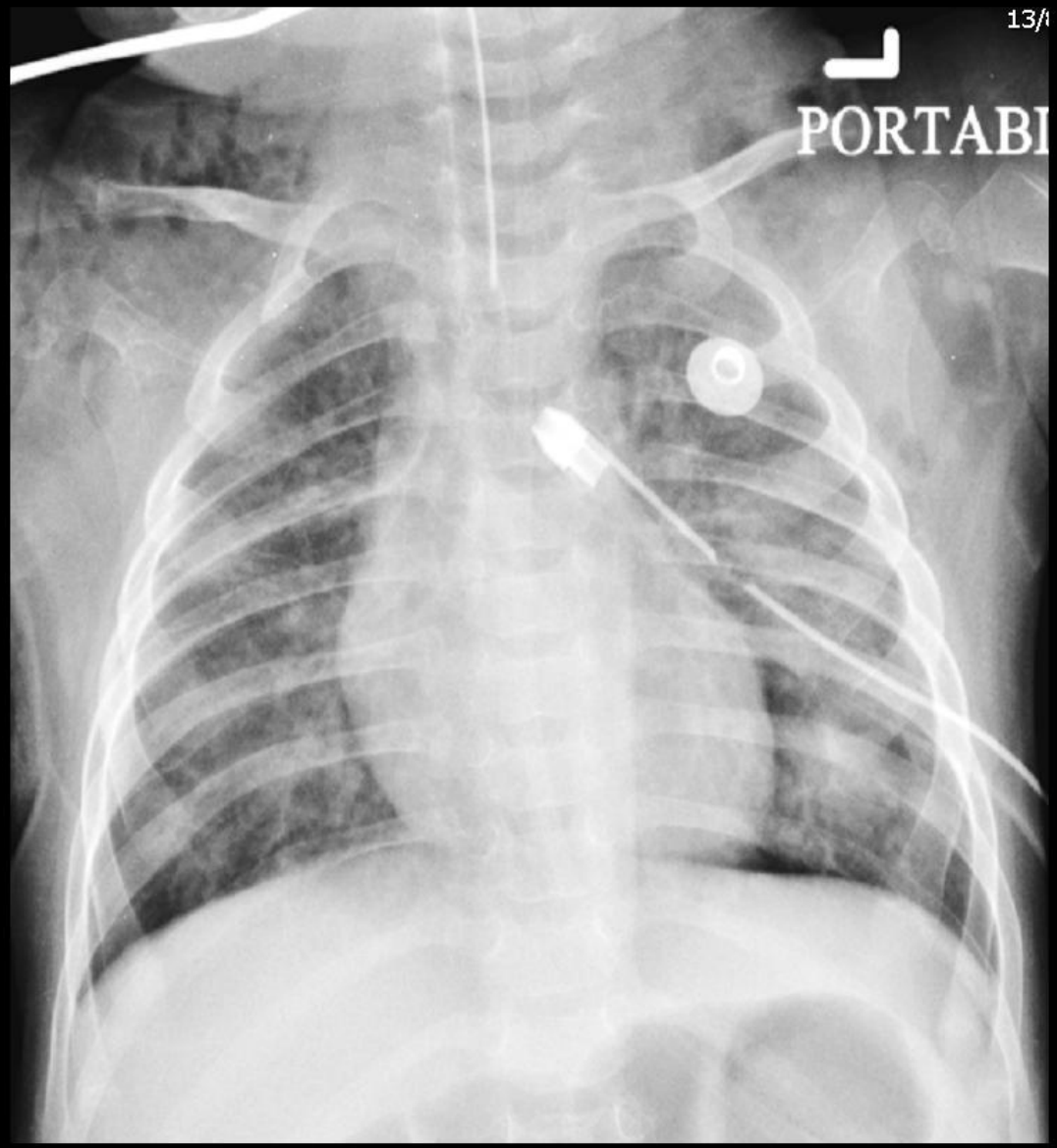





12/8/2552 ; Off Rt. ICD




13/8/2552

14/8/2552
off Lt.ICD
off ET-tube

# Clinical course

- Admission 9 July – 1 September 2552 (54 days)
- Admit PICU 27 July – 16 August 2552 (21 days)
- On ETT 27 July – 14 August 2552 (19 days)
- On respirator 27 July – 14 August 2552 (19 days)
- On Rt. ICD 27 July – 12 August 2552 (17 days)
- On Lt. ICD 28 July – 14 August 2552 (18 days)

# A 6 year-old girl with H1N1

- **Underlying : global delayed development and epilepsy**
- ***High grade fever 2 day prior to admission***
- **6 days PTA: developed high-grade fever with productive cough and diarrhea.**
- **2 days PTA: persistent high grade fever with increase productive cough and poor feeding. She was hospitalized.**
- **CBC:Hb 13.4 mg%, Hct 39%, WBC 1,400 /$mm^3$ (N 20%, L 65 %), platelet 120,000/$mm^3$, ATL 12 %**
- **Impression: suspected Dengue infection**
- **Next day, became drowsy, shock. Receive fluid resuscitation**
- **Then developed respiratory distress, RR 76 /min O2 Sat in room air = 60% → ET-tube**

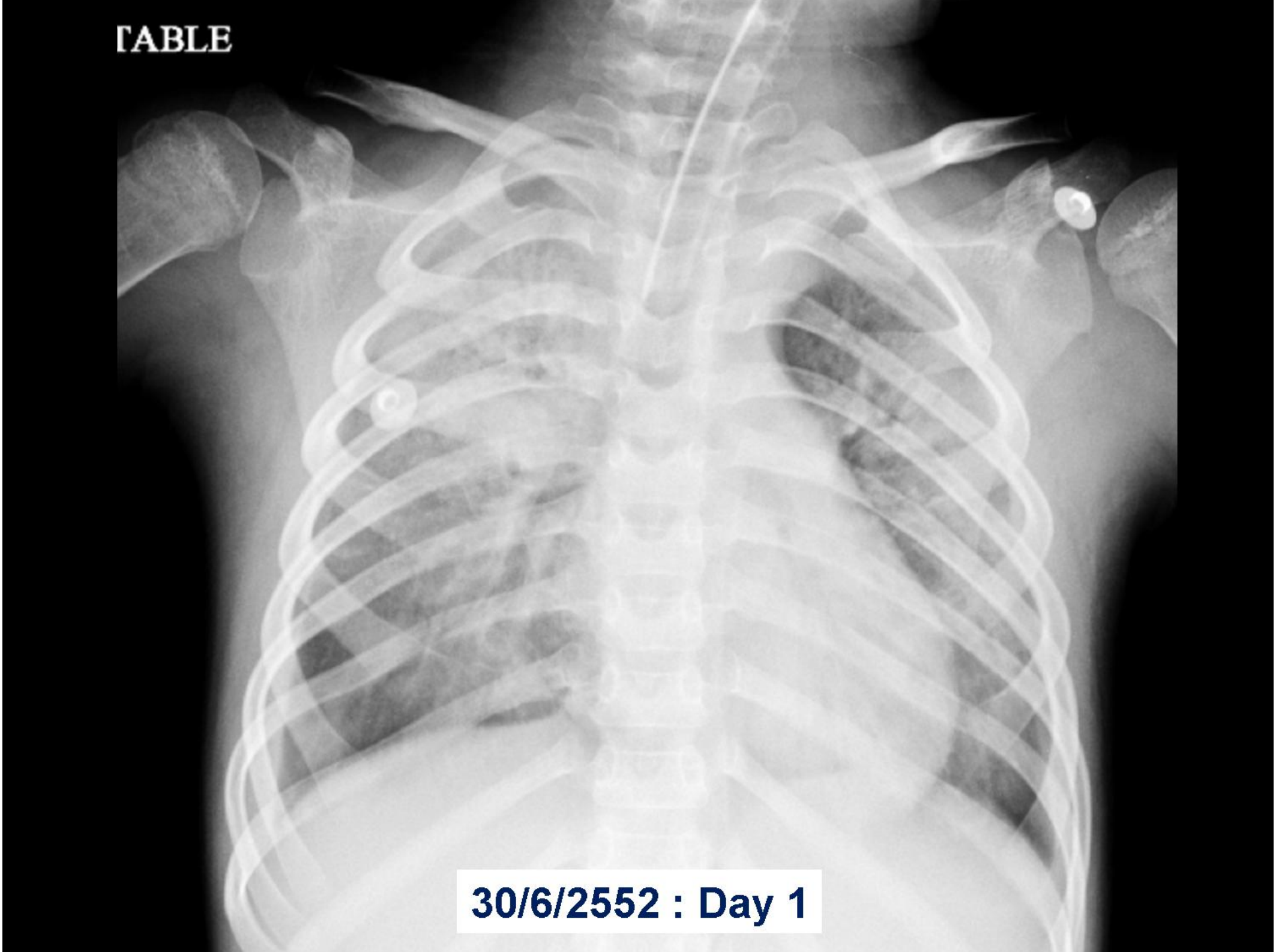
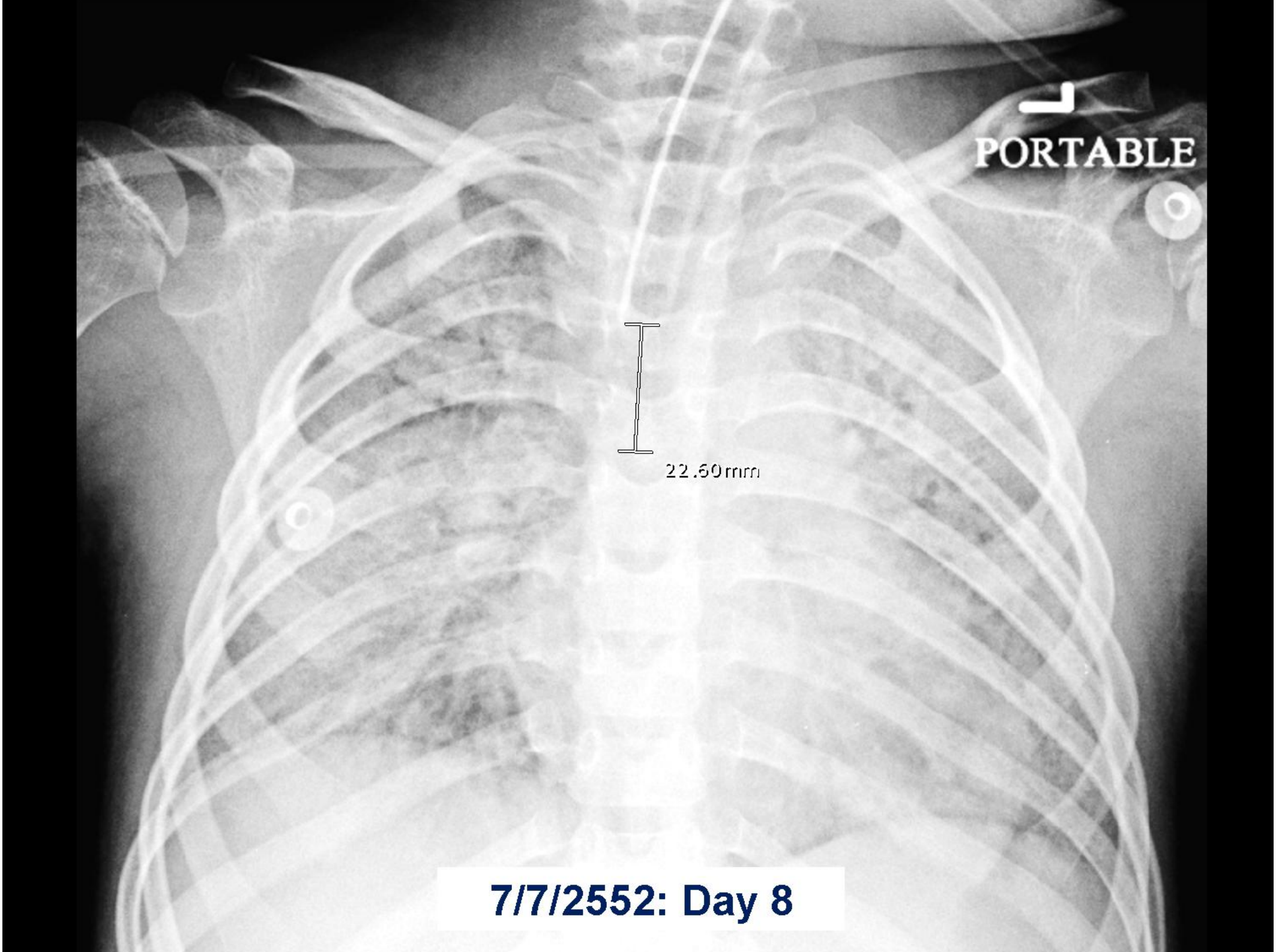


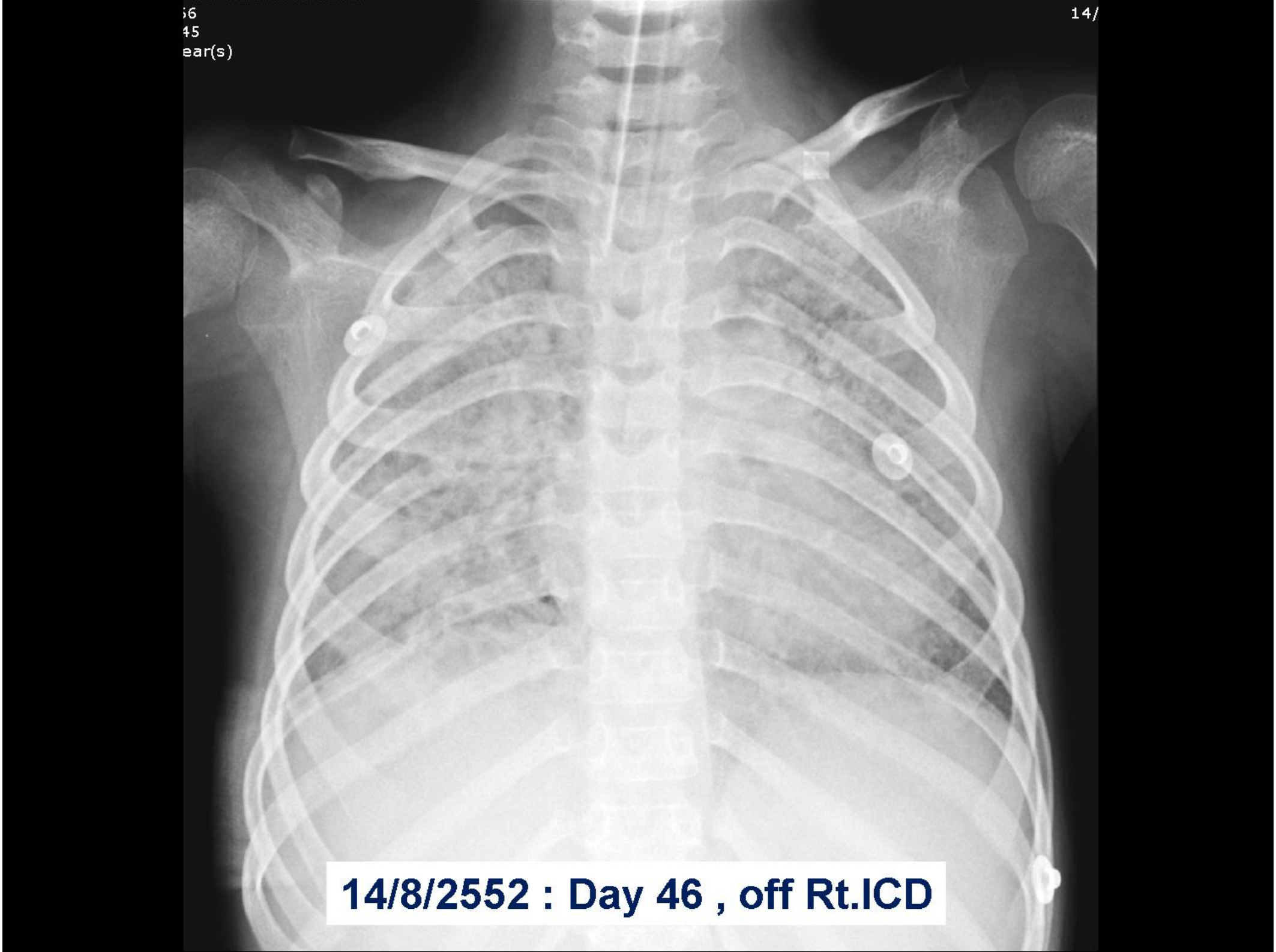
TABLE
30/6/2552 : Day 1

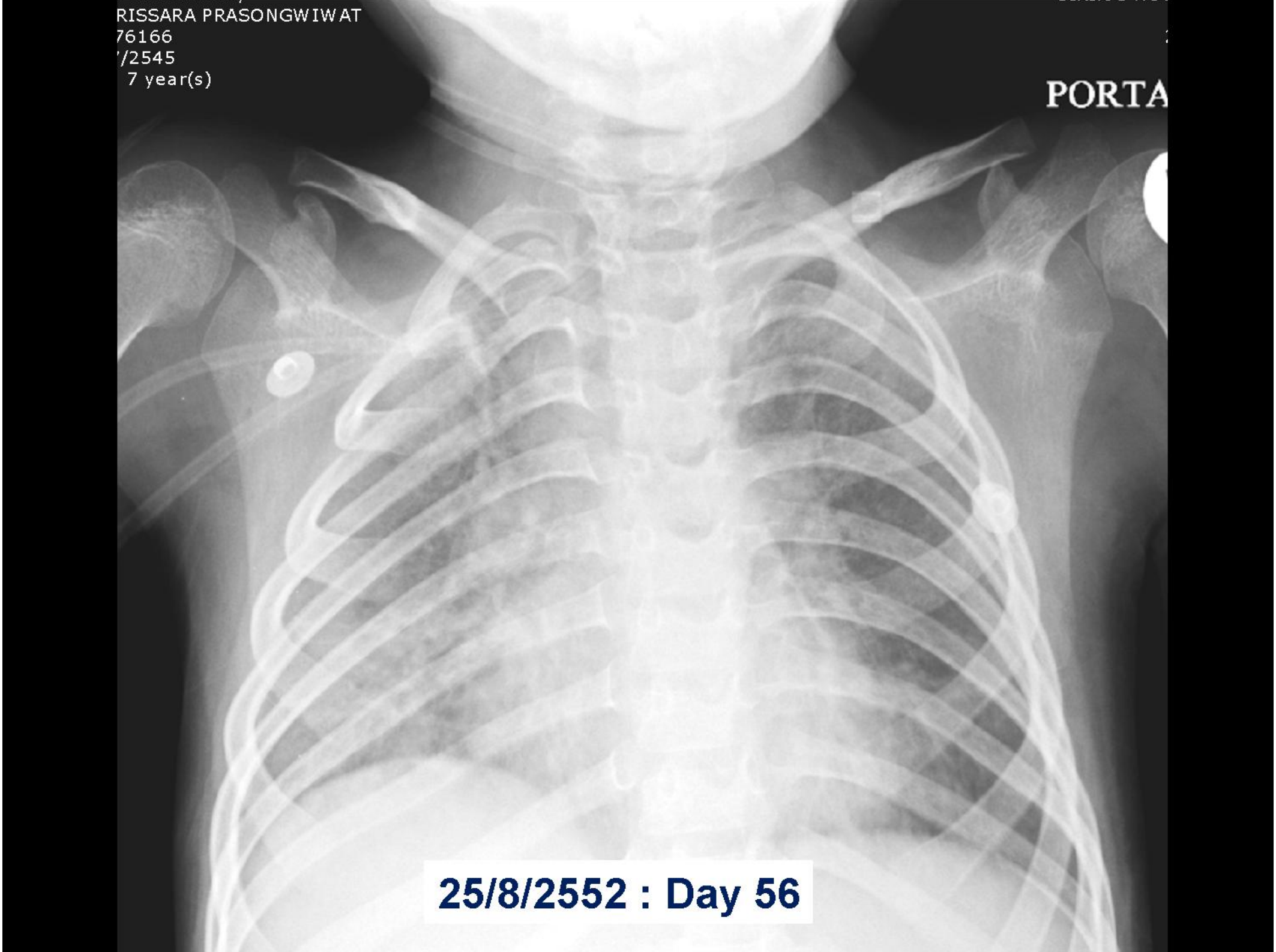



7/7/2552: Day 8



**31/7/2552 : Day 32**
**Pneumothorax at Rt.side**


14/8/2552 : Day 46 , off Rt.ICD


RISSARA PRASONGWIWAT
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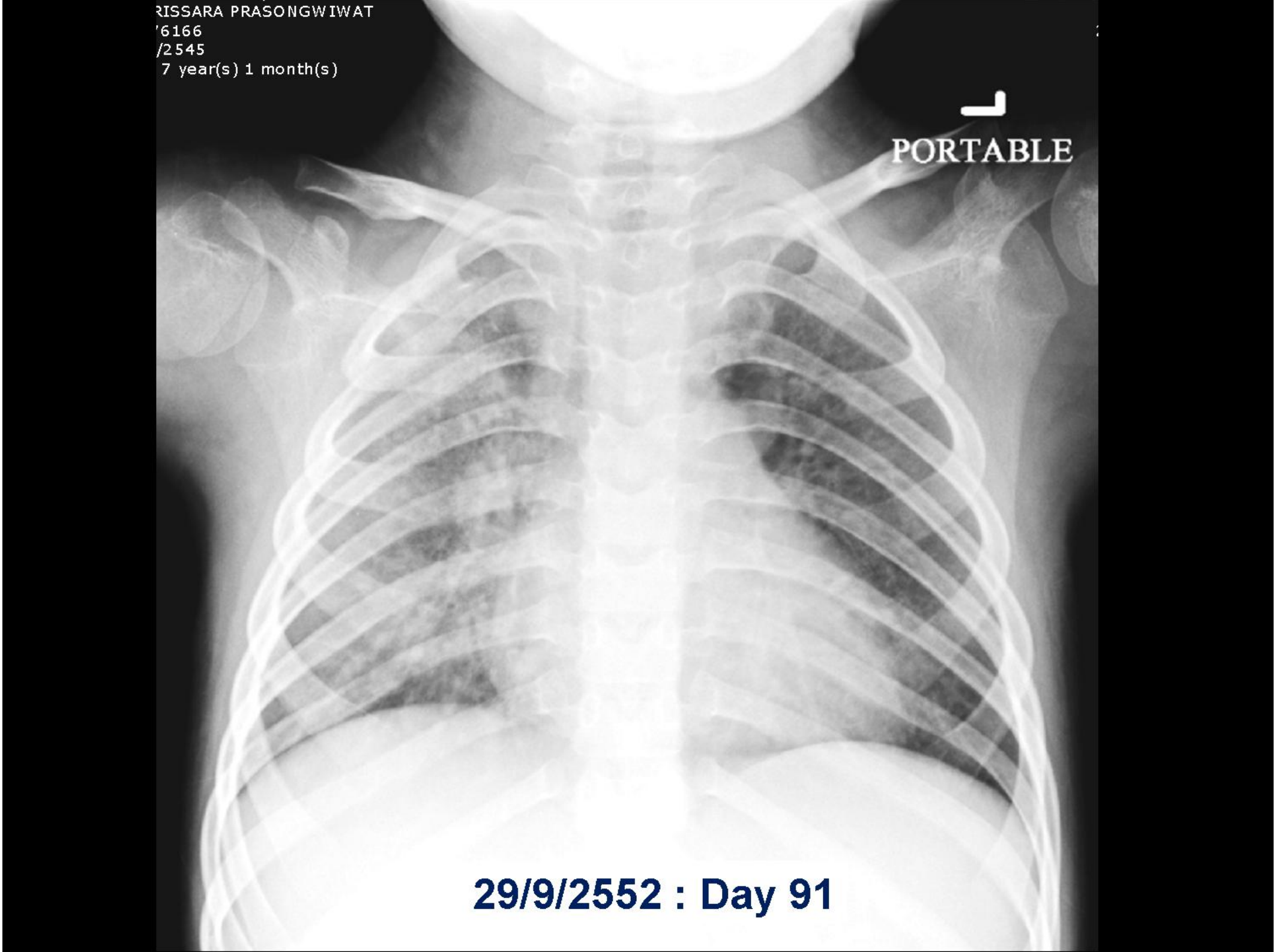
7 year(s)
PORTA
25/8/2552 : Day 56


RISSARA PRASONGWIWAT
'6166
/2545
7 year(s) 1 month(s)
PORTABLE
29/9/2552 : Day 91

# Clinical course

- **Admission 30 June – 1 Oct 2009**
- **On ETT 30 June – 19 August 2009 (51 days)**
- **Lt.ICD 13 July – 25 July 2009 (13 days)**
- **Rt.ICD 31 July – 14 August 2009 (15 days)**
- **Stay ICU 30 June - 26 August 2009 (3 months)**


# Thank you for your attention