流感與上下呼吸道感染：分與合

謝宗達

成大醫院內科部重症加護科 / 感染管制中心

2018/08/04

分

Typical influenza sympotms

- Appear suddenly after 1-2 days of incubation

- Systemic symptoms
  - Fever / chills
  - Headache
  - Myalgia
  - Malaise / anorexia

- Respiratory symptoms
  - Non-productive cough
  - Nasal discharge / obstrcution
  - Sore throat
- Ocular symptoms
  - Photophobia
  - Conjunctivitis

Paules C. *Lancet*. 2017;390:697-708.

類流感病例通報定義

需同時符合下列三項條件者：

1. 突然發病、有發燒 (耳溫≧ 38°C) 及呼吸道症狀
2. 肌肉酸痛或頭痛或極度倦怠感
3. 需排除單純性流鼻水、 扁桃腺炎及支氣管炎

有一條不符合就不是流感嗎？

- 75 歲男性，剛出院一週
- 嚴重失智，無法言語
- 安養機構說發燒痰多喘，送至急診，插管後入住加護病房
- 在醫院沒有發燒

Is it a cold or flu?

Signs and Symptoms	Influenza	Cold
Symptom onset	Abrupt	Gradual
Fever	Usual	Rare
Aches	Usual	Slight
Chills	Fairly common	Uncommon
Fatigue, weakness	Usual	Sometimes
Sneezing	Sometimes	Common
Stuffy nose	Sometimes	Common
Sore throat	Sometimes	Common
Chest discomfort, cough	Common	Mild to moderate
Headache	Common	Rare

Because colds and flu share many symptoms, it can be difficult (or even impossible) to tell the difference between them based on symptoms alone.

https://www.cdc.gov/flu/about/qa/coldflu.htm

Virus associated with common cold

Virus	Percentage
Rhinovirus	40 – 50
Coronavirus	10 – 15
Parainfluenza virus	5
Respiratory syncytial virus	5
Influenza virus	25 – 30
Adenovirus	5 – 10
Metapneumovirus	5

Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th Ed. 2014.
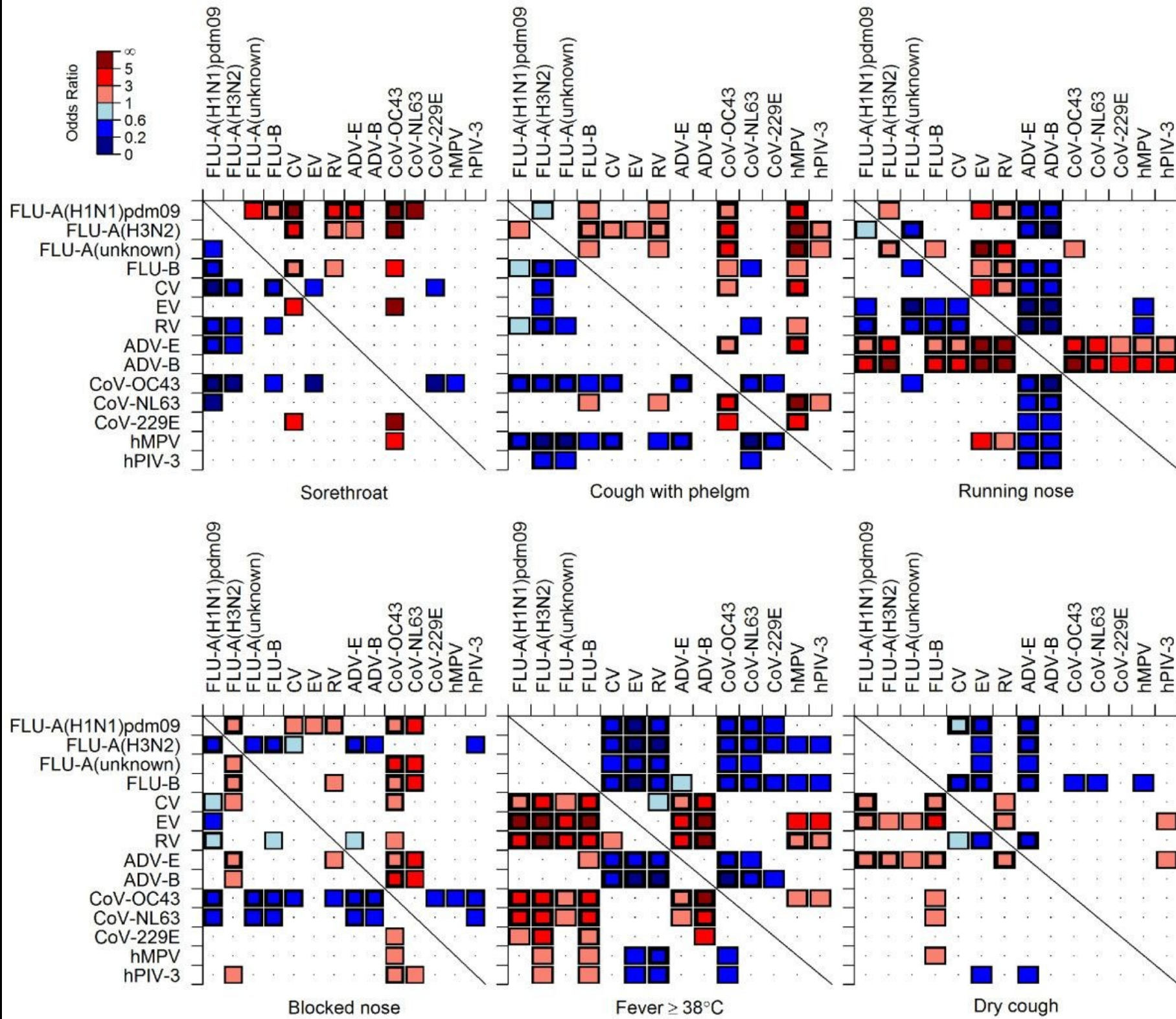
Cause of influenza-like illness

- Belgium, during influenza A (2009) pandemic
  - Influenza virus 53%
  - Rhinovirus 13%, RSV 4%, PIV 4%, hMPV 1%

    Hombrouck A. *Eur J Clin Microbiol Infect Dis*. 2012;31(6):999-1007.

- Singapore, miliary servicemen, 2009-2012
  - Influenza virus 40.1%
  - Coxsackie/echovirus 7.9%, rhinovirus 5.1%, adenovirus 4.8%, coronavirus 3.5%

    Tan XQ. *BMC Infect Dis*. 2014;14:204.

Sorethroat

Cough with phelgm

Running nose

Blocked nose

Fever ≥ 38°C

Dry cough

Tan XQ. *BMC Infect Dis.* 2014;14:204.

流感比較會重症？
不完全正確

Respiratory virus infection other than influenza in MICU, NCKUH 2017.05 – 2018.07

Parainfluenza 1-4	8
Rhinovirus / enterovirus	6
Respiraotry syncitial virus	6
Human metapneumovirus	6
Adenovirus	5
Coronavirus	3

Unpublished data

同樣下呼吸道感染，
何時要想到流感？

Influenza pneumonia

- Pneumonia is the most common complication of influenza A (H1N1) infection
  - 40 – 66% hospitalized patients

Pattern of Chest X-Ray Abnormality	Distribution of Chest X-Ray Abnormality	Predominant Distribution of Chest X-Ray Abnormality
Consolidation	Unilateral	Upper
Ground-glass opacity	Bilateral	Middle
Nodular pattern	Focal	Lower
Reticular pattern	Multifocal	—
Pleural effusion	Diffuse	—
Pneumothorax	—	—
Pneumomediastinum	—	—
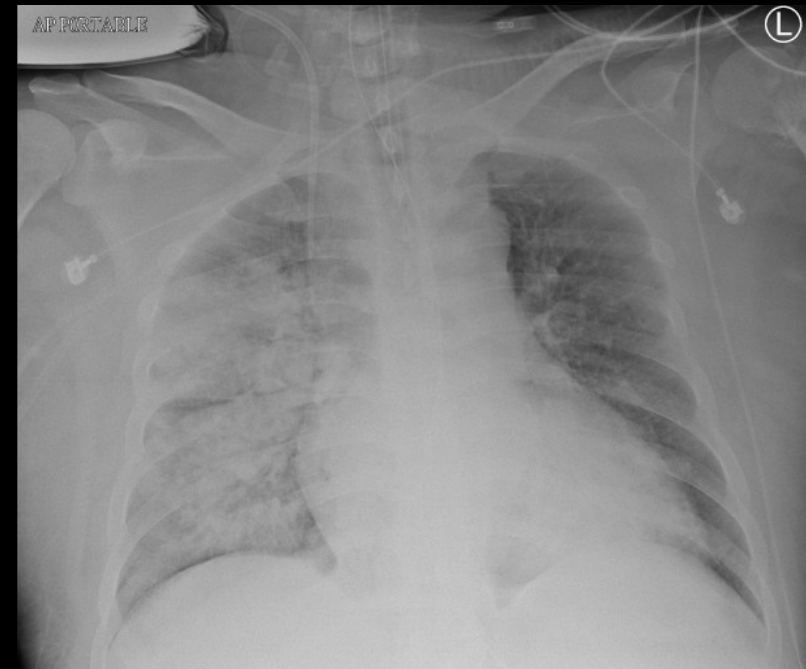
Influenza A(H1) pneumonia, 2017

Nicolini A. *Clin Pulm Med*. 2012:19(6):246-253

Predicting the unpredictable: is it possible clinically to separate H1N1 from non-H1N1 community-acquired pneumonia?

Nita Sehgal, Mark Woodhead

臨床及檢驗：不甚可靠

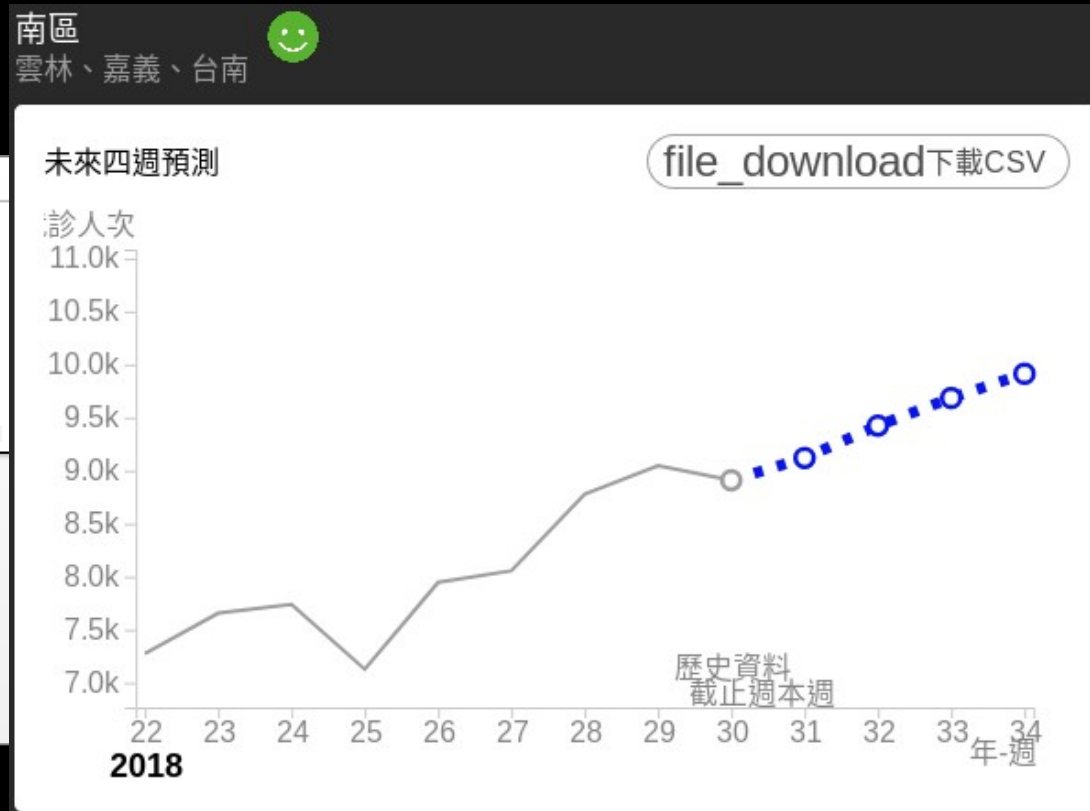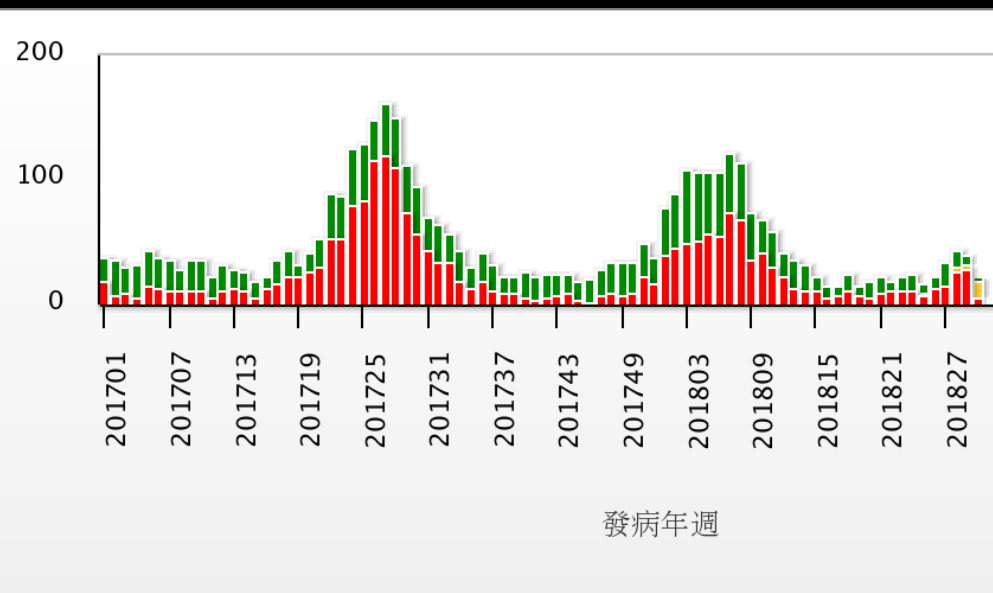**Table 3** Multivariate analysis of variables associated with H1N1 influenza-related pneumonia

Characteristic	Odds ratio	95% CI	p Value
Age ≤ 65 years	12.7	7.2 to 22.2	<0.001
White cell count $\leq 12 \times 10^9$/l	9.7	6.1 to 15.6	<0.001
Bilateral radiographic change	3.3	2.1 to 5.4	<0.001
Oriented in time/place/person	2.6	1.2 to 5.3	0.012
Temperature $\geq 38°C$	1.9	1.3 to 3.0	0.003

Points	Bacterial $n = 151$	(H1N1)pdm09 $n = 90$
0	1 (0.7)	1 (1.1)
1	35 (23.2)	2 (2.2)
2	56 (37.1)	15 (16.7)
3	48 (31.8)	21 (23.3)
4	9 (6)	32 (35.6)
5	2 (1.3)	16 (21.1)
AUROC (95% CI)	NA	0.77 (0.71−0.82)

Bewick T. *Thorax*. 2011;66(3):247-52.
Viasus D. *J Infect*. 2013;67(3):185-93.

Procalcitonin 也不夠好用

- Significant higher in patients with bacterial pneumonia (p = 0.0001)

- AUC 0.72, no good cut-off value

- Positive predictive value 52.8 – 61.8%

- Negative predictive value 69.4 – 82.2%

Pfister R. *Crit Care*. 2014;18(2):R44.

流行期遇到肺炎一定要想
非流行期沒有明顯病原也得考慮

南區
雲林、嘉義、台南

未來四週預測　　　　　file_download下載CSV

2018

https://nidss.cdc.gov.tw/
https://fluforecast.cdc.gov.tw/

合

In May 2017, a 72-year-old man with CAD s/p CABG, DM, CKD, HTN visisted the ED due to fever, dyspnea and wheezes for 4 days.

More information

- Symptoms
  - Fever
  - Sore throat
  - Dyspnea
  - Mild cough
- Clustered URI+
- WBC 41300, PMN 90%
- CRP 370 mg/L

Pathogens

- Blood culture: *Staphylococcus aureus*
- Sputum influenza PCR: influenza A(H1)
- Sputum culutre: *Staphylococcus aureus*

    Aspergillus flavus

- BAL influenza PCR: influenza A(H1)
- BAL culture: *Staphylococcus aureus*
- BAL Aspergillus Ag (galactomannan): 3.16

流感合併其他病原感染
死亡率高
住院天數長

Co-infections in Influenza, 1918-19

- 5266 autopsies in 96 series

Streptococcus pneumoniae	23.5%
Streptococcus haemolyticus	17.0%
Staphylococcus aureus	8.1%
Mixed pneumopathogen	21.0%
Bacillus influenzae	9.9%
Other bacteria	15.6%
No growth	4.2%

Bacterial co-infections in influenza

- 0.5% in young healthy individuals

- At least 2.5% in older individuals and those with predisposing conditions

- 34% of ICU patients

- High risk patients

  Age ≥ 65 y or < 5 y

  Pregnant woman

  Morbid obesity

  Pre-existing medical conditions

Metersky ML. *Int J Infect Dis*. 2012;16(5):e321-31.
Chertow DS. *JAMA*. 2013;309(3):275-82.

Co-pathogens in the US

- 2003-04
  - 959 adults with influenza
  - 125 needed intubation
  - 97 with co-infection
    - *S. aureus* 31
      MRSA 24
    - *S. pneumoniae* 16
    - *S. pyogenes* 2
    - Other 4

- 2009-10
  - Bacterial infection in 13 – 55% fatal cases
  - 77 lung tissue specimens
    - *S. pneumoniae* 10
    - *S. aureus* 7
      MRSA 5
    - *S. pyogenes* 6
    - *S. mitis* 2
    - Other 5

Metersky ML. *Int J Infect Dis*. 2012;16(5):e321-31.

Co-pathogens in Spainish ICUs

- 2009 – 2015, 184 ICUs in Spain, 2901 patients
- Patients with co-infections: 482 (16.6%)

Streptococcus pneumoniae	246	51.0%
Pseudomonas aeruginosa	55	11.4%
MSSA	42	8.7%
Aspergillus spp	35	7.2%
Haemophilus influenzae	17	3.5%
Acinetobacter baumannii	14	2.9%
MRSA	12	2.4%
Klebsiella pneumoniae	12	2.4%

Martin-Loeches I. *Intensive Care Med*. 2017;43(1):48-58.

Co-infection pathogens in Taiwan

- 7 centers in Taiwan, Jan – Mar 2016
- 233 critically ill patients with influenza
- Co-infections in 91 specimen
- Most common comunity-acquired respiratory infection – MSSA (12 patients, 7.3%)
- Late-onset VAP

Acinetobacter baumanii	20	12.1%
Pseudomonas aeruginosa	11	6.7%
Klebsiella pneumoniae	10	6.1%

Chen WC. *Am J Respir Crit Care Med* 2017;195:A6066

Co-pathogens in NCKUH

- 2017/01 - 2018/06，共 72 位通報流感重症病人
- 31 位 (43%) 在住院 7 天內有 co-infections

Klebsiella pneumoniae	12	38.7%
Staphylococcus aureus	8	25.8%
MRSA	4	12.9%
Aspergillus spp	8	25.8%
Pseudomonas aeruginosa	5	16.1%
Mycoplasma pneumoniae	3	9.7%
Streptococcus pneumoniae	2	6.5%
Haemophilus influenzae	2	6.5%

本院 2017/01–2018/06 流感重症病人
co-infection 與單純 influenza 者比較

死亡率

25.8% v.s. 17.07%

存活者住院天數 (中位數)

20 v.s. 13 天

流感病人有肺炎
建議經驗性抗生素需涵蓋

Methicillin-sensitive *Staphylococcus aureus*

Streptococcus pneuomniae

Klebsiella pneumoniae

部份病人需考慮

MRSA, *P. aeruginosa*, *Aspergillus* spp

所有流感肺炎
都該進行完整微生物檢驗

Procalcitonin for detecting bacterial co-infections

- AUCROC 0.68
- Positive likelihood ratio   2.31 (1.93 – 2.78)
- Negative likelihood ratio 0.26 (0.17 – 0.40)

如 PCT ≤ 0.5, bacterial co-infection 機率不大

但 PCT 偏高，尚無法 rule-in 細菌感染

Wu MH. *Influenza Other Respir Viruses*. 2013;7(3):349-55.

流感會和其他病毒一起來嗎？
很少

A 54-year-old man without known chronic disease came to NCKUH ED in July 2017 due to dyspnea for 3 days.

During the ED stay...

- Cough & fever

- Diabetic ketoacidosis

- WBC 12.4k, Seg 51%, Band 23%, Meta 2%

- 流感快篩陰性

- Blood culture:
  Klebsiella pneumoniae

- Abdominal CT: BLL pneumoniae, no IAI
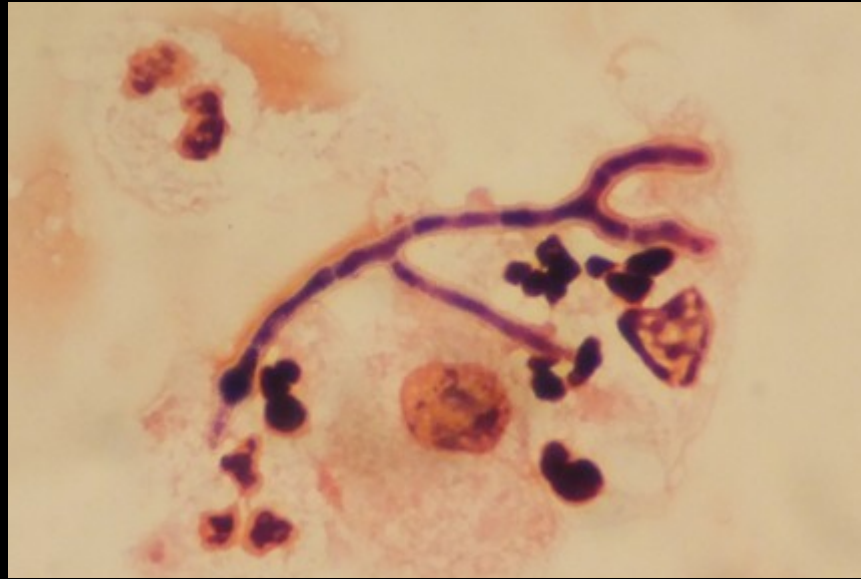
Admision after 2 days of ED stay

- Soon Intubated after ward admission

- Transfer to ICU

- ARDS

- HbA1c 14.8%

Clinically worsening
(5 days after admission)

- Sputum 2018/07/12
  - *K. pneumoniae*
  - *P. aeruginosa*
  - *Aspergillus fumigatus*
- Sputum 2017/07/15
  - *K. pneumoniae*
  - *A. baumannii* (XDR)
  - *Aspergillus fumigatus*

BAL, Gram stain

看到 aspergillosis 沒有其他危險因子
檢驗 influenza PCR

鼻咽拭子： 陰性
氣管內抽痰：influenza A(H3)

這位病人在醫院住了 56 天才出院

流行季節看到這些 co-infection 病原，也要想到可能和流感有關。

Take home messages

- 流感的典型表現為突然間高燒合併全身及呼吸道症狀。有時表現與一般上呼吸道感染類似，其他病毒有時也可以造成類流感症狀。

- 流感本身就會導致肺炎，也會合併細菌肺炎及呼吸道黴菌感染，造成較高的死亡率及延長住院。

- 常見的 co-pathogens 包含 *S. aureus, K. pneumoniae, S. pneumoniae, P. aerugionsa*, 以及 *Aspergillus* spp. 治療病人時應努力找出致病原。

- 在流行期，疑似呼吸道感染的病人都應小心流感的可能性。