社区获得性肺炎病原学与抗生素选择的变迁

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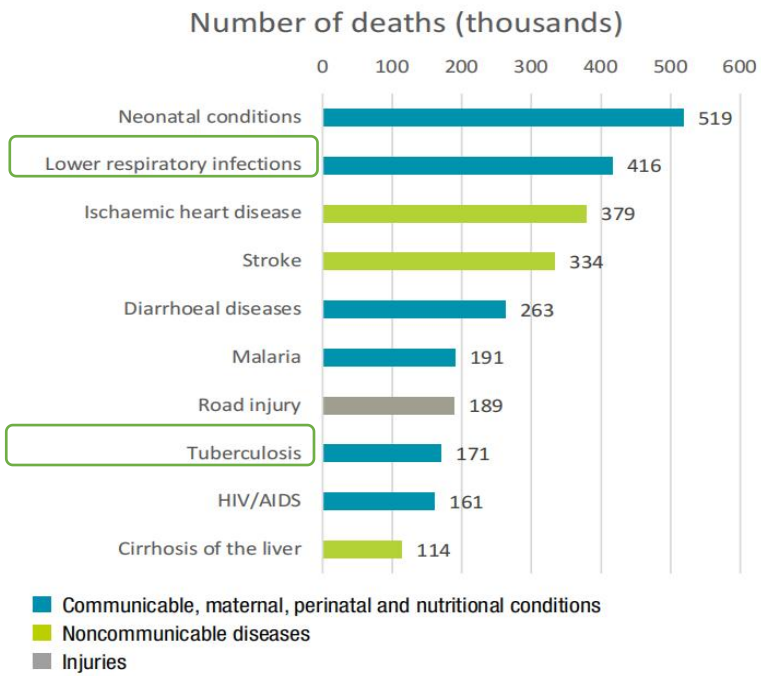
社区获得性肺炎（CAP）的公共卫生负担

- 全球前10死因中**传染病**占5个
  - 下呼吸道感染位列全球疾病死因**第二位**



Source: WHO Global Health Estimates, 2019 *(1)*.

https://www.who.int/data/gho/publications/world-health-statistics

医师应在保证充分治疗的同时避免过度治疗

- 建立在对CAP患者病情严重程度、病原倾向性、耐药风险充分评估后的经验性治疗
- 病原学检查手段的合理使用，以期尽快转换为精准治疗
- 动态评估患者疗效，抗感染治疗疗程和出院时机的选择

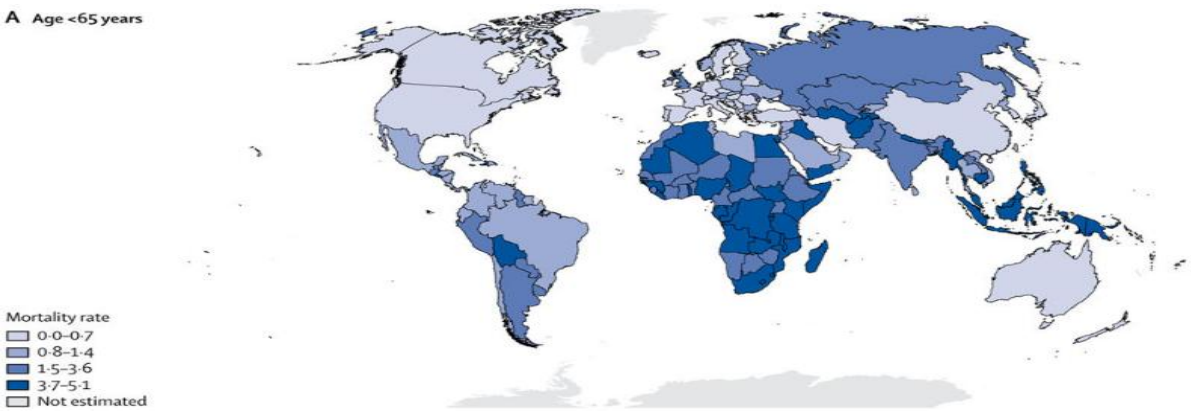
CAP病死率

中国住院社区获得性肺炎30天病死率 4.2%！

1. Kolditz M, et al. Eur Respir J 2016; In press | DOI: 10.1183/13993003.00113-2016
2. Tashiro et al. BMC Pulmonary Medicine (2016) 16:39
3. Egger et al. BMC Medical Informatics and Decision Making (2016) 16:34
4. Chen L, et al. BMJ Open 2018;8:e018709.

CAP病死率

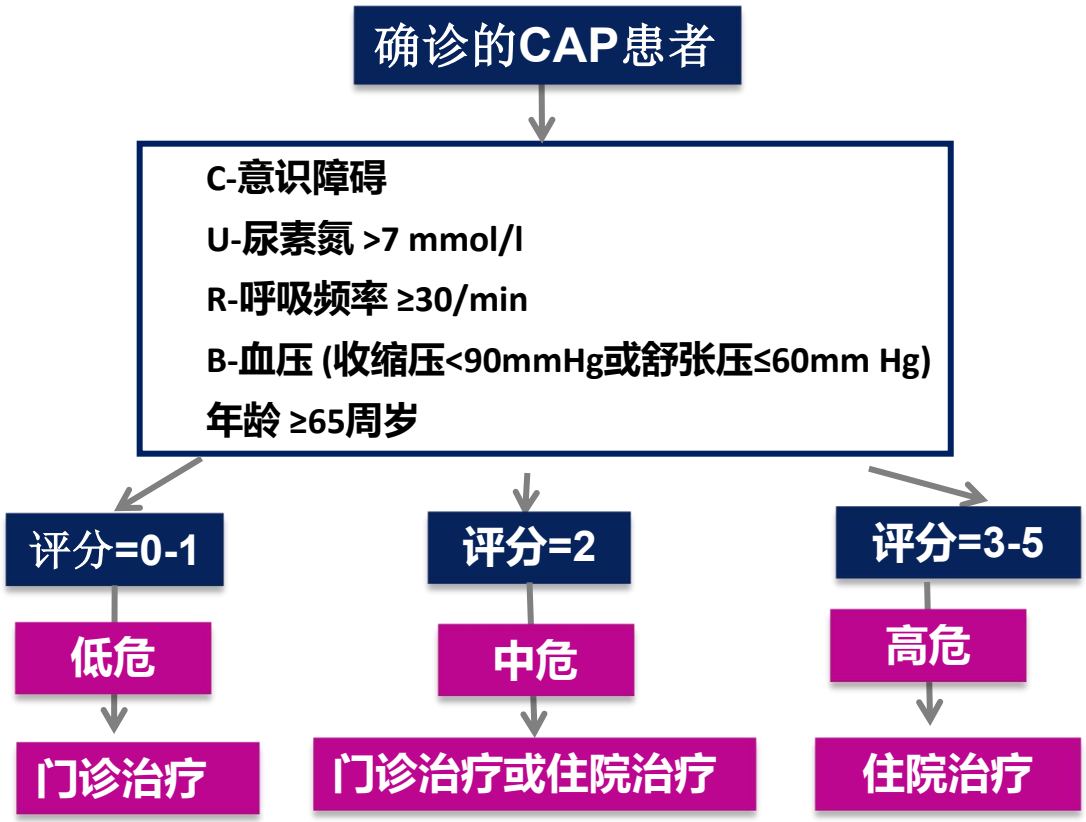
- **季节性流感：**
  - 全球流感相关死亡人数**29万-65万/年**

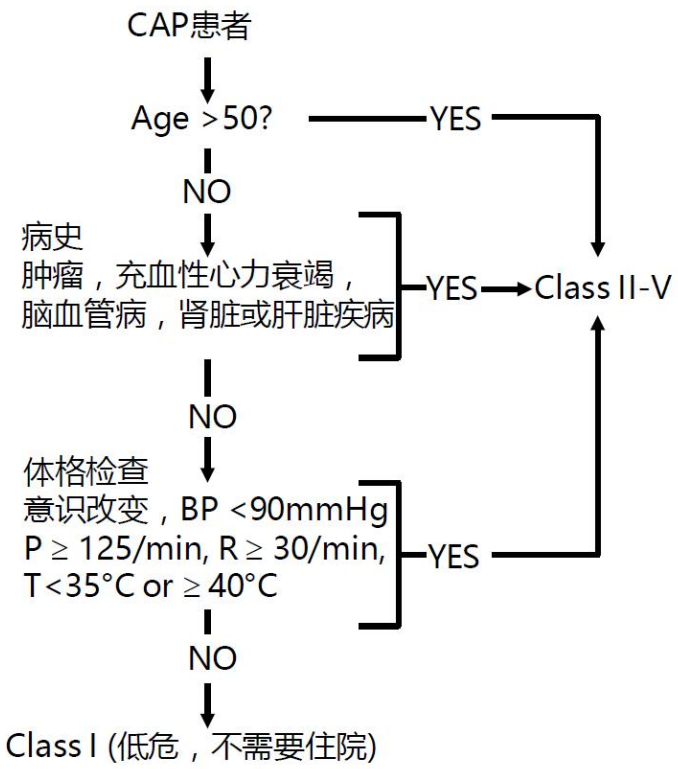


- **新发突发呼吸道传染病：**
  - 2003年SARS
  - 2009年新甲型H1N1流感
  - 2013年人感染H7N9禽流感
  - 2020-2021年新冠肺炎**超额死亡1400万**

William et al., Nature. 2022. Online ahead of print.

分层首先应评价患者病情严重程度选择治疗地点





PSI评分

Fine MJ, et al. *N Engl J Med.* 1997;336:243-250.
Lim WS et al Thorax. 2003;58:377-382.

但任何评分系统都应结合患者年龄、基础疾病、社会经济状况、胃肠功能、治疗依从性等综合判断

中华医学会呼吸病学分会. 中国成人社区获得性肺炎诊断和治疗指南（2016版）. 中华结核和呼吸杂志, 2016, 39(4):253-279.

重症CAP诊断标准

主要标准：

①有创机械通气

②脓毒性休克需要血管加压素

次要标准：

①呼吸频率≥30次/分；

②PaO_2/FiO_2≤250；

③多肺叶浸润；

④意识模糊、定力向障碍

⑤高尿素血症（尿素氮≥20mg/dl）；

⑥感染致白细胞减少（<4×10^9/L）；

⑦血小板减少（<100×10^9/L）；

⑧低体温（肛温<36℃）；

⑨低血压需要积极的液体复苏。

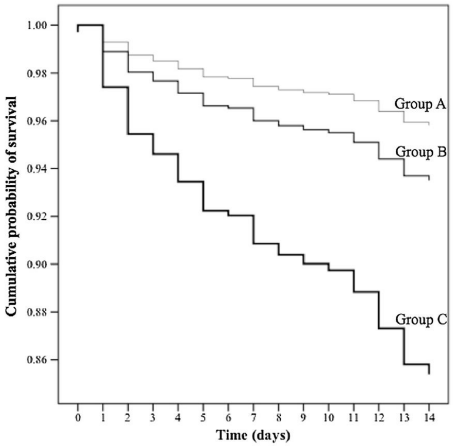
诊断：符合 1项主要标准，或 3项次要标准

Clin Infect Dis 2007;44(suppl):S27-72. Current Infectious Disease Reports2009，11（5）：349-356

重症CAP：危害巨大，但病原学检出率低

- **2~24%CAP住院患者进入ICU治疗**
- **在ICU接受治疗的CAP患者病死率高达17~49%**

.Crit Care. 2012;16:R141
Intensive Care Med. 2011;37:1409–20.
N Engl J Med. 2015;375:415–27.
Am J Respir Crit Care Med. 2002;166:717–23



A: CAP
B: CAP with ARF
C: CAP with ARF&SS

当合并呼吸衰竭和血流动力学异常时病死率极高

Respir Res 2014, 15:27

- **西班牙多中心：432例重症社区获得性肺炎 (SCAP)病原学检出率53%**
- **法国多中心：956例入住 ICU 的 SCAP，病原学检出率56.3%**
- **CAP China：SCAP病原学诊断率29.7%**

Eur Respir J. 2018, 51 (3) 1702215
Crit Care. 2013. 17:R265
部分数据未发表

CAP临床新特点

病原学特点

- **病原谱更为广泛**
- **新发、突发呼吸道病毒**

  H5N1/H7N9高致病性禽流感

  新型H1N1甲型流感

  腺病毒55型
- **CAP常见病原微生物的耐药**
- **混合感染**

  原发性

  继发性

宿主特点

- **逐年增多**

  器官移植

  肿瘤放化疗的广泛开展

  HIV感染者增多

  免疫抑制剂的应用：糖皮质激素、细胞毒药物、生物制剂

  糖尿病，老龄化
- **严重并发症发生率高**

  肺部并发症最为常见

  急性呼吸衰竭，特别是SCAP是入ICU最常见的原因

CAP：抗生素合理使用

- 病原学的倾向性判断是进行抗感染治疗决策的最重要一步
- 常见的CAP病原菌中耐药株比例逐渐增加
- 但重症CAP不等同于耐药菌感染
- 在危重症患者中强调抗生素尽早应用

病原学的倾向性判断

对CAP病原流行病学有充分的了解和认识，以覆盖可能病原

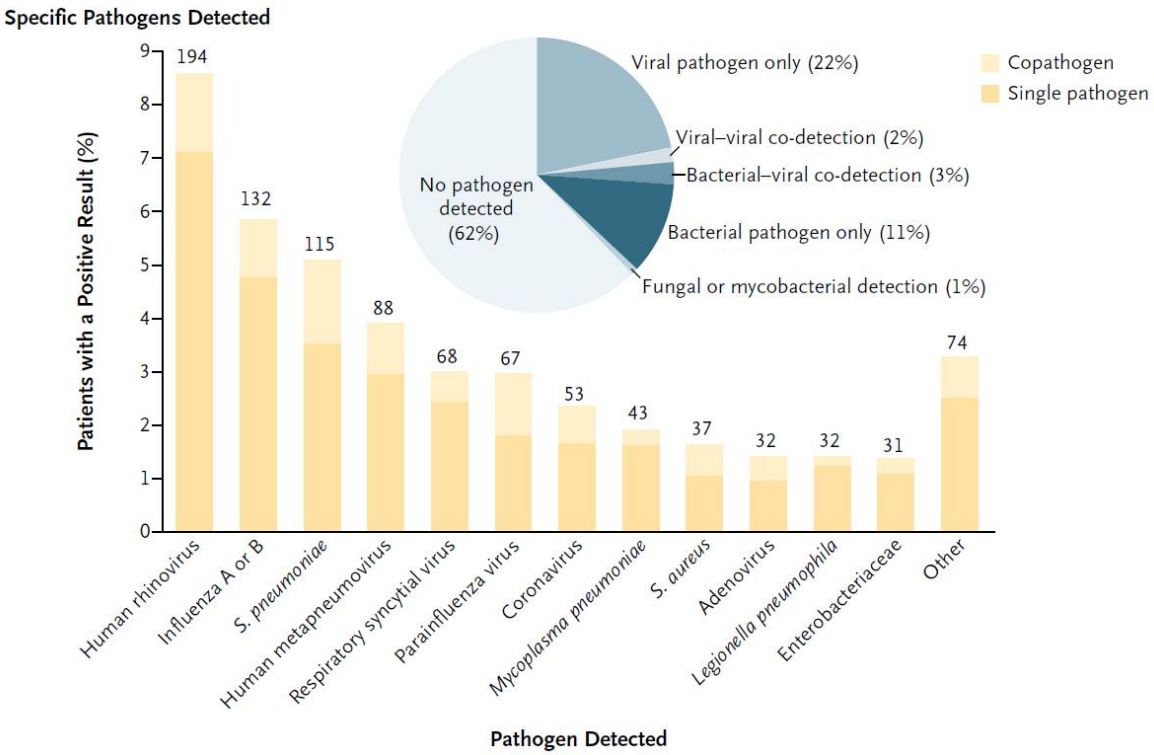
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults

病毒是重要的病原微生物

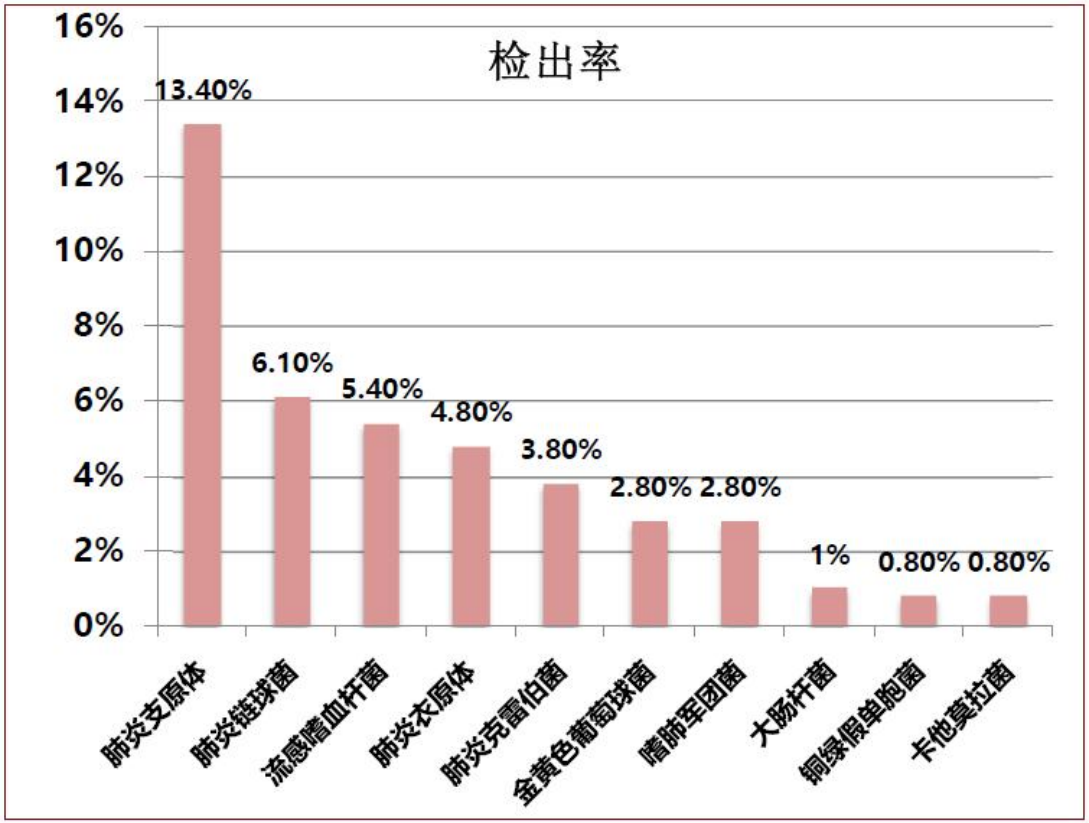
- 鼻病毒
- 流感病毒
- 肺炎链球菌
- 巨细胞病毒
- 呼吸道合胞病毒
- 副流感病毒
- 冠状病毒
- 肺炎支原体
- 金黄色葡萄菌
- 腺病毒
- 嗜肺军团菌
- 肠杆菌属



S Jain, et al. N Engl J Med 2015;373:415-27.

病原学的倾向性判断

对我国CAP病原流行病学有充分的了解和认识，以覆盖可能病原



肺炎支原体和肺炎链球菌是常见病原体，病毒同样是重要病原体

Qu JX et al. BMC Infectious Diseases (2015) 15:89
Liu Y et al. BMC Infectious Diseases. 2009;9:31.

常见的CAP病原菌中耐药株比例逐渐增加

我国肺炎链球菌耐药形势严峻

Table 2 Prevalence of *S. pneumoniae* penicillin resistance in different countries[a]

	United States	Canada	China	Spain
Penicillin V (oral)	20.7	6.7–15.9	24.5	37
Penicillin G[b]	1.5	2.5	1.9	0
Ceftriaxone	1.6	0.8	10.2	/
Cefotaxime	24.3	8.5	42.1	9.7
Erythromycin	42.7	54.5	93.8	19–21.1
Clarithromycin	/	15.9	87.4	20.9
Levofloxacin	1.0	0–1.4	2.6	0.5–5.6

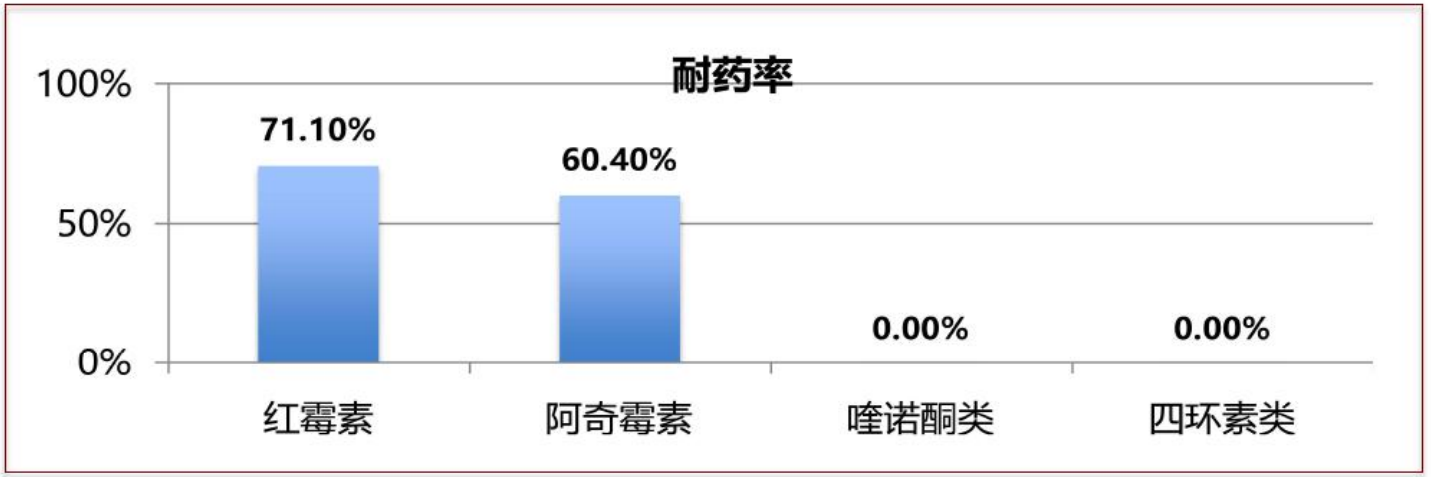
- 肺炎链球菌虽然对口服青霉素耐药率高，但对**静脉青霉素**敏感性高
- 二代头孢对肺炎链球菌耐药率39.9%-50.7%
- 我国肺炎链球菌对大环内酯类药物耐药率高

年龄＞65岁，存在基础疾病（慢性心脏、肺、肝、肾基础疾病、糖尿病、免疫抑制）、酗酒、3月内接受β内酰胺药物治疗是耐药肺炎链球菌感染的危险因素

Wunderink RG et al.Semin Respir Crit Care Med. 2016;37(6):829-838.
赵春江 等. 中华结核和呼吸杂志. 2015,3(18):18-22
中国成人社区获得性肺炎诊断和治疗指南（2016年版）.中华结核和呼吸杂志，2016,3(4)：1-27.

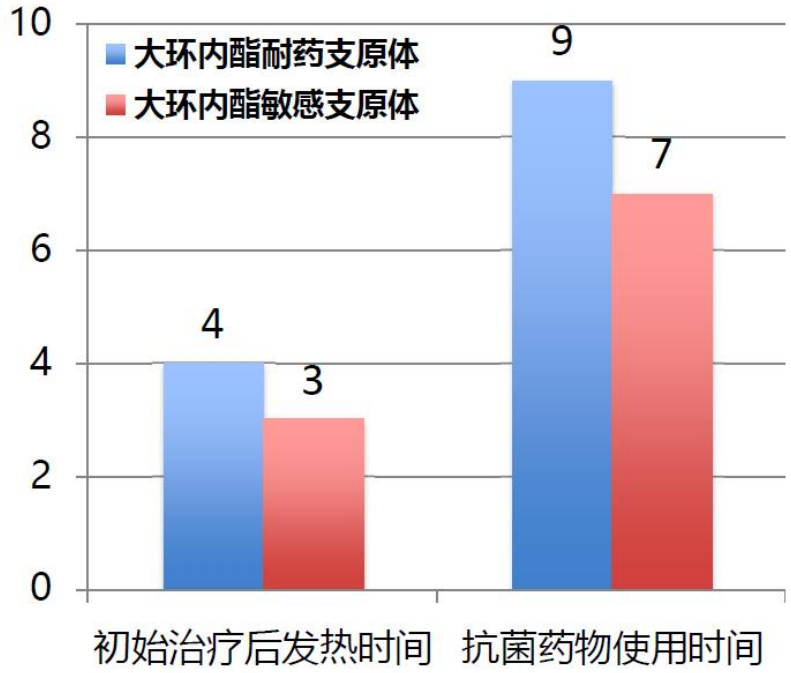
常见的CAP病原菌中耐药株比例逐渐增加

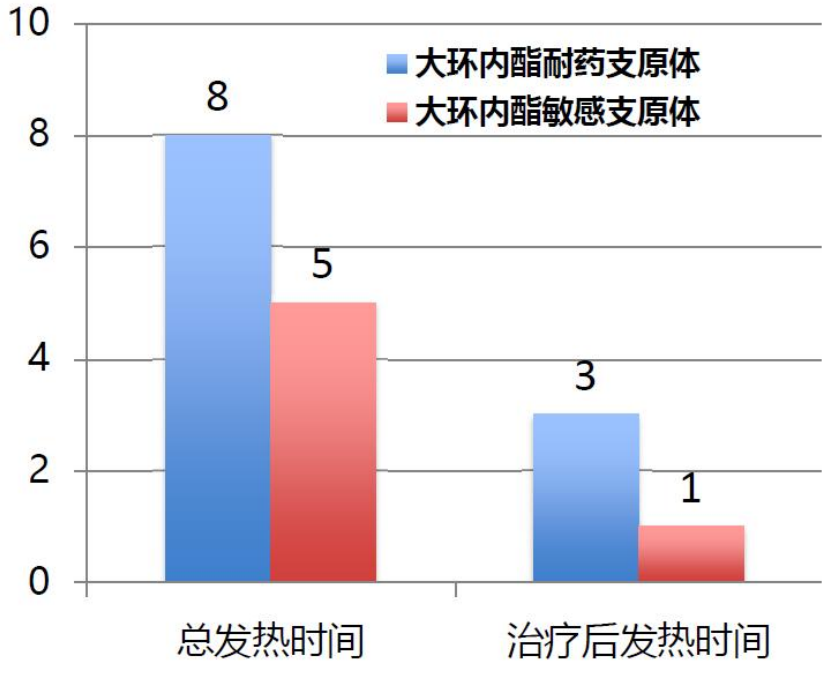
肺炎支原体对大环内酯类药物普遍耐药



Zhao F, et al. Antimicrob Agents Chemother. 2013 Mar;57(3):1521-3.
尹玉东等.中华结核和呼吸杂志,2013,36:954-958
Cao B,et al.Clin Infect Dis,2010,51:189-194.

耐药肺炎支原体经验性抗感染治疗





- **我国研究显示大环内酯耐药支原体感染的发热时间延长，需要更长时间抗感染药物治疗**
- **日本研究显示大环内酯耐药支原体总发热时间和治疗后发热时间长于大环内酯敏感支原体感染**

住院患者怀疑支原体感染时，首选四环素或喹诺酮类药物

常见的CAP病原菌中耐药株比例逐渐增加

我国CA-MRSA发病率低

- 2009-2010中国成人社区获得性呼吸道感染病原耐药监测未发现CA-MRSA

CA-MRSA感染临床特点	CA-MRSA易感人群
肺坏死性病变	与MRSA感染者接触
早期即出现肺部空洞	流感病毒感染
肺部渗出快速进展	监狱服刑人员
出现胸腔积液	同性恋人群
中性粒细胞减低	男性同性性行为
咯血	静脉吸毒
腹泻	竞技类体育运动员
既往身体健康	近期服兵役
夏季发病	使用蒸气浴
红色斑疹	

咯血CA-MRSA患者肺组织

因此，不推荐在无危险因素的重症CAP患者中常规覆盖MRSA
但在重症甲流患者中应常规覆盖MRSA

常见的CAP病原菌中耐药株比例逐渐增加

- 嗜肺军团菌：因对大环内酯类药物耐药率高，FDA推荐在重症患者中考虑应用呼吸喹诺酮类
- 新型H1N1甲型流感：发现奥司他韦耐药突变（H275Y）
- ……

重症CAP不等同于耐药菌感染

欧洲2892名社区获得性肺炎患者，297名血培养阳性

TABLE 6 Significant univariate and multivariate logistic regression analyses for the prediction of patients with antibiotic-resistant pathogen bacteraemia

	Univariate		Multivariate#	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Previous antibiotic	2.55 (1.00–6.50)	0.051	3.70 (1.24–11.03)	0.019
Neurological disease	2.20 (0.94–5.14)	0.067		
Nursing-home¶	6.21 (1.00–38.78)	0.051		
Pleuritic pain	0.39 (0.18–0.87)	0.022	0.24 (0.09–0.63)	0.004
C-reactive protein <22.2 mg·dL^{-1}	4.64 (1.86–11.61)	0.001	4.09 (1.55–10.78)	0.004
CURB-65 risk class 3–5	2.07 (0.95–4.53)	0.068		

CURB-65: confusion, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) ⩽60 mmHg (diastolic), age ⩾65 years. #: Hosmer–Lemeshow goodness-of-fit test, p=0.70; ¶: variables included in the definition of healthcare associated pneumonia.

尽管重症患者中耐药菌感染相对常见，
但重症并不是耐药菌感染的独立危险因素，应充分评估耐药菌危险因素

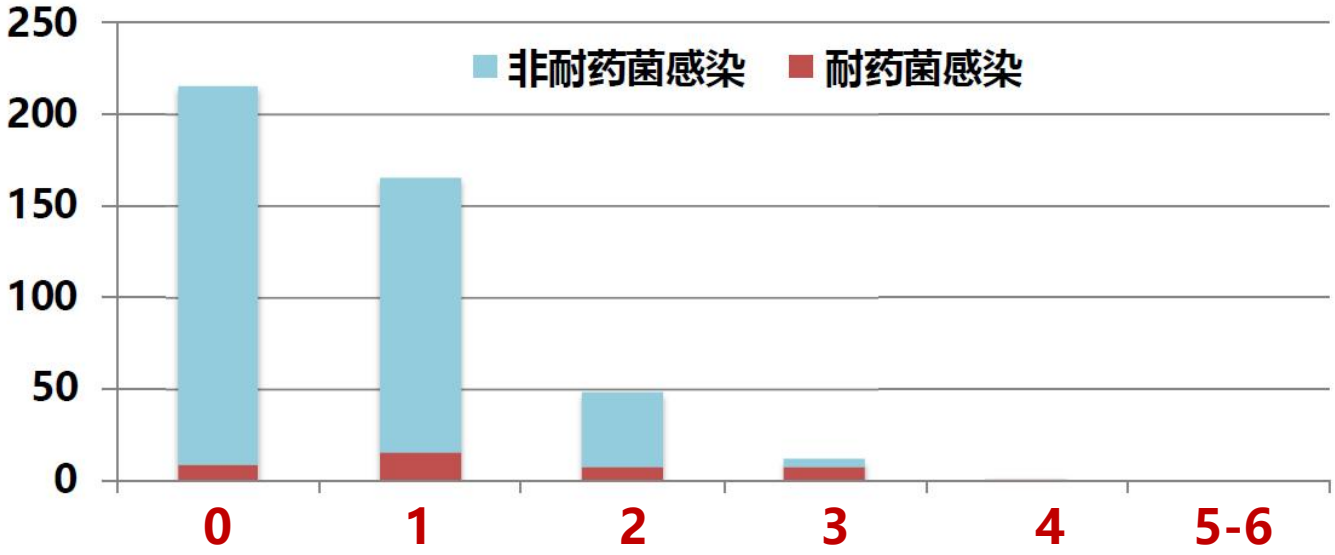
Torres A et al.Eur Respir J. 2015;45(5):1353-63.

抗感染药物选择亦应评估患者耐药菌感染风险

社区获得性肺炎患者耐药菌感染的危险因素：

（1）90天内住院≥2天；（2）免疫抑制；（3）胃酸抑制药物；（4）90天内曾应用抗菌药物；（5）鼻饲；（6）不能活动

Am J Respir Crit Care Med. 2013;188(8):985-95



危险因素个数	0	1	2	3	4	5-6
CAP患者数	216	166	48	11	1	0
耐药菌感染n(%)	8(3.7)	15(9.0)	7(14.6)	7(63.6)	1(100.0)	0

避免选择过度抗感染治疗方案

低危患者不住院，综合患者年龄/基础疾病特点以及病原学倾向性判断选择适合门诊药物

不同人群	常见病原体	抗感染药物选择
门诊患者（推荐口服药物治疗）		
无基础疾病青壮年	肺炎链球菌、肺炎支原体、流感嗜血杆菌、肺炎衣原体、流感病毒、腺病毒、卡他莫拉菌	(1)氨基青霉素、青霉素类/酶抑制剂复合物；(2)一代、二代头孢菌素；(3)多西环素或米诺环素；(4)呼吸喹诺酮类；(5)大环内酯类
有基础疾病或老年人（年龄≥65 岁）	肺炎链球菌、流感嗜血杆菌、肺炎克雷伯菌等肠杆菌科菌、肺炎衣原体、流感病毒、RSV 病毒、卡他莫拉菌	(1)青霉素类/酶抑制剂复合物；(2)二代、三代头孢菌素(口服)；(3)呼吸喹诺酮类；(4)青霉素类/酶抑制剂复合物、二代头孢菌素、三代头孢菌素联合多西环素、米诺环素或大环内酯类

门诊选择口服、利用度高的药物：阿莫西林或阿莫西林克拉维酸
青年无基础疾病怀疑支原体感染患者可口服多西环素或米诺环素
经验性抗感染治疗方案选择：“够用”即可

中国成人社区获得性肺炎诊断和治疗指南（2016年版）

避免选择过度抗感染治疗方案

不同人群	常见病原体	抗感染药物选择
住ICU患者（推荐静脉药物治疗）		
无基础疾病青壮年	肺炎链球菌、金黄色葡萄球菌、流感病毒、腺病毒、军团菌	(1)青霉 类/酶抑制剂复合物、三代头孢菌素、头霉素类、氧头孢烯类、厄 他培南联合大环内酯类；(2)呼吸喹诺酮类
有基础疾病或老年人（年龄≥65 岁）	肺炎链球菌、军团菌、肺炎克雷伯菌等肠杆菌科菌、金黄色葡萄球菌、厌氧菌、流感病毒、RSV 病毒	(1)青霉 类/酶抑制剂复合物、三代头孢菌素或其酶抑制剂的复合物、厄 他培南等碳青霉烯类联合大环 酯类；(2)青霉素类/酶抑制剂 合物、三代头孢菌素或其酶抑制剂复合物、厄他培南等碳青霉 类联合呼吸喹诺酮类

- 除肺炎链球菌，重症患者需考虑军团菌、金黄色葡萄球菌感染可能
- 流感季节要考虑流感病毒感染可能
- 老年有基础疾病患者推荐联合用药

中国成人社区获得性肺炎诊断和治疗指南（2016年版）.中华结核和呼吸杂志，2016,3(4)：1-27.

避免选择过度抗感染治疗方案

EXPERT REVIEWS

The management of severe community acquired pneumonia in the intensive care unit

Box 4. Therapy of community-acquired pneumonia admitted to ICU.

No risk factors for *Psuedomonas aeruginosa*
Non antipseudomonal Cefalosporin III + macrolide
OR
Non antipseudomonal Cefalosporin III ± moxifloxacin or levofloxacin
Risk factors for *Psuedomonas aeruginosa*
Antipseudomonal cephalosporin or acylureidopenicillin/β-lactamase inhibitor or carbapenem (meropenem preferred, up to 6 g possible, 3 × 2 in 3 h infusion
PLUS
Ciprofloxacin†
OR
PLUS
Macrolide + aminoglycoside (gentamycin, tobramycin, amikacin)

要点

- 评估是否存在铜绿假单胞菌感染危险因素
- 结合常见病原学耐药特点，在重症CAP中增加了喹诺酮类推荐

The management of severe community acquired pneumonia in the intensive care unit, Expert Review of Respiratory Medicine,2014 8:3, 293-303.

避免过度应用具有抗铜绿假单胞菌作用药物

Table 4 Empirical antimicrobial regimen for patients with CAP (n=5716)*				
	Without risk factors for *Pseudomonas* infection (n=3852)			
Empirical antimicrobials (%)	Age <65 years and not in ICU (n=1881)	Age <65 years and in ICU (n=79)	Age ≥65 years and not in ICU (n=1742)	Age ≥65 years and in ICU (n=150)
β-Lactams (antipseudomonal)	178 (4.6)‡	21 (0. 5)	407 (10.6)‡	58 (1.5)
β-Lactams	331 (8.6)	9 (0.2)	482 (12.5)	20 (0.5)
Fluoroquinolones	502 (13.0)	10 (0.3)	273 (7.1)	6 (0.2)
Macrolides	20 (0.5)	0 (0.0)	17 (0.4)	0 (0.0)
β-Lactams (antipseudomonal)+fluoroquinolones	201 (5.2)‡	13 (0.3)‡	189 (4.9)‡	30 (0.8)
β-Lactams+fluoroquinolones	302 (7.8)‡	3 (0.1)‡	166 (4.3)‡	9 (0.2)
β-Lactams+macrolides	160 (4.2)	2 (0.1)	64 (1.7)	2 (0. 1)
β-Lactams (antipseudomonal)+macrolides	50 (1.3)‡	0 (0.0)	45 (1.2)‡	2 (0.1)
Fluoroquinolones+macrolides	24 (0.6)	0 (0.0)	11 (0.3)	0 (0.0)
Anti-MRSA drugs	9 (0.2)‡	8 (0.2)	12 (0.3)‡	6 (0.2)
Others	104 (2.7)	13 (0.3)	76 (2.0)	17 (0.4)

铜绿假单胞菌感染危险因素

（1）气道铜绿假单胞菌定植；

（2）因慢性气道疾病反复使用抗菌药物或糖皮质激素。

（3）结构性肺病

- 重症或明确耐药菌感染应联合药物治疗

我国住院CAP患者中27.5%无铜绿假单胞菌感染危险因素的患者使用了抗铜绿假单胞菌药物

应避免抗铜绿假单胞菌药物的过度使用，尤其是碳青霉烯类药物的使用，以减少耐药菌的出现

老年CAP患者应考虑的几个危险因素

需要评估的危险因素

铜绿假单胞菌感染

- 结构性肺病
- 90天内曾入院治疗/使用抗菌药物/使用激素
- 长期入住医疗护理机构
- 曾有铜绿假单胞菌定植

误吸的风险

- 脑血管或神经系统疾病（癫痫）
- 呕吐或吞咽困难
- 头、颈部肿瘤
- 口腔疾病或口卫生差

↓

厌氧菌感染/革兰阴性菌 → **阿莫西林克拉维酸钾**
氨苄西林舒巴坦
莫西沙星碳青霉烯
或联合甲硝唑/克林霉素

MDR感染风险（产ESBL）

- 有产ESBL细菌定植史
- 90天内住院≥2天
- 近期静脉注射抗菌药物
- 前期曾使用3代头孢菌素
- 反复长期住院史
- 留置医疗器械
- 肾脏替代治疗

↓ 有

头霉素
哌拉西林他唑巴坦
头孢哌酮舒巴坦
厄他培南（或其他碳青霉烯）

Faverio P et al. Eur J Intern Med. 2014;25(4):312-9

我国老年CAP患者不充分和过度治疗问题严重

- 不足：入住监护室患者单用β内酰胺类（有或不具有抗铜绿作用）
- 过度：普通病房患者使用具有抗铜绿假单胞菌作用的β内酰胺类

Han X et al. BMC Infect Dis. 2018;18(1):192.

早期应用抗感染药物与CAP预后

本课题组，单中心，回顾性研究，919住院CAP患者

	分析			筛选		
	P 值	HR	95% CI	P 值	HR	95% CI
TFAD 分组						
TFAD≤4h	—	1.000	—	—	—	—
TFAD＞4h	0.116	1.733	0.873-3.441	—	—	—
CUBR-65 评分	0.039			0.002		
0	—	1.000	—	—	1.000	—
1	0.106	3.008	0.790-11.445	0.129	2.634	0.755-9.196
2	0.144	3.079	0.682-13.900	0.169	2.538	0.674-9.560
≥3	0.007	9.474	1.827-49.121	0.001	9.159	2.419-34.678
既往口服糖皮质激素	＜0.001	7.951	2.987-21.163	＜0.001	7.831	3.108-19.733
长期卧床	0.037	5.433	1.110-26.595	—	—	—
诊治过程中发生并发症	＜0.001	19.257	5.730-64.713	＜0.001	19.561	5.876-65.123
基础疾病	0.265	1.810	0.638-5.140	—	—	—
入住 ICU	0.650	0.830	0.371-1.858	—	—	—
重症肺炎	0.730	1.171	0.479-2.863	—	—	—
年龄	0.408	0.989	0.964-1.015	—	—	—
吸入因素	0.661	1.277	0.428-3.813	—	—	—

抗感染药物应用时间与患者预后无关

对于整体住院CAP患者，早期（＜4h应用抗感染药物）未能提高患者预后

早期应用抗感染药物改善伴脓毒症重症CAP患者预后

4137住院CAP患者，2966伴有脓毒症，1572伴有严重脓毒症

TABLE 6 Multivariate analyses of mortality and length of stay (LOS) with combinations of processes of care adjusted by hospital and pneumonia severity index

	In-hospital mortality		Mortality at 30 days		LOS	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
All population						
Abx	0.61 (0.44–0.85)	0.004	0.63 (0.47–0.85)	0.003	0.76 (0.66–0.87)	0.001
Abx plus timing	0.61 (0.44–0.84)	0.003	0.67 (0.50–0.89)	0.007	0.80 (0.71–0.91)	0.001
Abx plus timing plus oxygen	0.64 (0.46–0.89)	0.009	0.70 (0.52–0.94)	0.02	0.79 (0.70–0.90)	0.001
Nonsevere sepsis						
Abx	0.33 (0.16–0.65)	0.001	0.27 (0.15–0.49)	<0.001	0.76 (0.59–0.97)	0.03
Abx plus timing	0.47 (0.23–0.95)	0.03	0.44 (0.24–0.82)	0.009	0.73 (0.58–0.92)	0.007
Abx plus timing plus oxygen	0.54 (0.26–1.1)	0.09	0.52 (0.28–0.96)	0.03	0.64 (0.51–0.81)	0.001
Severe sepsis						
Abx	0.75 (0.49–1.13)	0.2	0.86 (0.59–1.28)	0.4	0.82 (0.66–1.03)	0.08
Abx plus timing	0.60 (0.40–0.91)	0.01	0.69 (0.48–1.015)	0.06	0.94 (0.77–1.16)	0.6
Abx plus timing plus oxygen	0.62 (0.41–0.92)	0.02	0.70 (0.48–1.03)	0.07	0.91 (0.74–1.12)	0.3

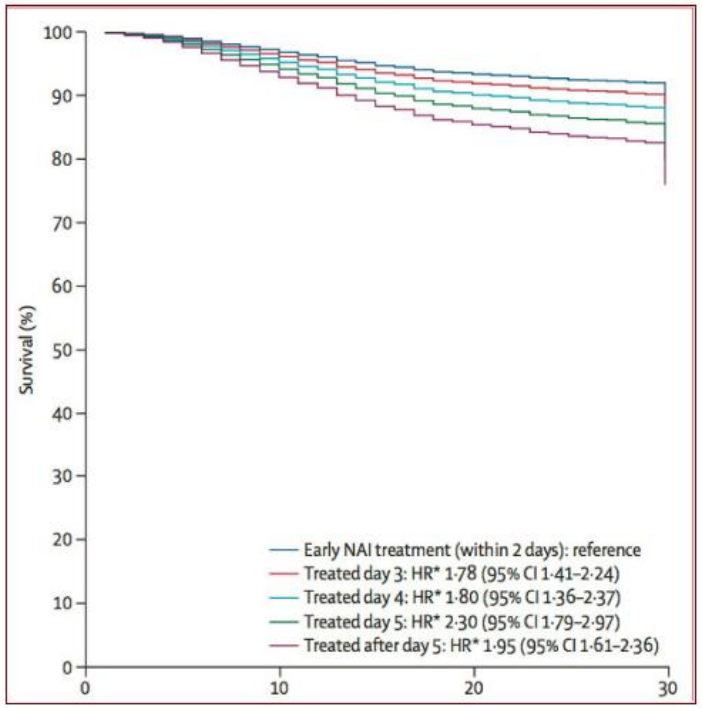
Abx: antibiotic adherence to guidelines; Timing: first antibiotic dose <6 h.

在合理使用抗感染药物前提下（符合指南），早期（＜6h）较延迟（＞6h）治疗的伴脓毒症CAP患者院内病死率和30天病死率低，住院时间更短

JJ et al.Eur Respir J. 2012;39(1):156-62

早期应用抗病毒药物改善重症流感患者预后

Meta分析，29234名住院重症A(H1N1)pdm 09 患者



	Crude analysis		Adjusted* analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Early treatment versus later treatment				
Laboratory confirmed or clinically diagnosed, all ages; n=13 254	0·36 (0·31–0·41)	<0·0001	0·48 (0·41–0·56)	<0·0001
Laboratory confirmed cases, all ages; n=12 992	0·36 (0·31–0·41)	<0·0001	0·48 (0·41–0·56)	<0·0001
Adults (≥16 years); n=9270	0·37 (0·32–0·44)	<0·0001	0·45 (0·38–0·54)	<0·0001
Children (<16 years); n=3899	0·53 (0·35–0·80)	0·0026	0·67 (0·44–1·03)	0·07
Pregnant women; n=917	0·20 (0·09–0·46)	0·0002	0·27 (0·11–0·63)	0·0026
Critical care patients				
Adults (≥16 years); n=3385	0·64 (0·51–0·79)	<0·0001	0·62 (0·49–0·77)	<0·0001
Children (<16 years); n=683	1·12 (0·63–1·99)	0·69	1·15 (0·64–2·06)	0·64

重症流感患者早期应用（发病＜2天）神经氨酸酶抑制剂较延迟治疗（＞2天），可降低患者死亡风险

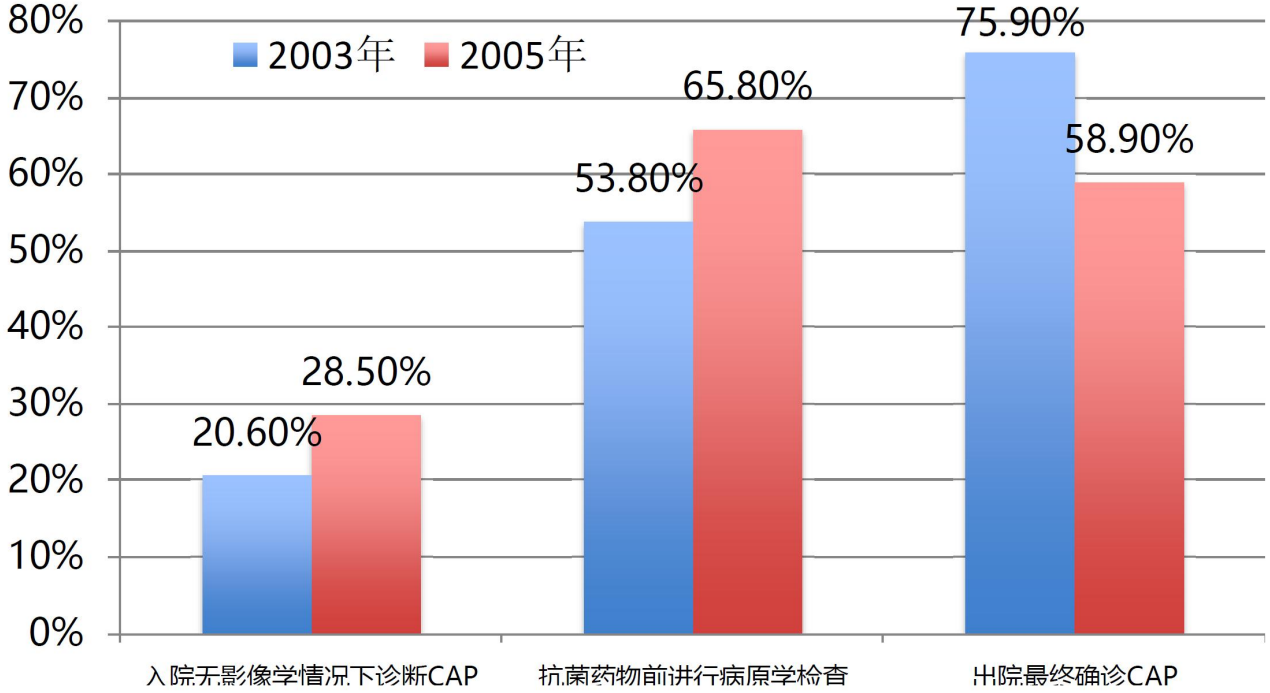
流感季怀疑流感病毒肺炎患者应，积极进行抗病毒治疗，不必等待病原学结果

Muthuri SG. Lancet Respir Med. 2014 ;2(5):395-404.

尽早应用抗感染药物应建立在正确诊断基础上

美国 734名住院CAP患者

在强调入院4小时内应用抗感染药物后，2005年在无影像学证据下诊断CAP的比例较2003年升高，但最终确诊的CAP患者比例显著降低



不能应追求抗感染的“早”而忽略必要的鉴别诊断

Kanwar M et al. Chest. 2007;131(6):1865-9.

在重症CAP患者中生物标志物效能尚待进一步证实

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection

N Engl J Med 2018; 379:236-249

结论：临床医生根据或不根据PCT结果对下呼吸道感染患者进行治疗，抗生素使用种类和时程上无统计学差异。

SCAP患者中生物标志物对初始抗生素指导意义缺乏更多循证证据

- 有**基础肺疾病或免疫抑制患者**，许多特殊病原微生物感染缺乏生物标志物指标
- **新发突发呼吸道传染病**，特别是呼吸道病毒
- 有**混合感染**时，初始抗生素难以完全覆盖致病菌

美国IDSA临床稳定标准是可靠的停药指标

- 实验组抗菌药物应用时间远低于对照组 5 vs 10 天 p<0.001

Table 4. Results for Secondary Study Outcomes in the Per-Protocol Analysis[a]

Outcome	Control Group (n = 137)	Intervention Group (n = 146)	*P* Value
Time, median (IQR), d			
Taking antibiotics	10 (10-11)	5 (5-6.5)	<.001
Not taking antibiotics	21 (10-27)	25 (5-32)	.001
Taking intravenous antibiotics	2 (1-4)	3 (2-4)	.22
Until clinical improvement	12 (8-18)	12 (7-15)	.41
Return to normal activity	18 (9-25)	15 (10-21)	.36
Radiographic resolution at day 30	93 (73.2)	112 (81.2)	.12
In-hospital mortality	2 (1.5)	3 (2.1)	>.99
30-d Mortality	3 (2.2)	3 (2.1)	>.99
Recurrence by day 30	6 (4.4)	4 (2.8)	.53
Readmission by day 30	9 (6.6)	2 (1.4)	.02
In-hospital complications			
Pleural effusion	10 (7.3)	5 (3.4)	.15
Treatment failure[b]	2 (1.5)	3 (2.1)	>.99
Respiratory failure[c]	26 (19.0)	31 (21.2)	.64
Severe sepsis[d]	7 (5.1)	8 (5.5)	.89
Renal failure[e]	5 (3.7)	6 (4.1)	.85
ICU admission	2 (1.5)	1 (0.7)	.61
Use of invasive mechanical ventilation	2 (1.5)	1 (0.7)	.61
Use of noninvasive mechanical ventilation	3 (2.2)	2 (1.4)	.67
Need for vasopressors	2 (1.5)	3 (2.1)	>.99
Antibiotic adverse effects by day 30	18 (13.1)	17 (11.7)	.72
Time with antibiotic adverse effects, mean (SD), d	3 (2.8)	1.7 (2.1)	.24
Length of hospital stay, mean (SD), d	5.5 (2.3)	5.7 (2.8)	.69

- 院内病死率、30天病死率、呼吸衰竭、入住ICU、机械通气、住院时间两组无统计学差别

Uranga A et al. JAMA Intern Med. 2016;176(9):1257-

美国IDSA停药标准有效指导临床用药时间

2014-2015年 美国 前后对照研究

在美国3家医疗中心推行 IDSA停药标准，培训6月后，比较培训前后患者治疗时间和结局

干预前（307名患者） 干预后（293名患者）

培训前后两组患者在年龄、基础疾病、免疫抑制、外周血中性粒细胞、淋巴细胞计数、病情严重程度无统计学差异

Table 1. IDSA/ATS DOT recommendations

Appropriate DOT	CAP-associated clinical signs of instability
• Five days of therapy if patients are afebrile for 48–72 h and exhibit no more than one sign of clinical instability • Longer durations of antibiotic therapy are recommended for patients with delayed clinical response, complications and extra-pulmonary infections	• Heart rate ≥100 beats per min • Respiratory rate ≥24 breaths per min • Systolic blood pressure ≤90 mmHg • Arterial O_2 saturation ≤90% or pO_2 ≤60 mmHg on room air • Altered mental status

美国IDSA停药标准

Table 5. Clinical outcomes

	Historical control group (*N* = 294), *n* (%)	Intervention group (*N* = 293), *n* (%)	*P*
CDI	0 (0)	0 (0)	–
Re-presented to emergency centre or clinic with pneumonia	20 (6.8)	13 (4.4)	0.22
Readmission with pneumonia[a]	21 (7.1)	11 (3.8)	0.075
Mortality[b]	7 (2.3)	3 (1)	0.233

临床结局比较

干预后，患者治疗时间明显缩短，但病死率、出院后因肺炎再次入院比例无统计学差异

Foolad F et al. J Antimicrob Chemother. 2018 Feb 16. doi: 10.1093/jac/dky021.

降钙素原有助于判断停药时间

PCT < 0.1pg/L: 强烈建议停药; 0.1 <PCT < 0.25pg/L:建议停药; 0.25<PCT< 0.5pg/L:建议使用抗菌药物；PCT > 0.5pg/L:强烈建议使用抗菌药物.

Study	Number of patients included	Initial prescription of antibiotherapy	Duration of antibiotherapy	Rate of clinical cure
Schuetz et al. [19]	925	90% PCT group and 99% control group ($P<0.001$)	7.2 days (interquartile: 4–10) PCT group and 10.7 days (interquartile: 8–12) control group ($P<0.001$)	At 1 month: composite clinical criterion of effectiveness: not inferior between both groups (−4.1%; 95% CI −9.1% to 0.9)
Christ-Crain et al. [32]	87	90.5% PCT group and 100% control group ($P=0.03$).	All lower tract respiratory infections: 10.9 days (± 3.6) PCT group and 12.8 days (± 5.5) control group ($P=0.03$)	At 1 month: 90% PCT group and 92% control group ($P=0.56$)
Christ-Crain et al. [33]	302	85% PCT group and 99% control group ($P<0.0001$)	5.8 ± 5.3 days PCT group and 12.9 ± 6.5 days control group ($P<0.001$)	At 1 month: 84% PCT group and 82% control group ($P=0.65$)
Long et al. [35]	156	84.4% PCT group and 97.5% control group ($P=0.004$)	5 days (interquartile: 3–6) PCT group and 7 days (interquartile: 5–9) control group ($P<0.001$)	At 1 month: no difference between both groups
Kristoffersen et al. [39]	97	Not evaluated	5.1 days (95% CI− 4.4 to 6.0%) PCT group and 6.8 days (95% CI− 5.9 to 7.7%) control group ($P=0.007$)	Not evaluated

PCT: procalcitonin

反复多次PCT的监测会增加患者总费用，与美国IDSA临床稳定标准的优劣尚无比较

Montassier E etal. Med Mal Infect. 2013;43(2):52-9

即使是重症CAP患者，达临床稳定且无其他并发症也应及时出院

- 住院时间延长可能导致院内感染风险的增加
- 在患者达临床稳定，可以口服药物治疗，且无其他需要处理的并发症或精神障碍时应考虑出院

（1）体温≤37.8°C；

（2）心率≤100次/min；

（3）呼吸频率≤24次/min；

（4）收缩压≥90 mmHg；

（5）氧饱和度≥90%（或者动脉氧分压≥60 mmHg，吸空气条件下）

无需要进一步处理的并发症，无精神障碍等情况时，可以考虑出院

中国成人社区获得性肺炎诊断和治疗指南（2016年版）.中华结核和呼吸杂志，2016,3(4)：1-27.

CAP：经验性的病原学判断

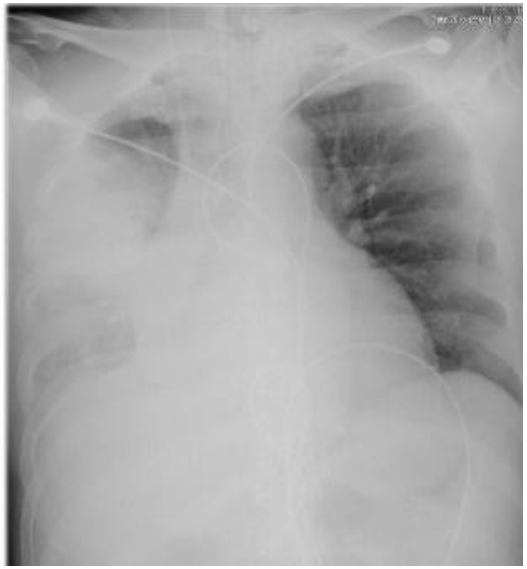
- 临床表现、辅助检查结果、影像学特点
- 季节性、地区性流行病学特点
- 宿主免疫特点

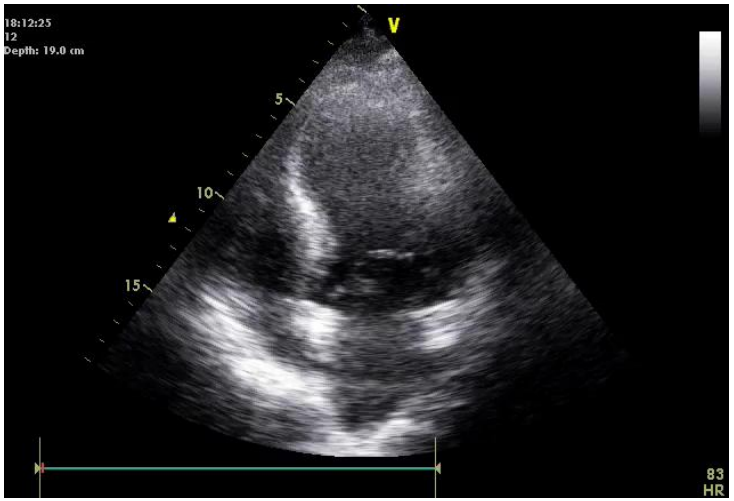
重视CAP患者不同临床表现和辅查结果

病例

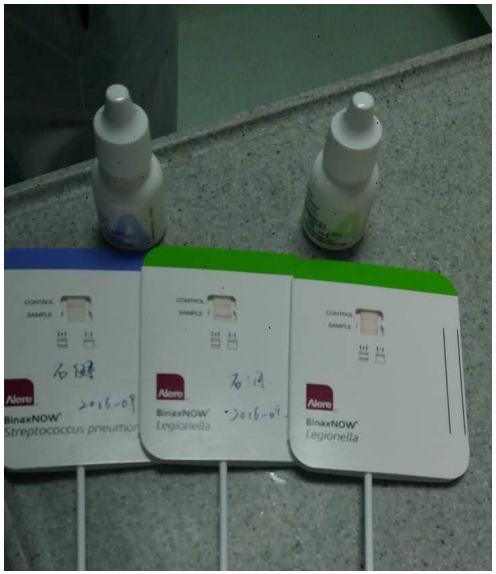
- 45岁，男性，主因发热3天，加重伴呼吸困难1小时入院，20:00入ICU
- 外院曾给予头孢尼西（Cefonicid）2天后更换为厄他培南（Ertapenem）0.5g qd、莫西沙星（moxifloxacin）400mg qd抗感染
- 典型伴随症状：意识障碍、低钠血症、心衰，影像学上以部分叶段实变为主

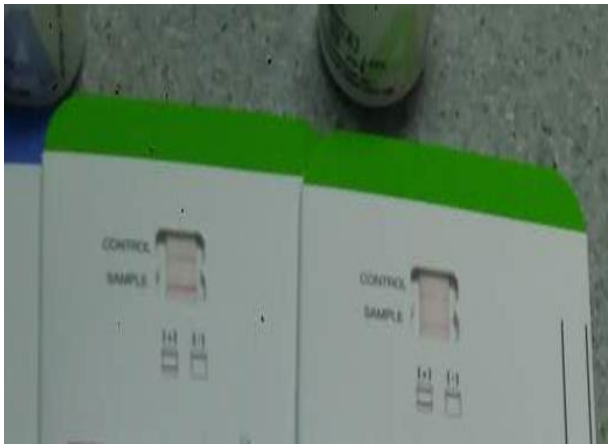
血气分析（FiO2 0.6）	9-8 16:00
pH	7.37
PaO2	69.7
PaCO2	19.1
HCO3-	10.7
BE	-12.3
cLac	1.5





重视CAP患者不同临床表现和辅查结果





尿抗原检测

肺炎链球菌：阴性　　嗜肺军团菌：阳性

入院20小时后核酸检测阳性结果回报

结合季节性、地区性流行病学特点

不同人群	常见病原体	抗感染药物选择
住ICU患者（推荐静脉药物治疗）		
无基础疾病青壮年	肺炎链球菌、金黄色葡萄球菌、流感病毒、腺病毒、军团菌	(1)青霉 类/酶抑制剂复合物、三代头孢菌素、头霉素类、氧头孢烯类、厄他培南联合大环内酯类；(2)呼吸喹诺酮类
有基础疾病或老年人（年龄≥65 岁）	肺炎链球菌、军团菌、肺炎克雷伯菌等肠杆菌科菌、金黄色葡萄球菌、厌氧菌、流感病毒、RSV 病毒	(1)青霉 类/酶抑制剂复合物、三代头孢菌素或其酶抑制剂的复合物、厄他培南等碳青霉烯类联合大环 酯类；(2)青霉素类/酶抑制剂 合物、三代头孢菌素或其酶抑制剂复合物、厄他培南等碳青霉 类联合呼吸喹诺酮类

中国成人社区获得性肺炎诊断和治疗指南（2016年版）

结合季节性、地区性流行病学特点

Table 3. Predicted and actual mortality rates among hospitalized patients with influenza pneumonia stratified by common use severity scores

Risk stratification	Patients, no.	Deaths, no	Actual mortality, %	Predicted mortality, % (7, 8)
PSI				
I	43	4	9.3	0.1
II	54	7	13.0	0.6
III	33	5	15.2	0.9
IV	37	11	26.2	9.3
V	3	3	100	27.0
CURB-65				
0	68	4	5.9	0.7
1	68	15	22.1	2.1
2	29	11	40.0	9.2
3	5	0	0	14.5
4	-	-	-	40
5	-	-	-	14

PSI class of I, II, or III and CURB-65 score of 0 or 1 are classified as low risk (predicted mortality 0–1.5%).

Table 4. AUC for mortality prediction in hospitalized patients with influenza pneumonia

Scores or indices	AUC	95% confidence interval	*P* value
PO_2/FiO_2 combined lymphocyte	0.945	0.910–0.979	Reference
PO_2/FiO_2	0.916	0.869–0.962	0.324
LIS	0.892	0.823–0.961	0.173
Lymphocyte	0.827	0.750–0.905	0.007*
SMART-COP	0.808	0.728–0.889	0.002*
CURB-65	0.675	0.574–0.776	<0.001*
PSI	0.666	0.549–0.784	<0.001*
CRB-65	0.607	0.500–0.714	<0.001*

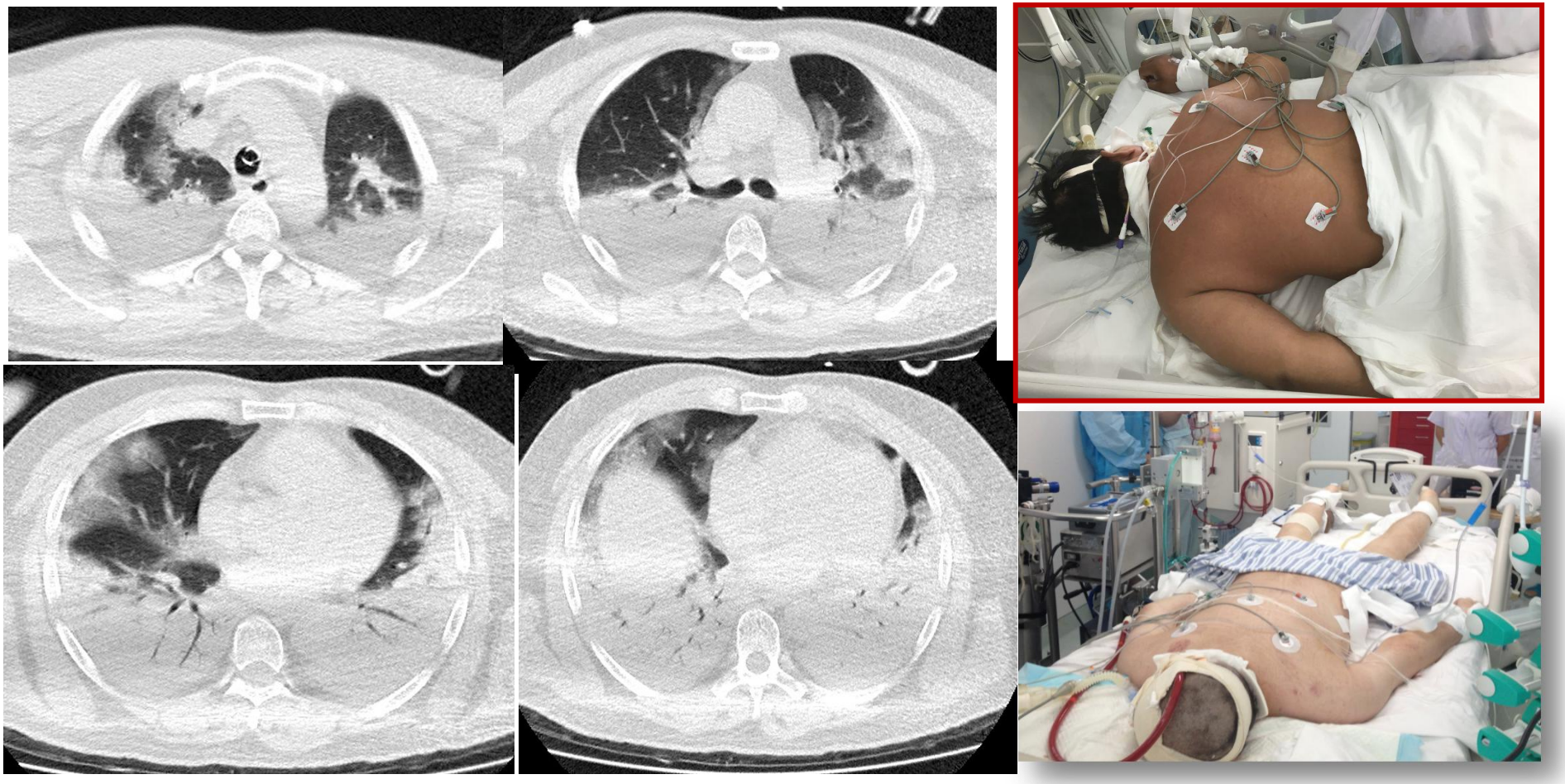
*$P < 0.05$.

氧合指数联合淋巴细胞减低可更好评估流感病毒肺炎患者病死率

Shi SJ et al.Clin Respir J. 2017;11(3):352-360.

CURB-65和PSI低估流感病毒肺炎患者病死率

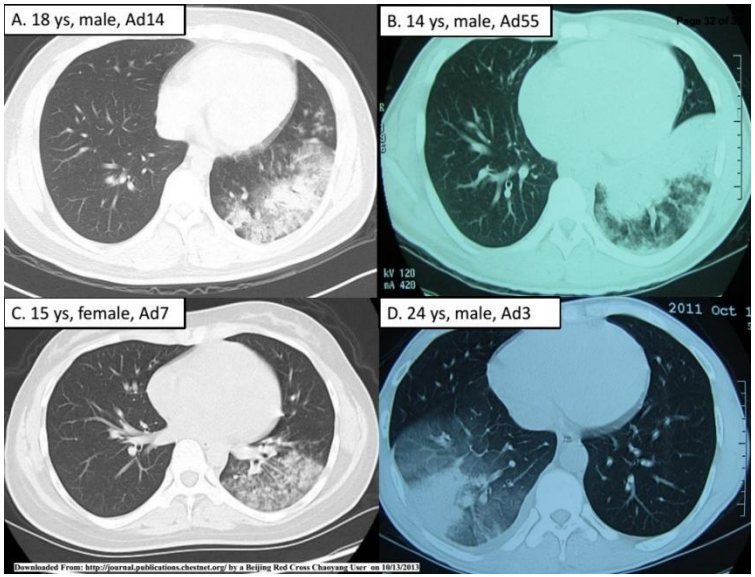
病例：45岁，男性，诊断新型H1N1重症甲流

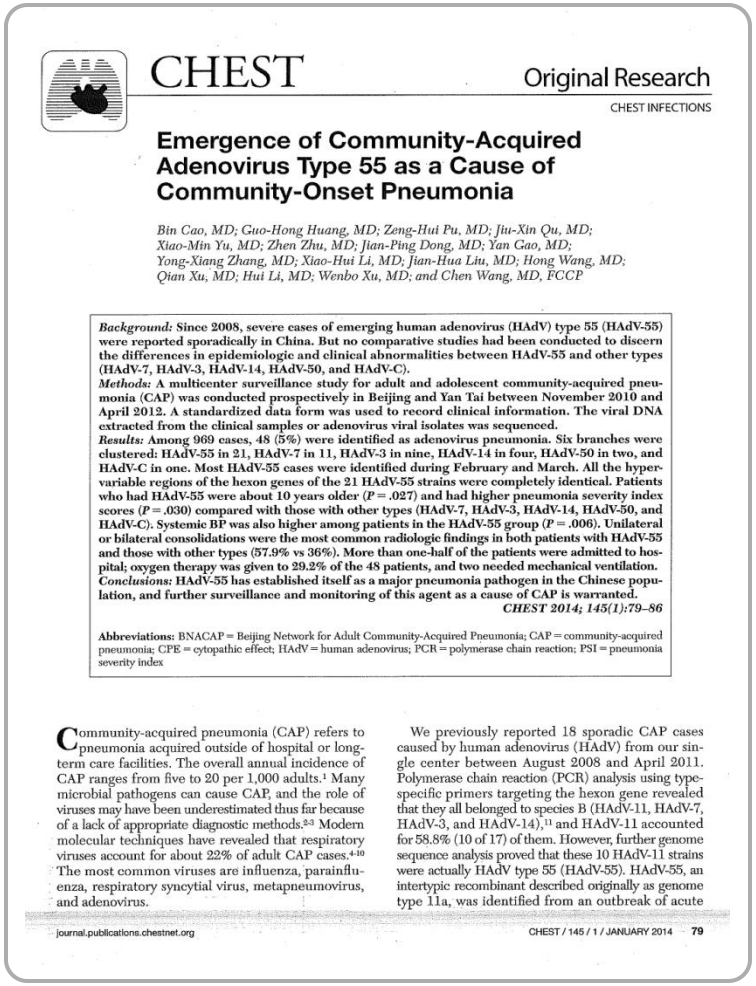


在青壮年人群中重症流感严重程度常被低估！

结合季节性、地区性流行病学特点

- 占成人腺病毒肺炎50%
- 较其他亚型腺病毒肺炎严重
- 肺实变为重要影像学特征





CHEST Original Research

CHEST INFECTIONS

Emergence of Community-Acquired Adenovirus Type 55 as a Cause of Community-Onset Pneumonia

Bin Cao, MD; Guo-Hong Huang, MD; Zeng-Hui Pu, MD; Jiu-Xin Qu, MD; Xiao-Min Yu, MD; Zhen Zhu, MD; Jian-Ping Dong, MD; Yan Gao, MD; Yong-Xiang Zhang, MD; Xiao-Hui Li, MD; Jian-Hua Liu, MD; Hong Wang, MD; Qian Xu, MD; Hui Li, MD; Wenbo Xu, MD; and Chen Wang, MD, FCCP

Background: Since 2008, severe cases of emerging human adenovirus (HAdV) type 55 (HAdV-55) were reported sporadically in China. But no comparative studies had been conducted to discern the differences in epidemiologic and clinical abnormalities between HAdV-55 and other types (HAdV-7, HAdV-3, HAdV-14, HAdV-50, and HAdV-C).
Methods: A multicenter surveillance study for adult and adolescent community-acquired pneumonia (CAP) was conducted prospectively in Beijing and Yan Tai between November 2010 and April 2012. A standardized data form was used to record clinical information. The viral DNA extracted from the clinical samples or adenovirus viral isolates was sequenced.
Results: Among 969 cases, 48 (5%) were identified as adenovirus pneumonia. Six branches were clustered: HAdV-55 in 21, HAdV-7 in 11, HAdV-3 in nine, HAdV-14 in four, HAdV-50 in two, and HAdV-C in one. Most HAdV-55 cases were identified during February and March. All the hypervariable regions of the hexon genes of the 21 HAdV-55 strains were completely identical. Patients who had HAdV-55 were about 10 years older ($P = .027$) and had higher pneumonia severity index scores ($P = .030$) compared with those with other types (HAdV-7, HAdV-3, HAdV-14, HAdV-50, and HAdV-C). Systemic BP was also higher among patients in the HAdV-55 group ($P = .006$). Unilateral or bilateral consolidations were the most common radiologic findings in both patients with HAdV-55 and those with other types (57.9% vs 36%). More than one-half of the patients were admitted to hospital; oxygen therapy was given to 29.2% of the 48 patients, and two needed mechanical ventilation.
Conclusions: HAdV-55 has established itself as a major pneumonia pathogen in the Chinese population, and further surveillance and monitoring of this agent as a cause of CAP is warranted.
CHEST 2014; 145(1):79–86

Abbreviations: BNACAP = Beijing Network for Adult Community-Acquired Pneumonia; CAP = community-acquired pneumonia; CPE = cytopathic effect; HAdV = human adenovirus; PCR = polymerase chain reaction; PSI = pneumonia severity index

Community-acquired pneumonia (CAP) refers to pneumonia acquired outside of hospital or long-term care facilities. The overall annual incidence of CAP ranges from five to 20 per 1,000 adults.[1] Many microbial pathogens can cause CAP, and the role of viruses may have been underestimated thus far because of a lack of appropriate diagnostic methods.[2,3] Modern molecular techniques have revealed that respiratory viruses account for about 22% of adult CAP cases.[4-10] The most common viruses are influenza, parainfluenza, respiratory syncytial virus, metapneumovirus, and adenovirus.

We previously reported 18 sporadic CAP cases caused by human adenovirus (HAdV) from our single center between August 2008 and April 2011. Polymerase chain reaction (PCR) analysis using type-specific primers targeting the hexon gene revealed that they all belonged to species B (HAdV-11, HAdV-7, HAdV-3, and HAdV-14),[11] and HAdV-11 accounted for 58.8% (10 of 17) of them. However, further genome sequence analysis proved that these 10 HAdV-11 strains were actually HAdV type 55 (HAdV-55). HAdV-55, an intertypic recombinant described originally as genome type 11a, was identified from an outbreak of acute

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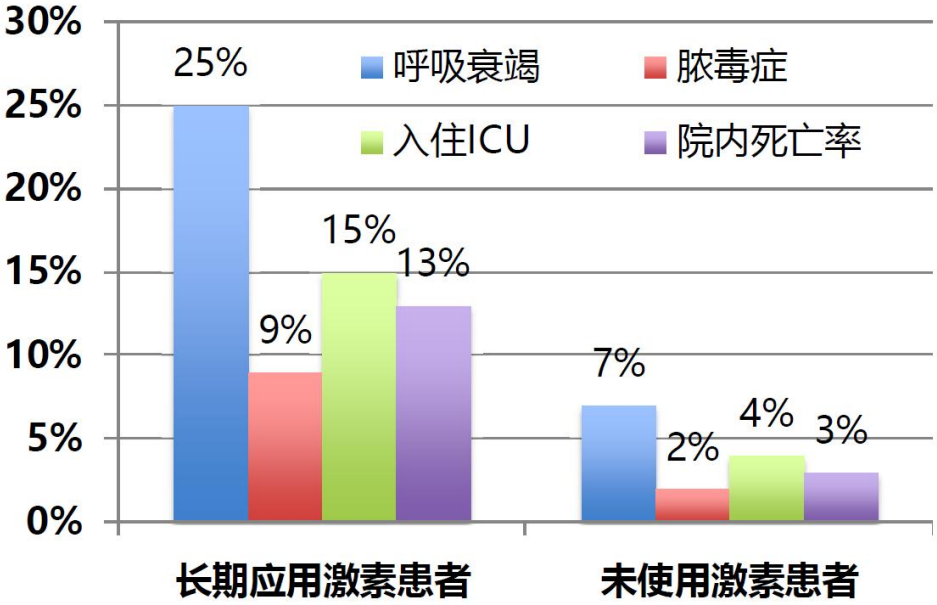
Chest. 2014;145(1): 79-86.

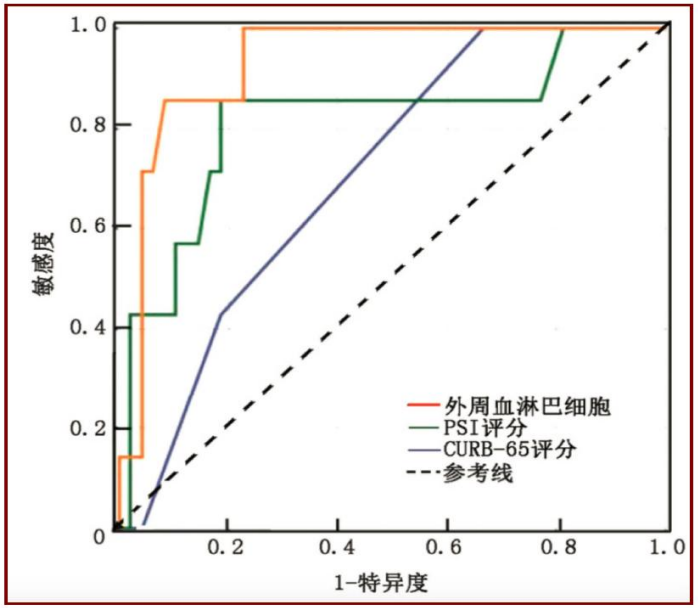
认识免疫抑制宿主合并重症CAP的病原学特点

长期使用激素CAP患者临床特点

糖皮质激素长期应用宿主定义：泼尼松≥10mg/d，持续3周以上。

- 糖皮质激素长期应用宿主肺炎外周血淋巴细胞绝对值中位值只有1060/ul，显著低于对照组（1440/ul）





外周血淋巴细胞计数可更好预测长期使用激素患者病死率，以<775/ul为分界值预测肺炎患者死亡，敏感性为79.2%，特异性为100%

李丽娟 等.中华医学杂志, 2018; 98 (10): 738-743

认识不同宿主的重症CAP病原学特点

老年患者因生理功能变化易导致吸入性肺炎

老年肺炎的诱发因素	与年龄相关的变化
纤毛清除能力降低	• 肺功能下降：↓胸壁顺应性、↓肺弹性回缩力、↓呼吸肌力、↑残气量 • 咳嗽反射降低 • 咽反射降低
口咽部病原体定植增加	• 免疫功能受损：↓呼吸功能适应性免疫(↓T/B细胞、↓抗原提呈功能) ↓先天免疫功能(↓自然杀死细胞、↓巨噬细胞、↓中性粒细胞) • 唾液清除率降低
胃内容物细菌增殖	• 胃酸缺乏症： 生理性、 药物(H2受体阻抗剂、质子泵抑制剂)
吸入风险增加	• 吞咽困难

Fung HB, et al. Am J Geriatr Pharmacother. 2010;8(1):47-62.

认识不同宿主的重症CAP病原学特点

老年患者、慢性呼吸系统疾病患者、长期滥用抗生素患者

铜绿假单胞菌感染

- 结构性肺病
- 90天内曾入院治疗/使用抗菌药物/使用激素
- 长期入住医疗护理机构
- 曾有铜绿假单胞菌定植

MDR感染风险（产ESBL）

- 有产ESBL细菌定植史
- 90天内住院≥2天
- 近期静脉注射抗菌药物
- 前期曾使用3代头孢菌素
- 反复长期住院史
- 留置医疗器械
- 肾脏替代治疗

需要评估的危险因素

误吸的风险

- 脑血管或神经系统疾病（癫痫）
- 呕吐或吞咽困难
- 头、颈部肿瘤
- 口腔疾病或口卫生差

→ **厌氧菌及G-杆菌感染**

Faverio P et al. Eur J Intern Med. 2014;25(4):312-9

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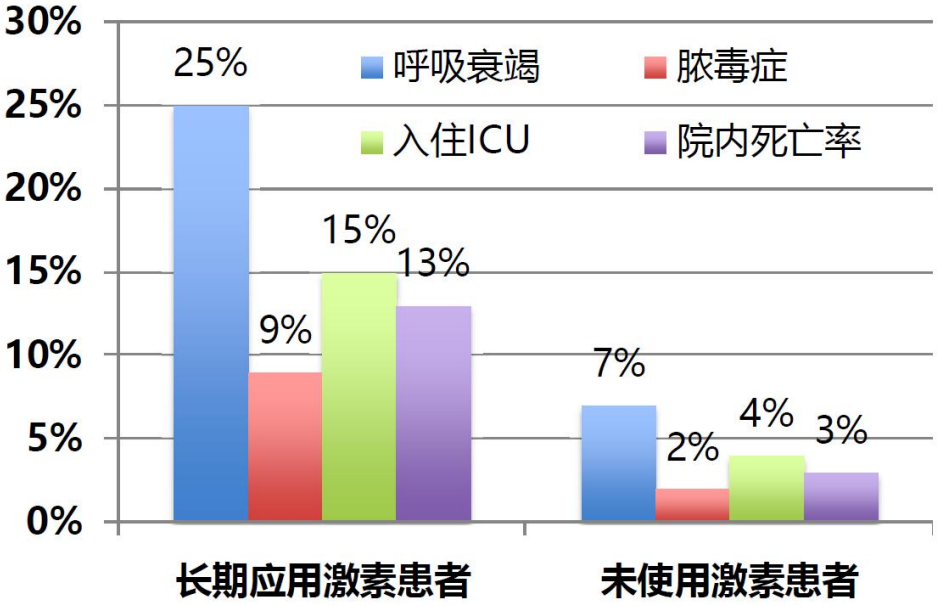

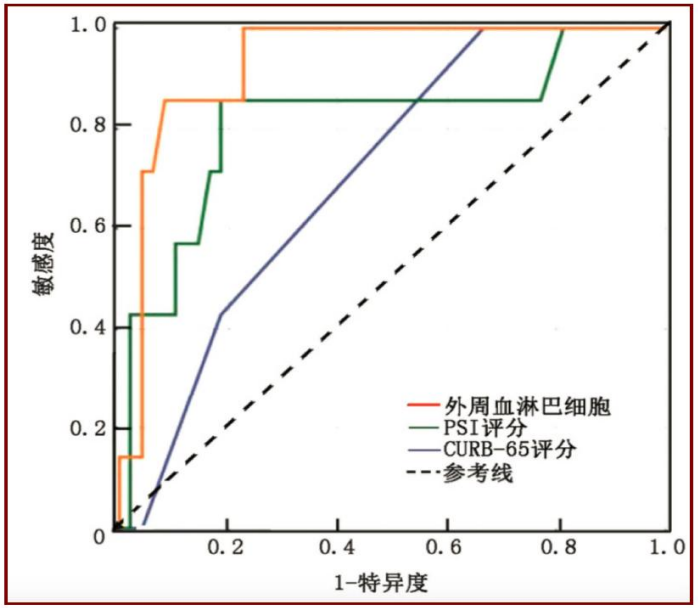

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认识免疫抑制宿主合并重症CAP的病原学特点

长期使用激素CAP患者临床特点

项目	G-CAP 组（100 例）	nICH-CAP 组（100 例）	*P* 值
病原学	31/100(31.0)	11/100(11.0)	0.005
BALF 病原学	6/15(40.0)	3/14(21.4)	0.431
痰病原学	28/74(37.8)	9/56(16.1)	0.039
细菌	19/31(61.3)	9/11(81.8)	0.589
不动杆菌	2/19(10.5)	1/9(11.1)	0.967
肠杆菌(埃希菌、肺炎克雷伯杆菌)	5/19(26.3)	2/9(22.2)	0.856
肺炎链球菌	2/19(10.5)	4/9(44.4)	0.114
铜绿假单胞菌	9/19(47.4)	2/9(22.2)	0.383
嗜麦芽窄单胞菌	1/19(5.3)	0(0)	–
真菌(PCP + 黄曲霉菌)	1/31(3.2)	0(0)	–
病毒	6/31(19.4)	2/11(18.2)	0.944
甲型/乙型流感病毒	3/6(50.0)	2/2(100)	0.514
CMV	3/6(50.0)	0/2(0)	–
混合感染	5/31(16.1)	0/0(0)	
MRSA + EB + CMV	1/5(20.0)	0/0(0)	–
鼻病毒 + EBV + PCP	1/5(20.0)	0/0(0)	–
CMV + EBV + PCP + 溶血葡萄	1/5(20.0)	0/0(0)	–
CMV + PCP + 嗜麦芽	1/5(20.0)	0/0(0)	–
甲型流感病毒 + CMV	1/5(20.0)	0/0(0)	

- 仍以细菌最常见，铜绿假单胞菌和肠杆菌科细菌最为常见
- 病毒性感染以流感病毒和巨细胞病毒感染常见
- 真菌或CPC感染占3.2%

对于长期使用激素患者的经验性抗感染治疗应考虑到革兰阴性菌感染，流感和CMV感染，同时应注意PCP感染可能

李丽娟 等.中华医学杂志, 2018; 98 (10): 738-743

认识免疫抑制宿主合并重症CAP的病原学特点

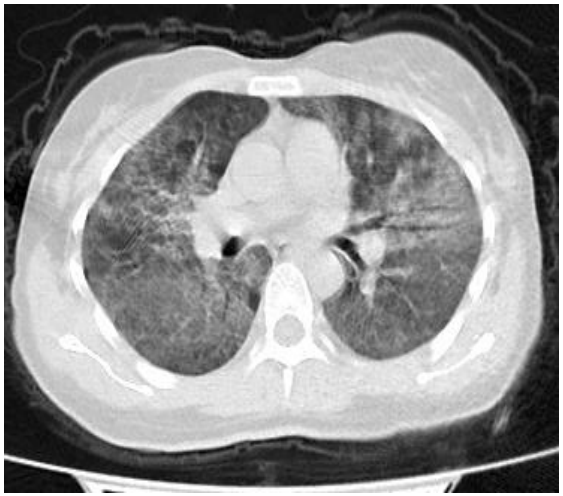
- 31岁，青年女性
- 主诉：关节痛、发热、皮疹7月，呼吸困难、干咳1月

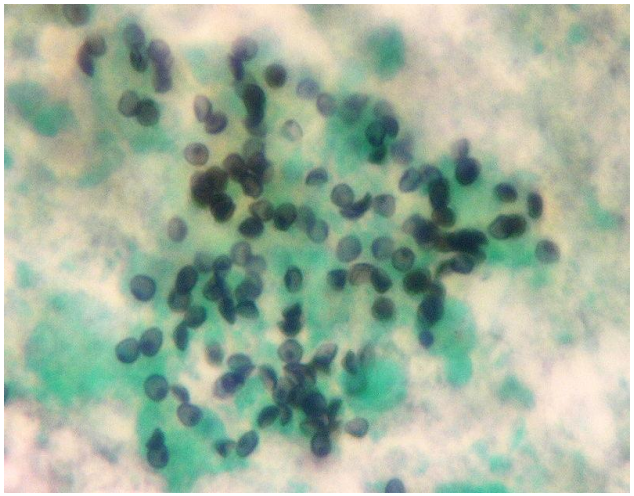
诊断为系统性红斑狼疮 噬血综合征

予甲泼尼龙冲击治疗，出院后甲泼尼龙60mg Qd➡20mg Qd，联合环孢素A、 羟氯喹

入院查CD4+ 124/mm^3

PCP及CMV核酸检测均阳性





认识免疫抑制宿主合并重症CAP的病原学特点

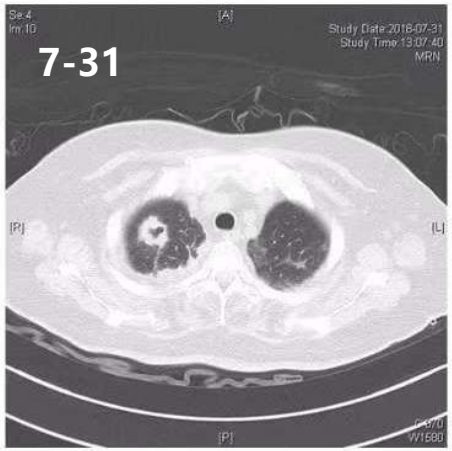
- 65岁，女性，主因咳嗽咳痰伴发热13天，胸痛9天入院
- 因肾病综合征接受激素治疗
- 入院查CD4+ 225/mm³

检测结果

1、检出细菌列表

类型*	属			种		
	中文名	拉丁文名	检出序列数[b]	中文名	拉丁文名	检出序列数[b]
G^+	诺卡菌属	*Nocardia*	205	鼻疽诺卡菌	*Nocardia farcinica*	173
				诺卡菌*	*Nocardia arizonensis*	3
G^-	罗尔斯顿菌属	*Ralstonia*	18	危害罗尔斯顿菌	*Ralstonia insidiosa*	14

类型：G^+（革兰氏阳性菌）/G^-（革兰氏阴性菌）



2、检出真菌列表

属			种		
中文名	拉丁文名	检出序列数[b]	中文名	拉丁文名	检出序列数[b]
肺孢子虫属	*Pneumocystis*	195	耶氏肺孢子虫	*Pneumocystis jirovecii*	193

3、检出病毒列表

免疫抑制患者

- 机会致病菌感染
- 混合感染

认识免疫抑制宿主合并重症CAP的病原学特点

A

CMV、PCP、FluA混合感染

B

CMV、PCP混合感染

在非HIV-PCP患者中，合并CMV感染的高达58%，合并曲霉菌感染者超过30%。

黄絮,翁利,易丽,等.非HIV免疫抑制患者肺孢子菌肺炎合并急性呼吸衰竭的临床特征.中华医学杂志, 2016, 96(38):3057-3061.

认识不同宿主的重症CAP病原学特点

妊娠状态

流感病毒的易感人群，感染后易发展为重症CAP

妊娠

- **T细胞功能下降**
- **病变进展迅速**
- **孕妇耗氧量大**

—易发展为呼吸衰竭

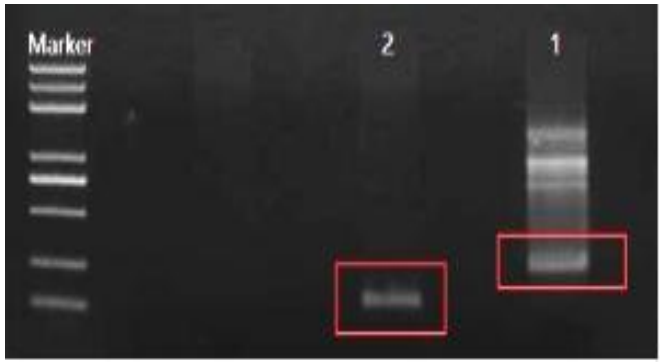
认识不同宿主的重症CAP病原学特点

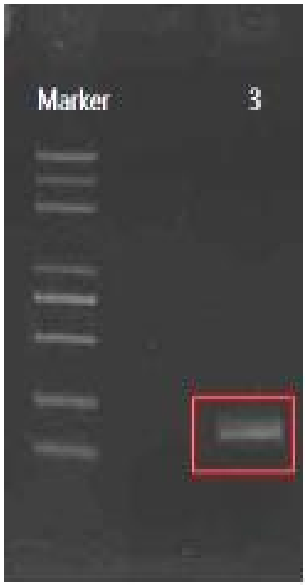
妊娠状态

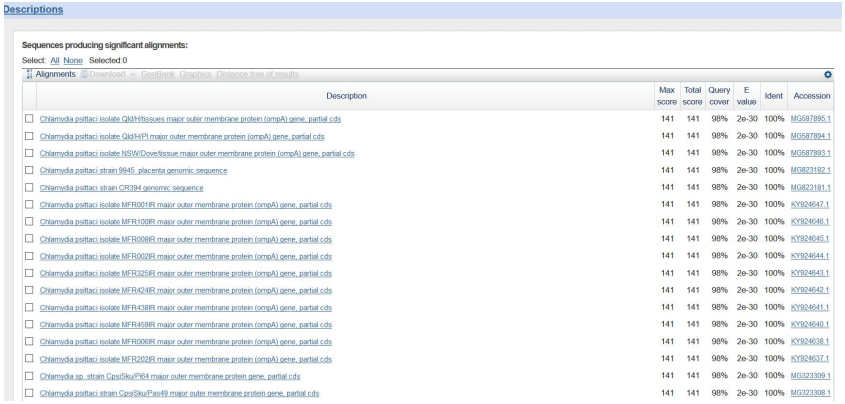
28岁，女性，主因咳嗽咳痰伴发热2周，呼吸困难7天入院

- 孕28周

- 二代测序结果示鹦鹉热衣原体（Chlamydophila psittaci）片段
- 协和医院检测特异性抗体IgM及IgG 4倍以上滴度升高







Descriptions

Sequences producing significant alignments:

Select: All None Selected:0

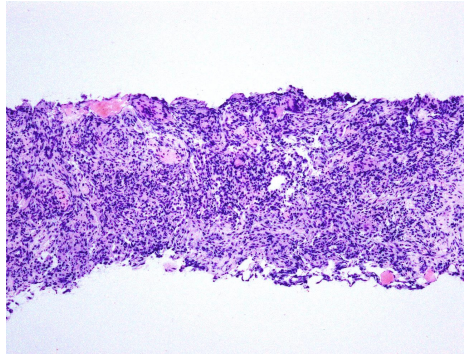
Alignments Download GenBank Graphics Distance tree of results

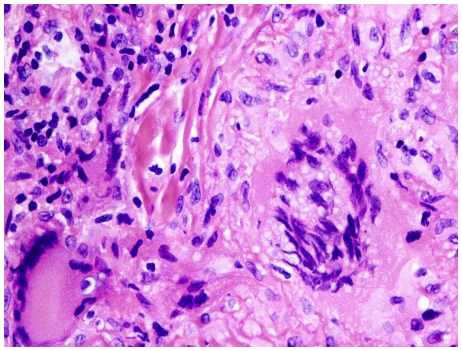
	Description	Max score	Total score	Query cover	E value	Ident	Accession
☐	Chlamydia psittaci isolate Qld/H/tissues major outer membrane protein (ompA) gene, partial cds	141	141	98%	2e-30	100%	MG587895.1
☐	Chlamydia psittaci isolate Qld/H/PI major outer membrane protein (ompA) gene, partial cds	141	141	98%	2e-30	100%	MG587894.1
☐	Chlamydia psittaci isolate NSW/Dove/tissue major outer membrane protein (ompA) gene, partial cds	141	141	98%	2e-30	100%	MG587893.1
☐	Chlamydia psittaci strain 9945 placenta genomic sequence	141	141	98%	2e-30	100%	MG823182.1
☐	Chlamydia psittaci strain CR394 genomic sequence	141	141	98%	2e-30	100%	MG823181.1
☐	Chlamydia psittaci isolate MFR001R major outer membrane protein (ompA) gene, partial cds	141	141	98%	2e-30	100%	KY924647.1
☐	Chlamydia psittaci isolate MFR100R major outer membrane protein (ompA) gene, partial cds	141	141	98%	2e-30	100%	KY924646.1
☐	Chlamydia psittaci isolate MFR008R major outer membrane protein (ompA) gene, partial cds	141	141	98%	2e-30	100%	KY924645.1
☐	Chlamydia psittaci isolate MFR002R major outer membrane protein (ompA) gene, partial cds	141	141	98%	2e-30	100%	KY924644.1
☐	Chlamydia psittaci isolate MFR325R major outer membrane protein (ompA) gene, partial cds	141	141	98%	2e-30	100%	KY924643.1
☐	Chlamydia psittaci isolate MFR424R major outer membrane protein (ompA) gene, partial cds	141	141	98%	2e-30	100%	KY924642.1
☐	Chlamydia psittaci isolate MFR438R major outer membrane protein (ompA) gene, partial cds	141	141	98%	2e-30	100%	KY924641.1
☐	Chlamydia psittaci isolate MFR459R major outer membrane protein (ompA) gene, partial cds	141	141	98%	2e-30	100%	KY924640.1
☐	Chlamydia psittaci isolate MFR006R major outer membrane protein (ompA) gene, partial cds	141	141	98%	2e-30	100%	KY924638.1
☐	Chlamydia psittaci isolate MFR202R major outer membrane protein (ompA) gene, partial cds	141	141	98%	2e-30	100%	KY924637.1
☐	Chlamydia sp. strain CpsSku/P64 major outer membrane protein gene, partial cds	141	141	98%	2e-30	100%	MG323309.1
☐	Chlamydia psittaci strain CpsSku/Pas49 major outer membrane protein gene, partial cds	141	141	98%	2e-30	100%	MG323308.1

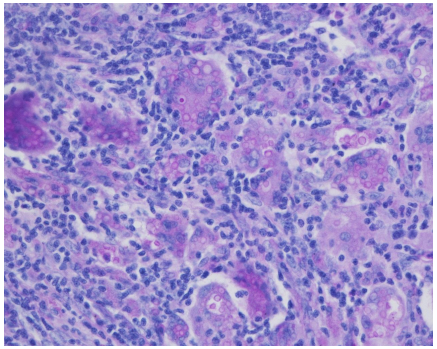
认识不同宿主的重症CAP病原学特点

糖尿病，血糖控制不佳

老年男性，呼吸困难，肺部实变，常规抗生素治疗无效—隐球菌肺炎

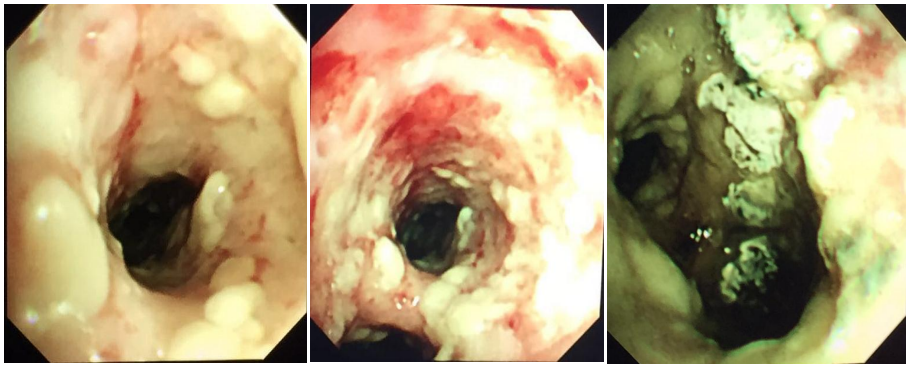


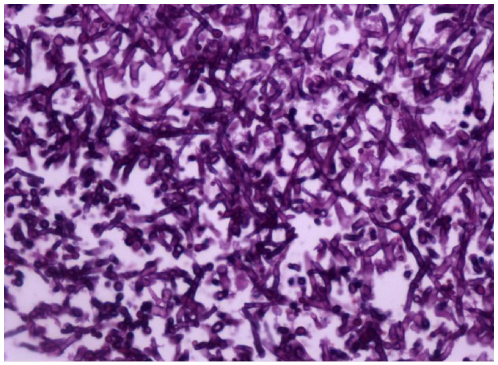




中日医院 病理科 提供图片

老年男性，清扫旧屋后，呼吸困难5天——侵袭性肺曲霉菌病





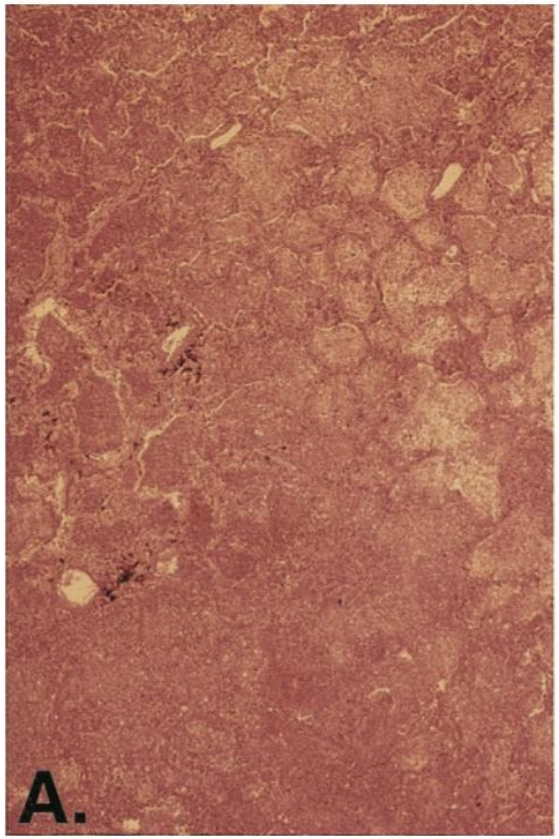
重视重症甲流后合并感染

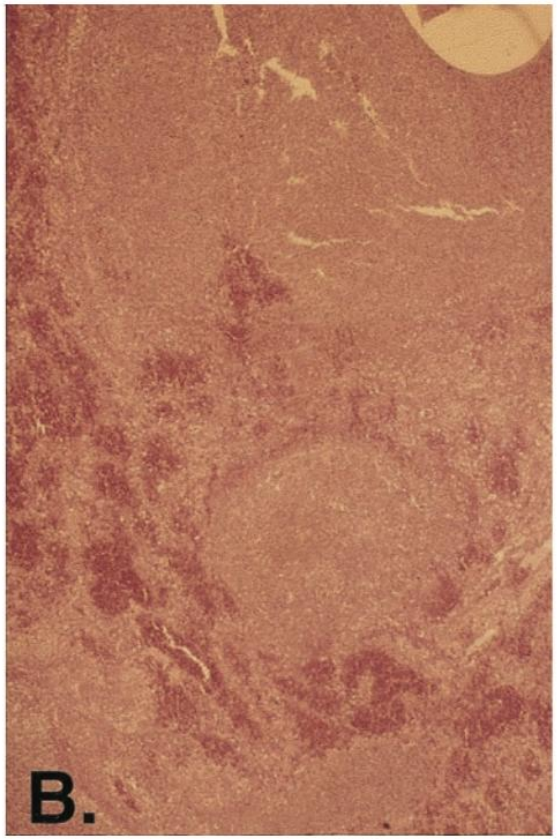
The 1918 Influenza Pandemic: Insights for the 21st Century

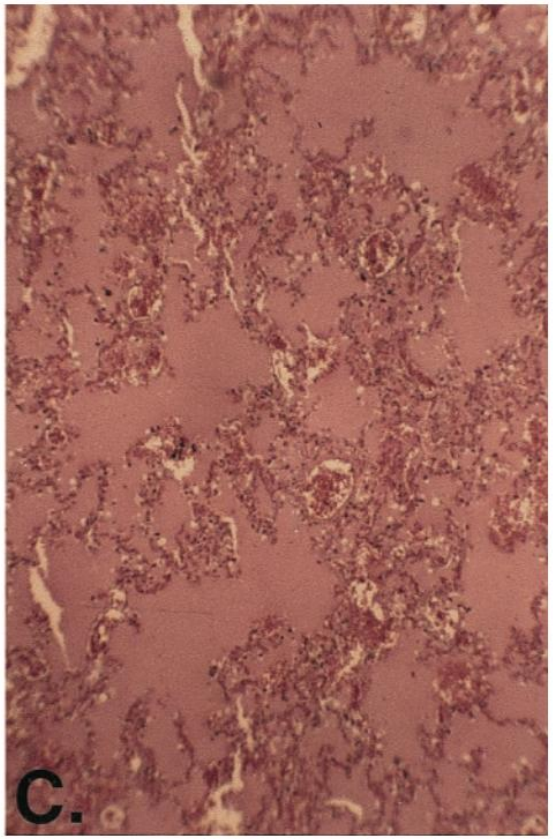
Question	Answer
Where did the 1918 virus originate?	Unknown; unlike H5N1, from an avian influenza lineage genetically distinct from those currently known
What was the pathogenesis, and why did so many people die?	Different pathogenesis in 1918 not documented: causes of death in 1918 similar to those during other pandemics; most fatalities had secondary pneumonias caused by common bacteria or, in a minority of cases, ARDS-like syndromes; higher proportion of severe cases at all ages; 1918 virus-virulence determinants not yet mapped
Why were there so many deaths among the young and healthy?	Unknown; unappreciated host or environmental variables possible, such as robust immunological response to the virus in younger individuals, resulting in enhanced tissue damage
Why was mortality among the elderly lower than expected?	Unknown; evidence is consistent with prior exposure to a virus—conceivably the virus associated with the 1847 pandemic—eliciting protective immunity
Why were there 3 pandemic waves during 1918–1919, and what are the implications for predicting future pandemic spread?	Unknown; at least 2 virus variants during second wave; identity of viruses during first and third waves not known; epidemiology of rapidly recurrent waves not understood
Do influenza pandemics occur in predictable cycles?	Insufficient evidence for pandemic cyclicity; steps in pandemic emergence not fully understood
Are we better able to prevent morbidity and mortality today?	Yes, in developed world with advanced medical care, antibiotics, antivirals, and effective public health; preventive vaccines would be critical if available in time; however, developing world still at great risk

The Journal of Infectious Diseases 2007;195:1018–28

重视重症甲流后合并感染







necrotizing/hemorrhagic bronchopneumonia	Severe bacterial bronchopneumonia	acute respiratory distress syndrome

重视重症甲流后合并感染

Why did so many people die?

- **Bacterial superinfections： caused perhaps one-third of all deaths**
  - ***Streptococcus pneumoniae***
  - ***Haemophilus influenzae***
  - ***Staphylococcus aureus***

  在青霉素发明之前

  - **MRSA** → 广泛使用万古霉素

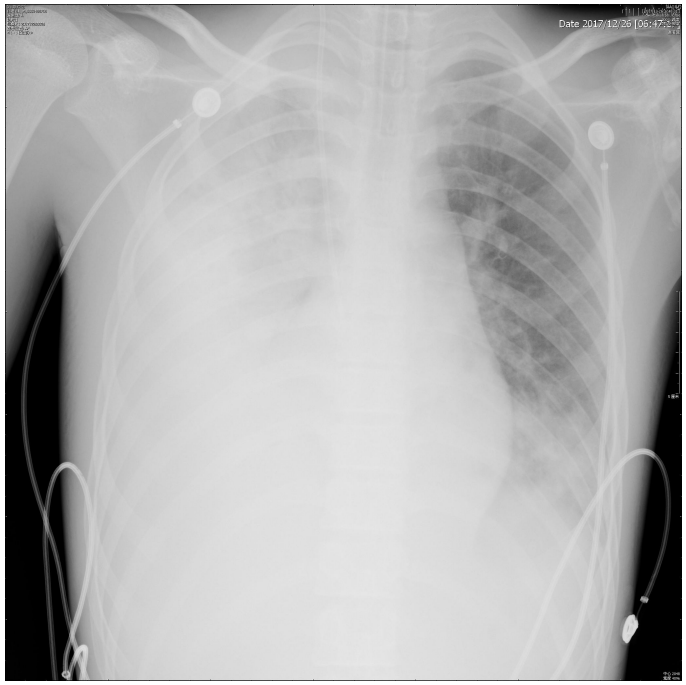
The 1918 Influenza Pandemic: Insights for the 21st Century .
The Journal of Infectious Diseases.2007;195:1018–28
Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness.
Lancet Infect Dis 2006;6:303–312

我们总结了55例重症流感合并感染（co-infection）

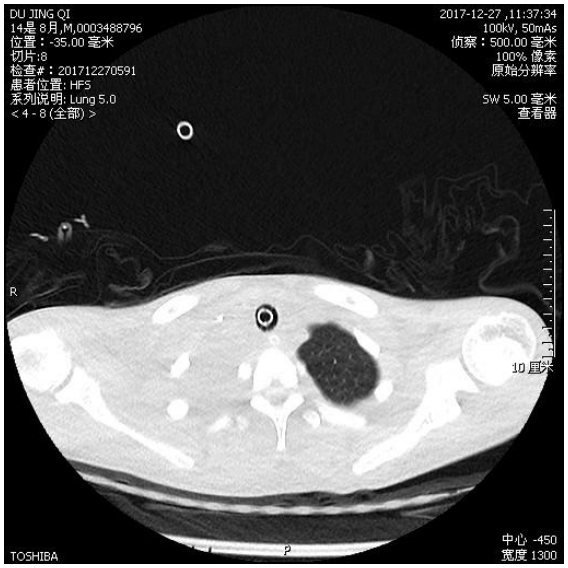
MRSA n=2　　MSSA n=2　　发病3-6天后确诊

重视重症甲流后合并感染

- 男性，14岁，学生
- 发热7天(39.0℃)，加重伴意识障碍1天，
- ABG（面罩吸氧）：PH 7.308，PCO2 39.1，PO2 53.8
- 气管插管呼吸机辅助通气
- WBC 0.62×10^9/L，N% 48.3，PCT 42.60ng/ml
- T淋巴细胞：N 300，CD4+ 62，CD8+ 92
- 12-25痰涂片示G+球菌（+++）
- 血压进行性下降，2017-12-26入院



2017-12-27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100% 像素
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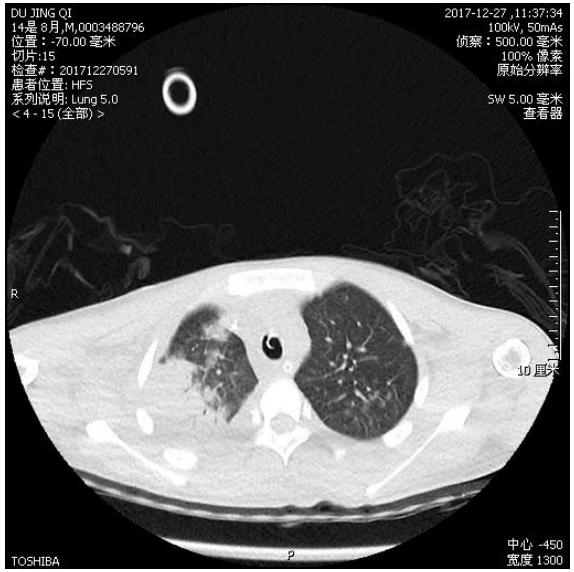
查看器
R
10 厘米
TOSHIBA
P
中心 -450
宽度 1300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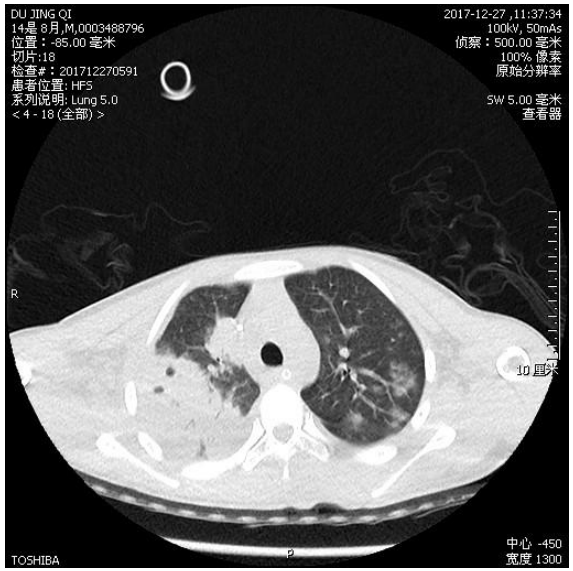
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100% 像素
原始分辨率
SW 5.00 毫米
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R
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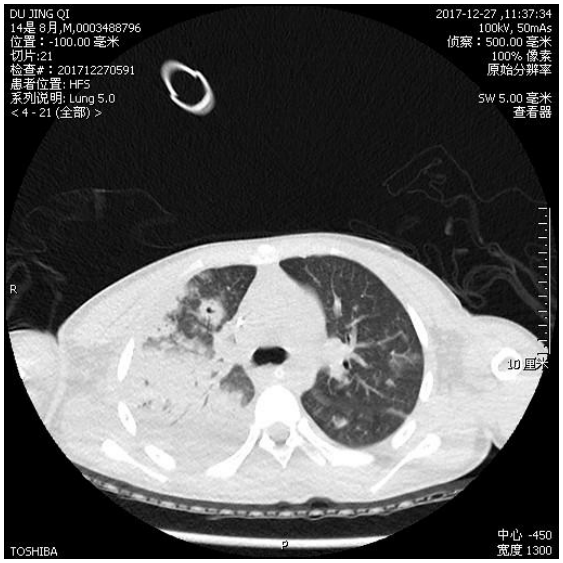
TOSHIBA
P
中心 -450
宽度 1300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100% 像素
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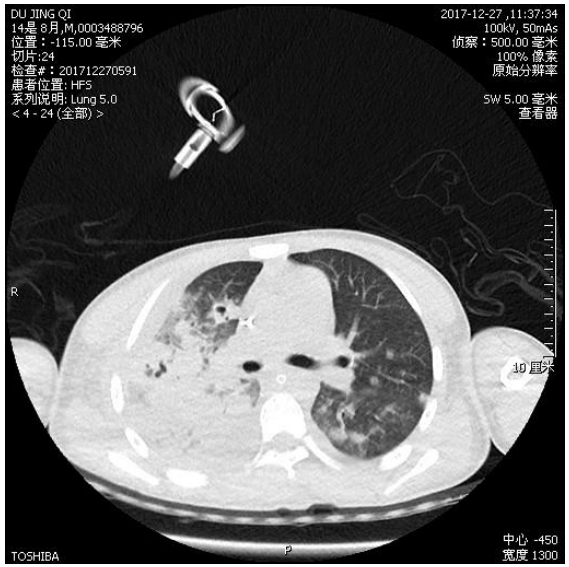
SW 5.00 毫米
查看器
R
10 厘米
TOSHIBA
P
中心 -450
宽度 1300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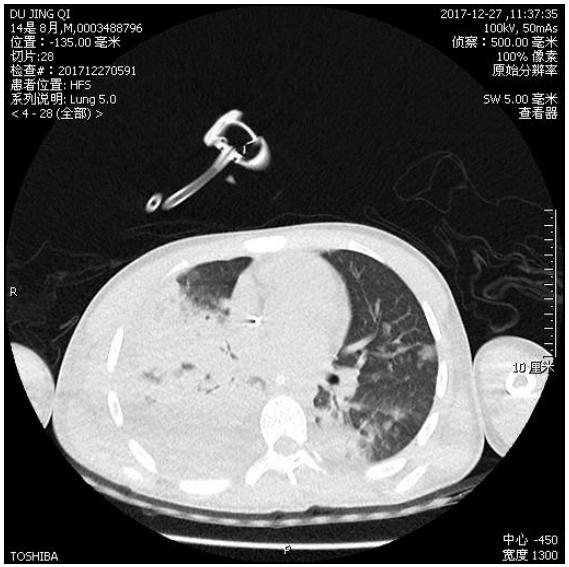
侦察：500.00 毫米
100% 像素
原始分辨率
SW 5.00 毫米
查看器
R
10 厘米
TOSHIBA
P
中心 -450
宽度 1300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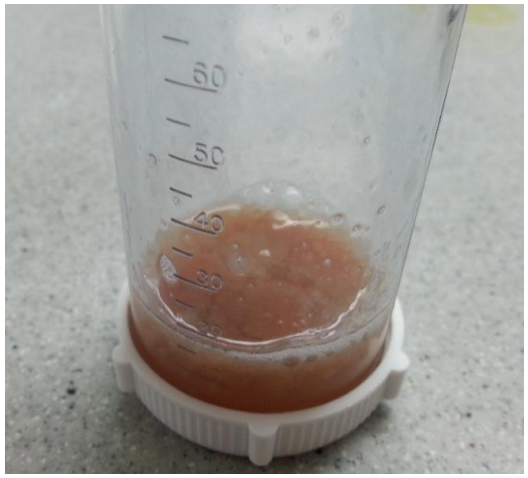
侦察：500.00 毫米
100% 像素
原始分辨率
SW 5.00 毫米
查看器
R
10 厘米
TOSHIBA
P
中心 -450
宽度 1300

D1气管镜检查

- 左右肺各叶段开口通畅，粘膜充血水肿明显，触之易出血，其上可见黄白苔附着，可见多发片状出血（右中叶明显），各叶段均可见大量黄色或脓血性粘稠分泌物，吸除困难



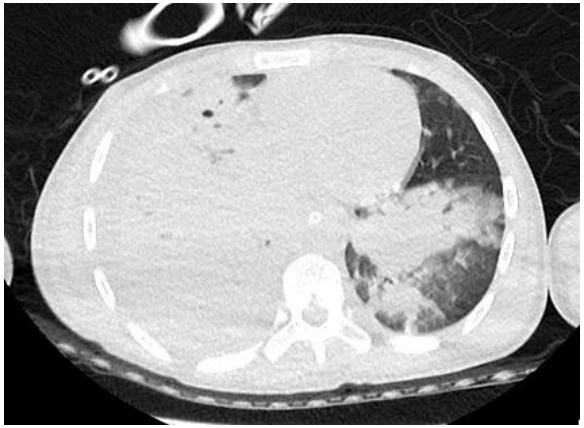
D3-D5气管镜吸痰病原学

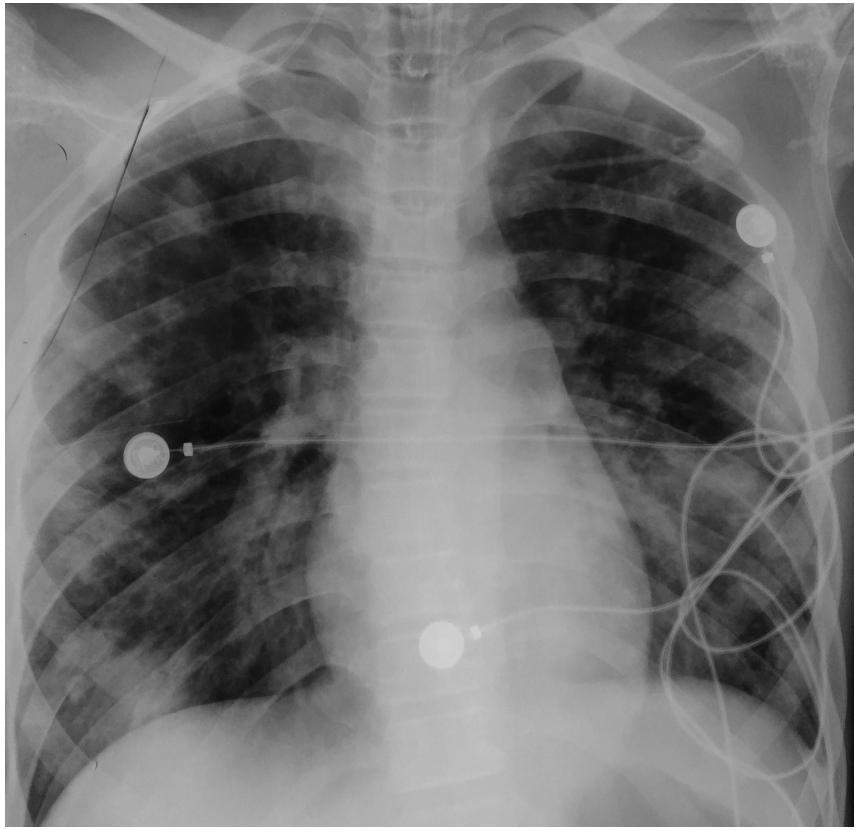
- 新甲型H1N1流感病毒核酸（+）
- 追踪当地医院病原学回报：MRSA
  - MRSA耐药基因检测：MecA阳性
- 细菌涂片：G+球菌成堆中等量
  - 培养：肺炎克雷伯菌（CRE，ESBL+ ）
- 真菌、结核、病毒及肺炎支原体、衣原体核酸（-）

D10

- V-V ECMO，血流量5.03L/分

- 持续泵入去甲，血压难以维持，BNP 2145pg/ml，Lac 14.4mmol/L。
- 血培养危急值（1-2）：G-杆菌。1月5日血培养及药敏：洋葱伯克霍尔德菌（全敏感）
- 灌洗液细菌培养：洋葱伯克霍尔德菌，肺炎克雷伯菌（ESBL+）





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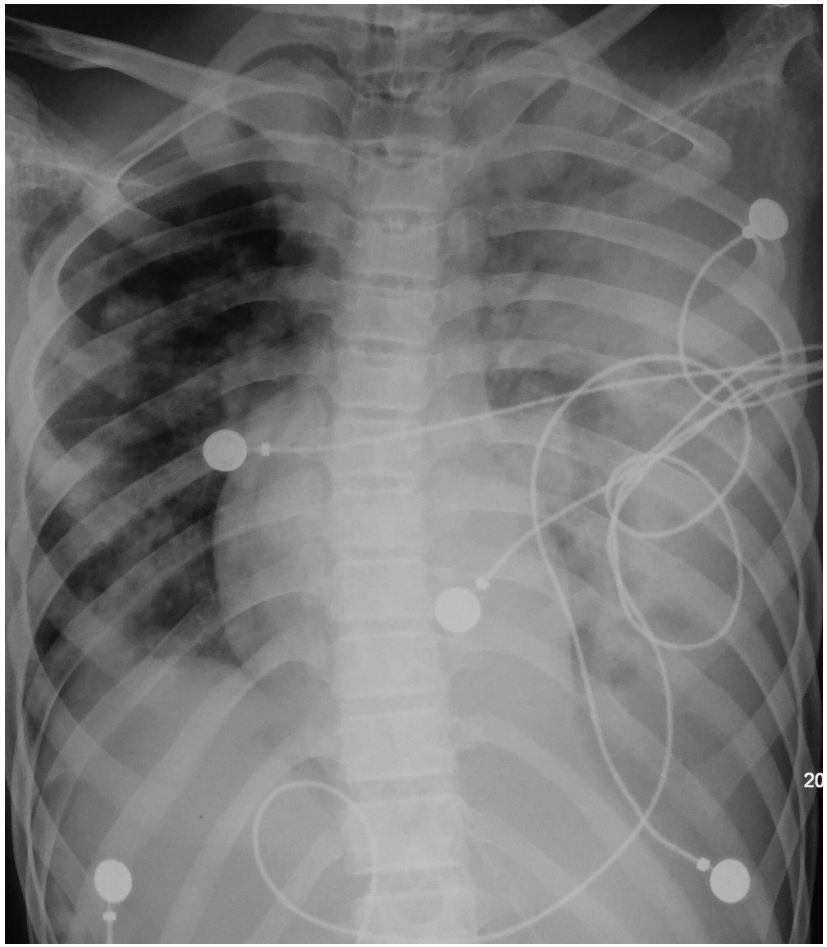
3-28



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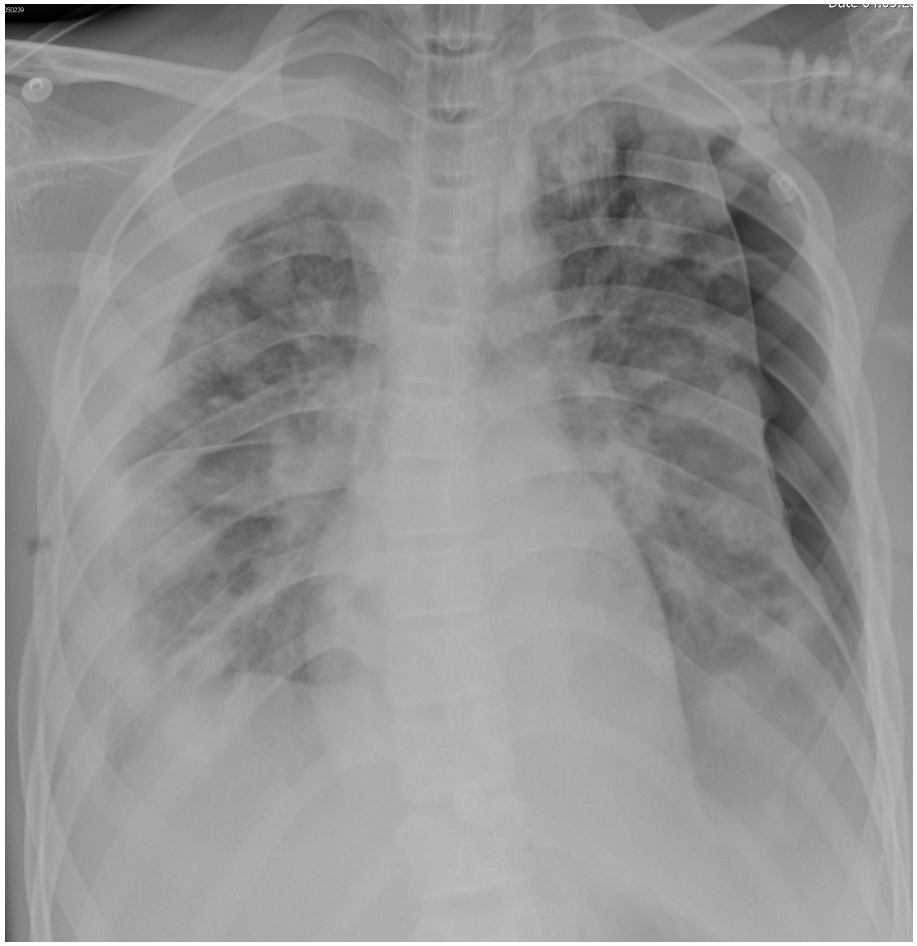
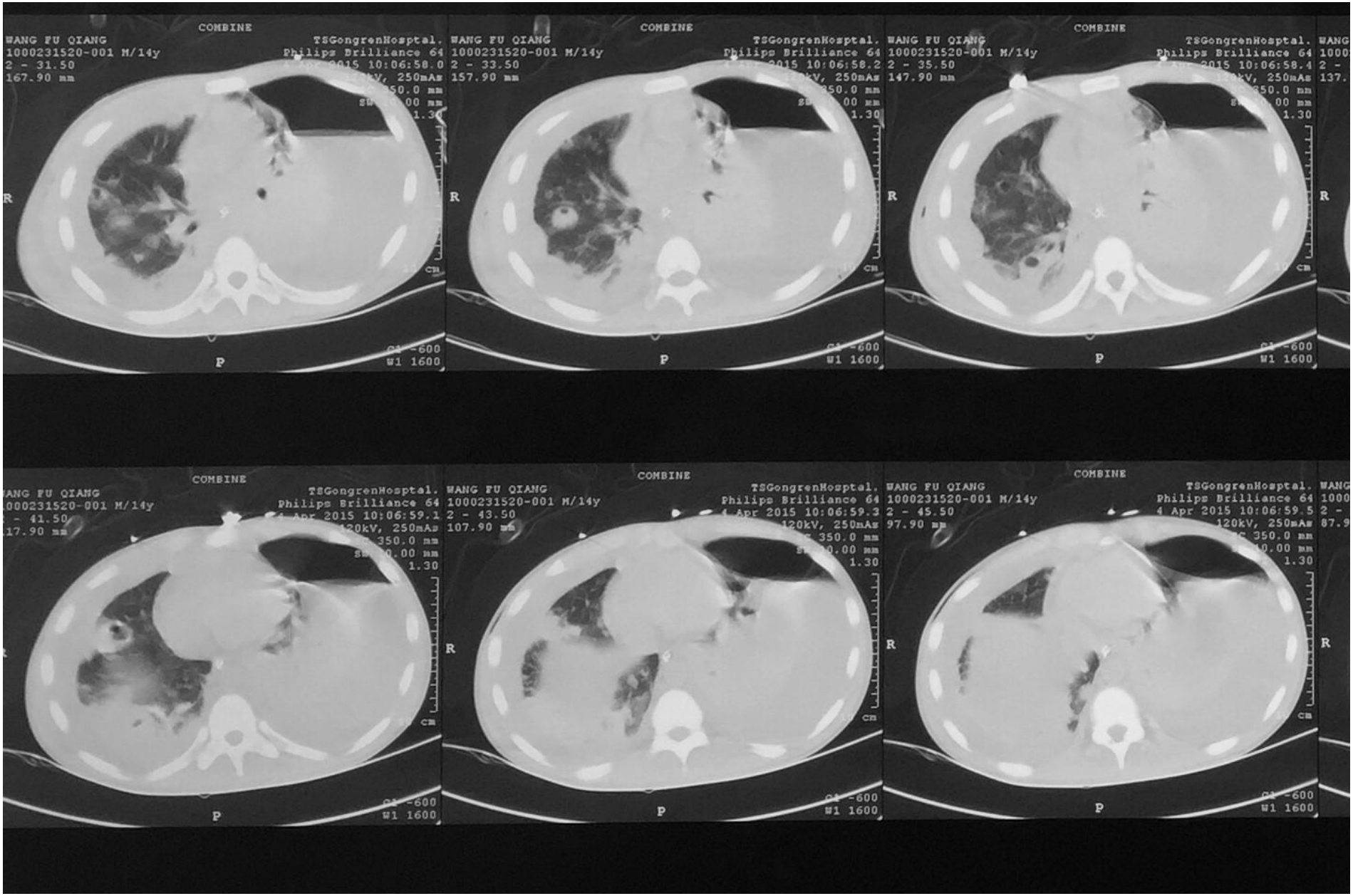


4-5

4-4（发病13天）


COMBINE
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Philips Brilliance 64
WANG FU QIANG
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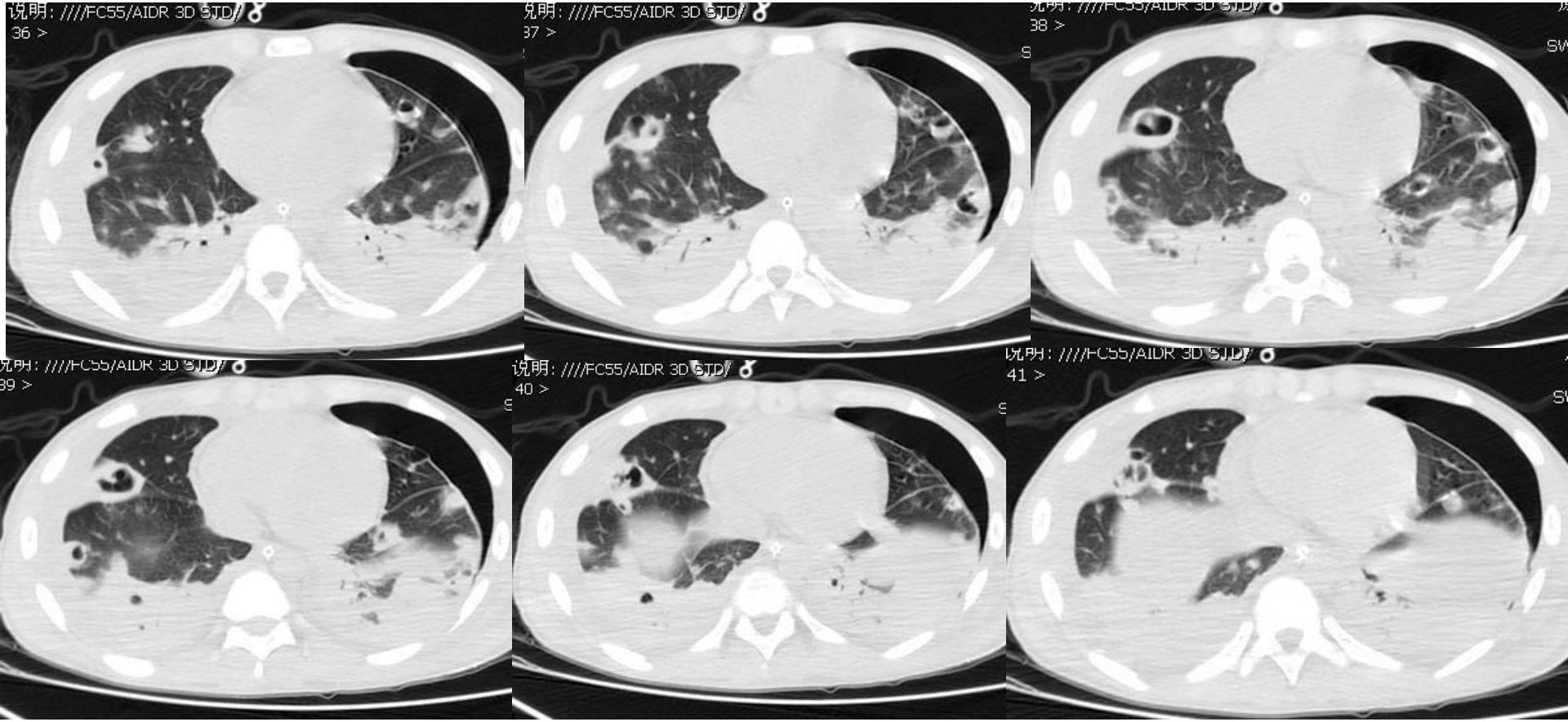
2 - 33.50
157.90 mm
2 - 35.50
147.90 mm
2 - 43.50
107.90 mm
2 - 45.50
97.90 mm
R
P
W1 1600

4-6（发病15天）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41 >

重视重症甲流后合并感染

Risk factors of CA-MRSA

Risk groups
Children <2 years old
Athletes (mainly contact-sport participants)
Injection drug users
Men who have sex with men
Military personnel
Inmates of correctional facilities, residential homes or shelters
Vets, pet owners and pig farmers
Patients with post-flu-like illness and/or severe pneumonia
Patients with concurrent SSTI
History of colonization or recent infection with CA-MRSA
History of antibiotic consumption in the previous year, particularly quinolones or macrolides

J Antimicrob Chemother, 2009, 63(5):849.861.

CA-MRSA 发病率-EPIC II 研究

在美国

- ✓ 2-3%CAP致病菌是金葡菌
- ✓ 50%为MRSA

Richard G Wunderink. Infect Dis Clin N Am 2013（27）:177–188

重视重症甲流后合并感染

社区获得性金黄色葡萄球菌感染合并流感病毒感染显著增加死亡风险

Table 2. Adjusted regression analysis of the association between influenza and 30-d in-hospital deaths among patients with *Staphylococcus aureus*–positive respiratory cultures, Maryland and Iowa, USA*

Model and variable	Odds ratio (95% CI)	p value
Unadjusted		
Influenza-positive test	3.15 (1.27–7.86)	0.021
Adjusted†		
Influenza-positive test	4.31 (1.57–11.83)	0.005
First positive *S. aureus* culture collected ≤2 d after hospital admission	3.00 (1.18–7.61)	0.021
Year of first positive *S. aureus* culture, 2008–2009†	1.71 (0.70–4.13)	0.237

*Defined as death occurring in the hospital within 30 d of the first respiratory culture that grew *S. aureus*.
†Reference 2003–2007.

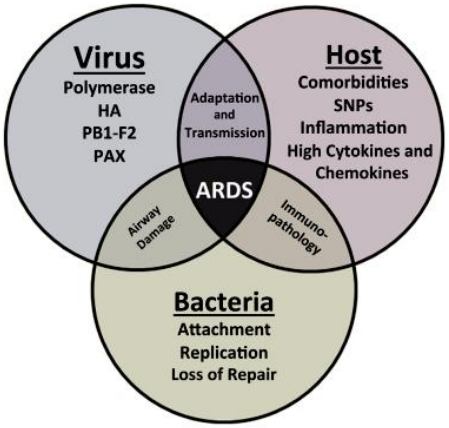
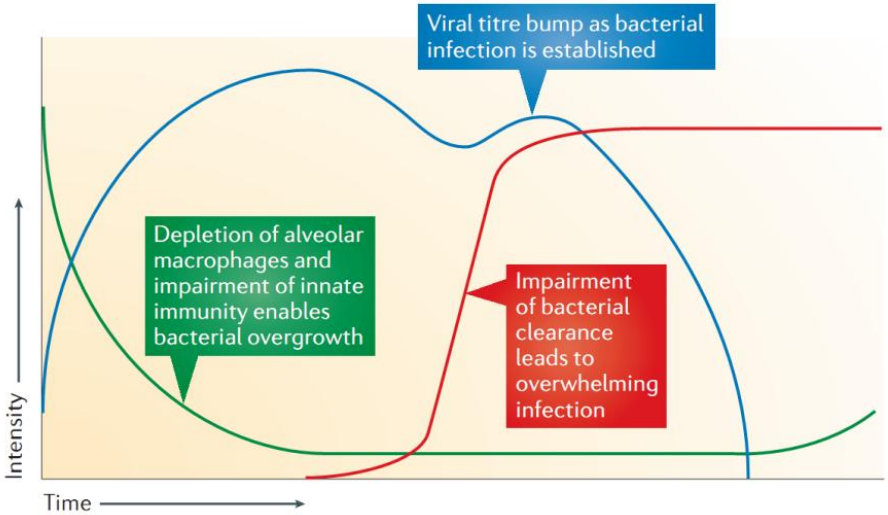


Figure 1 Diagram showing interrelationships between viral genes, host factors, and secondary bacterial infections associated with development of severe pathology and disease. ARDS, acute respiratory distress syndrome; HA, hemagglutinin; PAX, polymerase acidic frameshift protein; PB1, polymerase basic protein 1 frame 2 protein; SNP, single-nucleotide polymorphism.



Am J Pathol 2015, 185: 1528e1536
Curr Opin Immunol. 2015 June ; 34: 59–67.

重视重症甲流后合并感染

曲霉菌感染：n=19（19/55，34.5%）

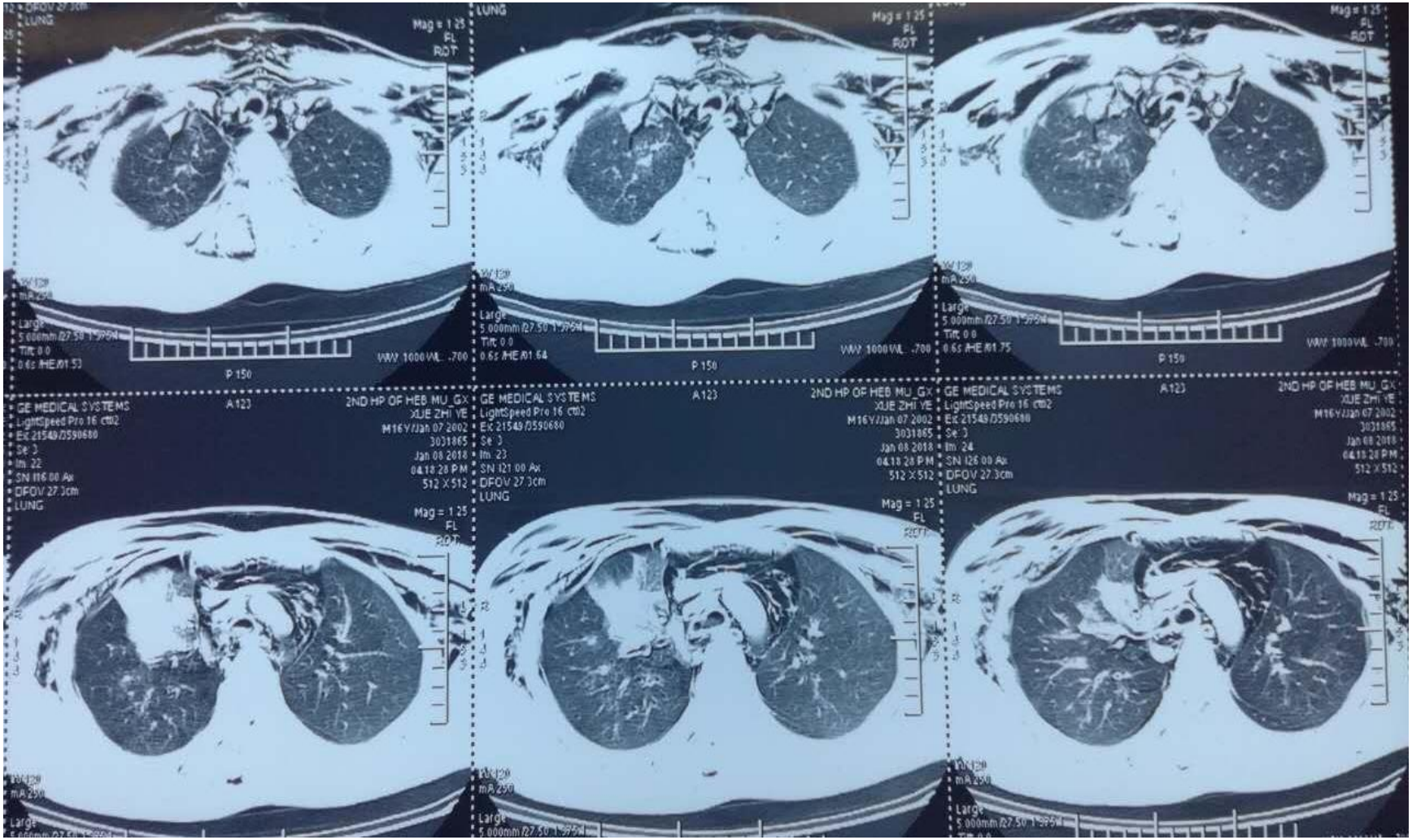
- 9例 LRT分泌物培养：4烟曲，2黄曲，2曲霉，1黄曲＋烟曲
- 7例 血＋BALF GM 试验阳性
- 发病至临床诊断：6-27天，平均14.3（±6.3）天

重视重症甲流后合并感染

- 男，15岁，学生，河北省
- 发热、干咳17天，加重伴呼吸困难8天
- 入ICU时间：2018-1-16
- 死亡时间：2018-1-26
- 17天前（2017-12-30）无明显诱因出现发热，体温最高达39.0℃，伴干咳、咽痛，10天前（2018-01-07）出现呼吸困难
- ABG示II型呼衰，WBC 24.1*10^9/L，NE% 90%，PCT 3.3ng/ml
- 抗生素：头孢曲松，亚胺培南，阿奇霉素，利耐唑胺

1-7

1-8 胸部CT


LUNG
Mag = 1.25
FL
ROT
P 150
A123
GE MEDICAL SYSTEMS
LightSpeed Pro 16
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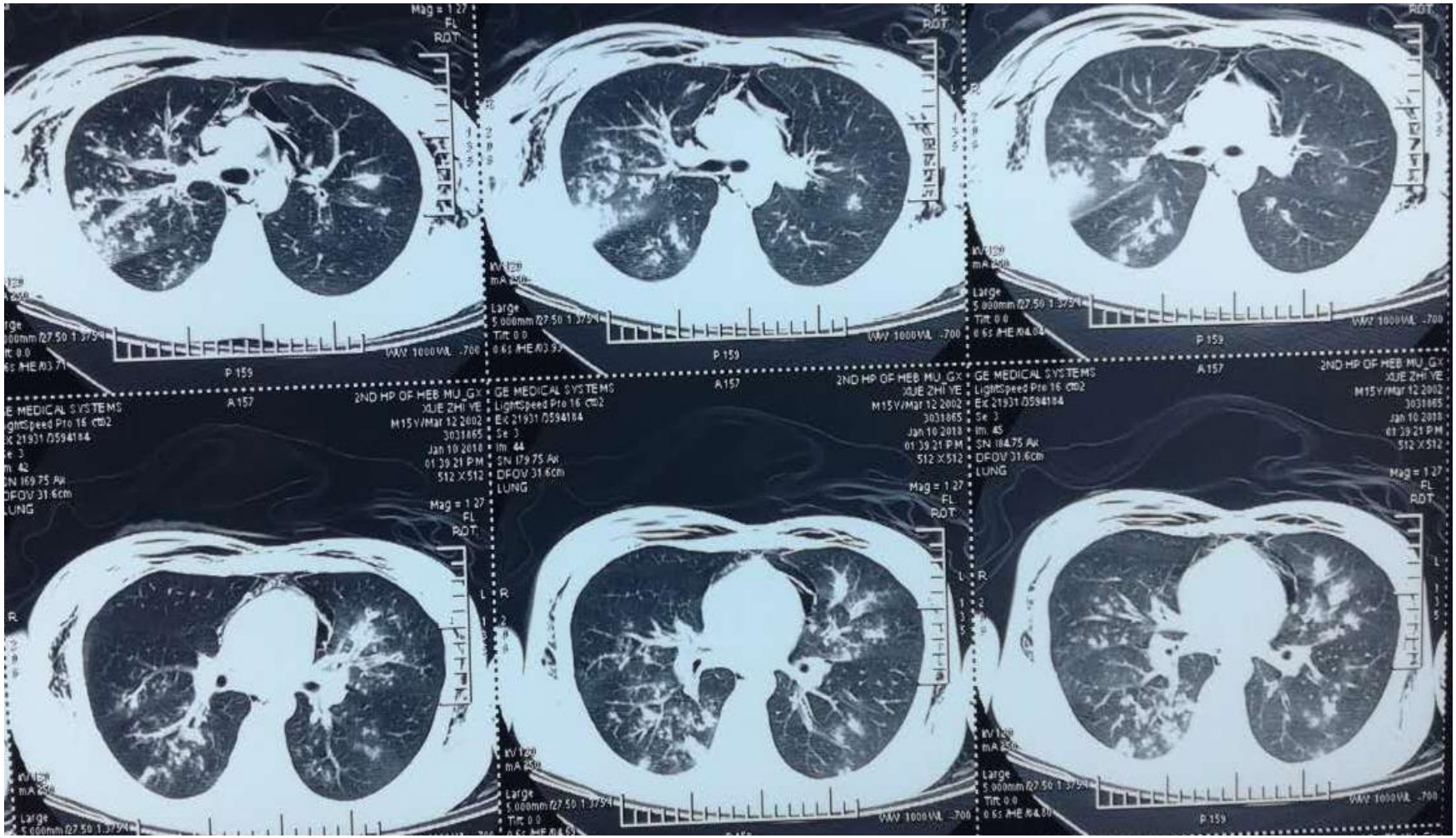
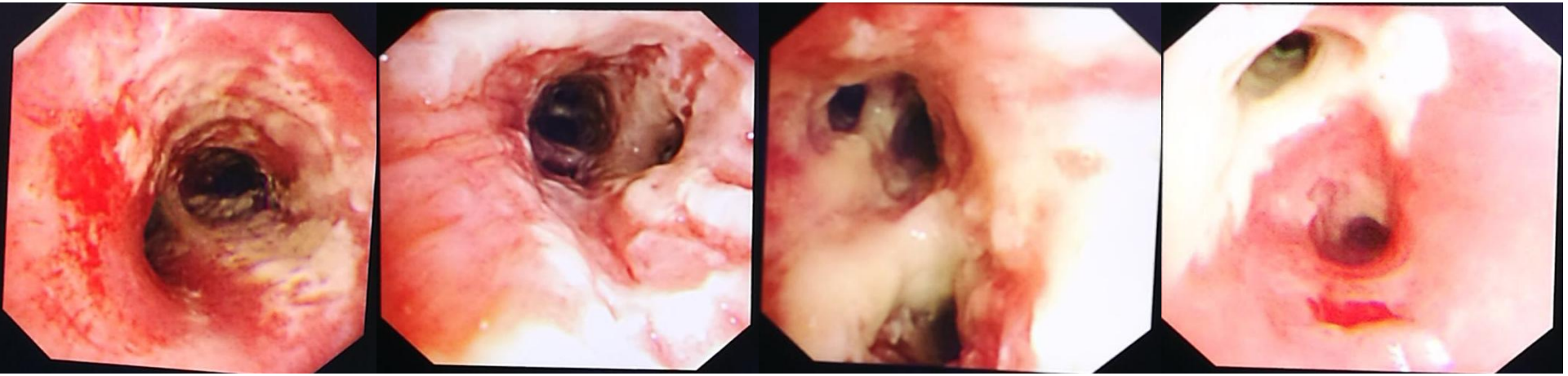
XUE ZHI YE
DFOV 27.3cm
512 X 512

1-8 胸部CT


GE MEDICAL SYSTEMS
LightSpeed Pro 16
2ND HP OF HEB MU_GX
XUE ZHI YE
LUNG

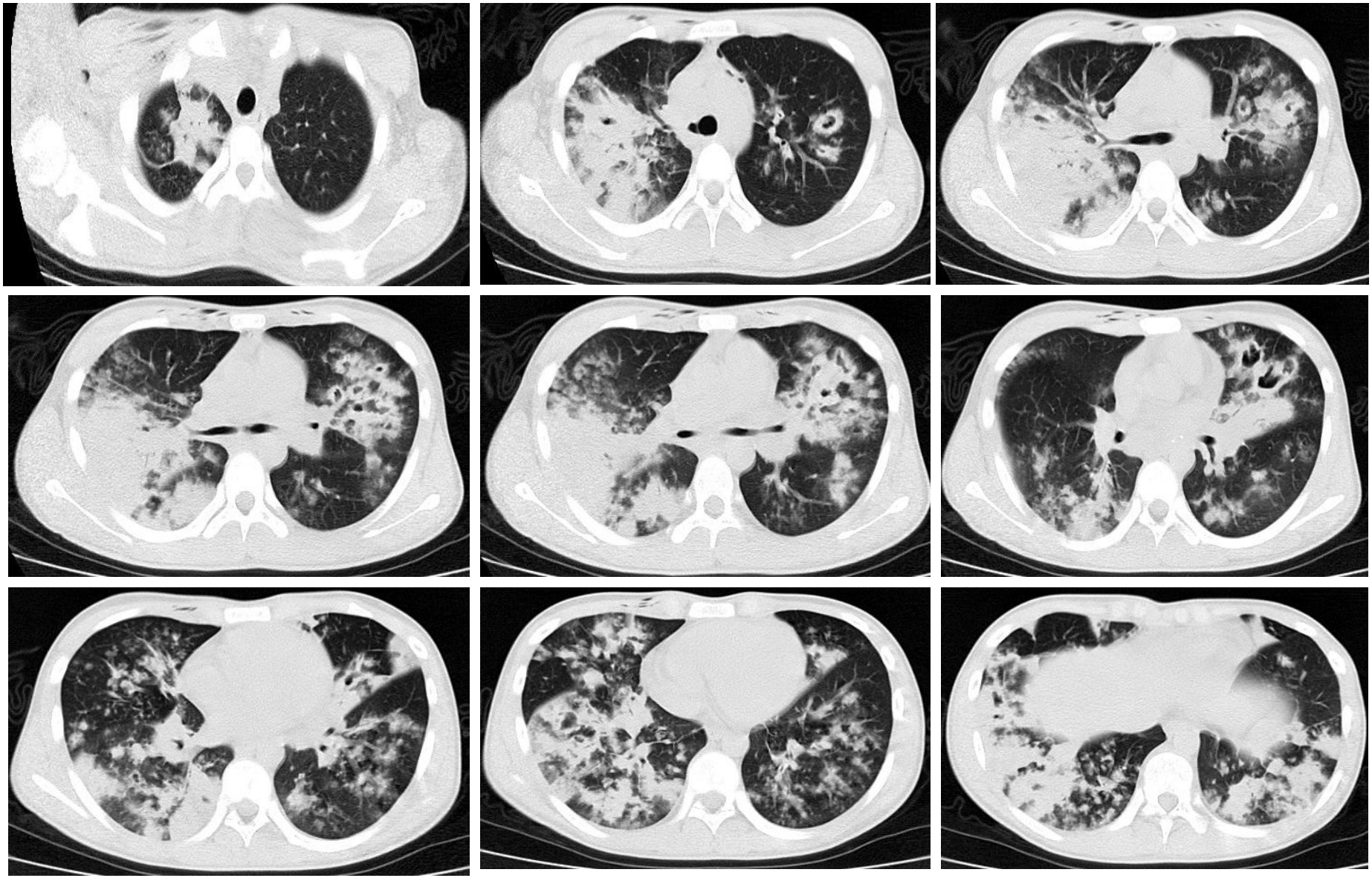
气管镜下表现及病原学检测

- 粘膜充血水肿明显，表面大量白苔，触之易出血

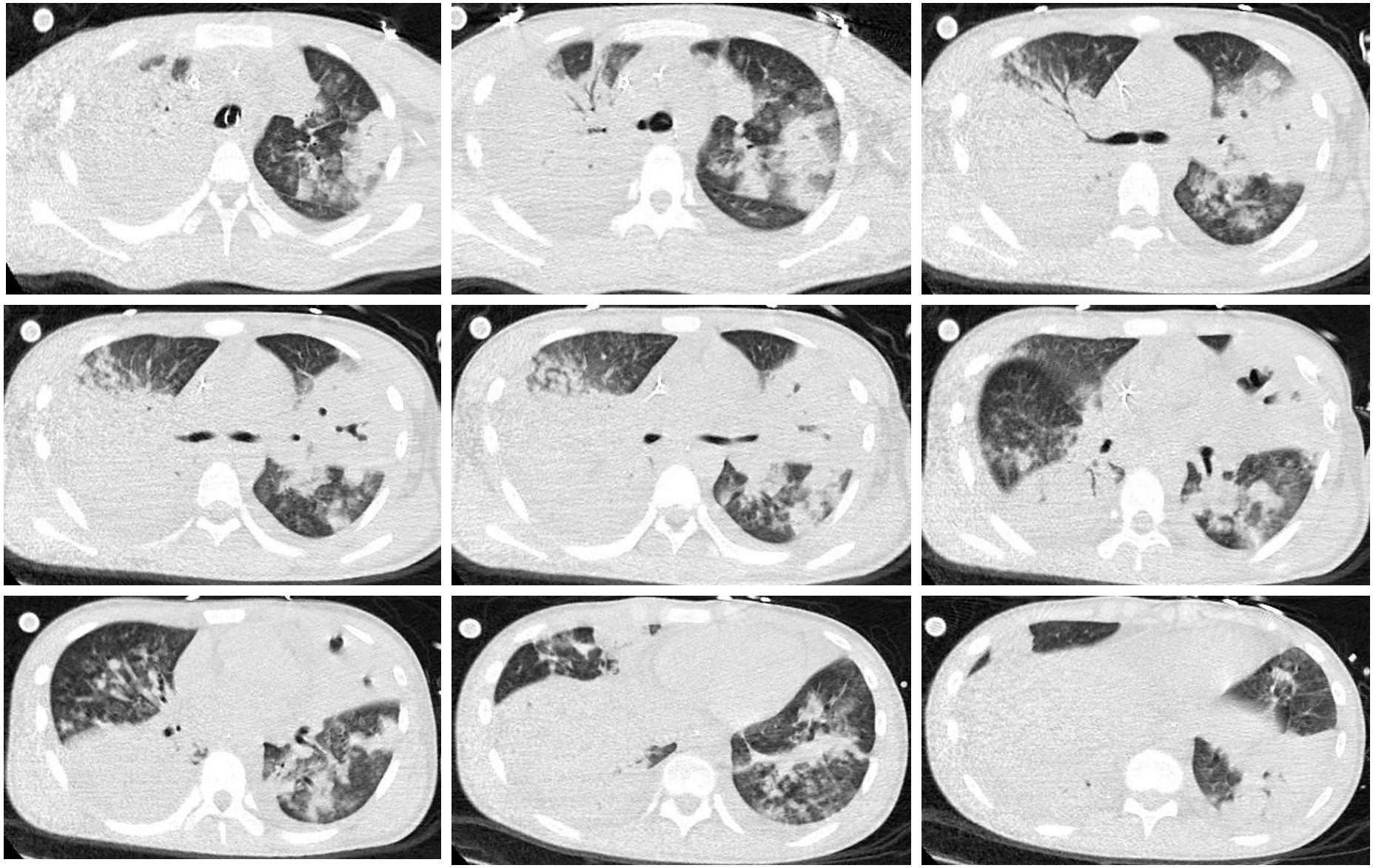


- 痰：烟曲霉*2次，CRAB*1次
- BALF：烟曲霉*1次，CRAB*2次

影像学表现（1-15）



影像学表现（1-22 ）



重视重症甲流后合并感染

Intensive Care Med (2012) 38:1761–1768
DOI 10.1007/s00134-012-2673-2

ORIGINAL

Joost Wauters
Ingrid Baar
Philippe Meersseman
Wouter Meersseman
Karolien Dams

Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study

- Of 40 critically ill patients with confirmed H1N1,
  - 9 (23 %) developed IPA 3 days after ICU admission.

Patient	GM BAL	GM blood	Fungi BAL	Bronchoscopic lesion	Fungi biopsy	Infiltrates	EORTC definition	Day of first indication of IPA after ICU admission	Predisposing condition
1	Y	Y	N	Y	NA	Y	Probable[a]	3	CS before IPA
2	Y	N	Y	N	NA	Y	Probable[a]	5	CS before IPA
3	Y	Y	Y	N	Y	Y	Proven	−5	Kidney transplant
4	Y	N	Y	N	N	Y	Probable[a]	10	COPD
5	Y	Y	Y	N	Y	Y	Proven	0	Kidney transplant
6	Y	Y	Y	Y	Y	Y	Proven	−3	Lung transplant
7	Y	Y	Y	Y	NA	Y	Probable[a]	0	TTP
8	Y	Y	Y	Y	Y	Y	Proven	8	CS before IPA
9[b]	Y	Y	Y	Y	Y	Y	Proven	5	CS before IPA

Intensive Care Med (2012) 38:1761–1768

重视重症甲流后合并感染

Table 2. Summary of 57 Cases of Invasive *Aspergillus* During Influenza Infection: Current Cases and Literature Review

Characteristic	
Demographics	
Age, years	
Sex, male	
Underlying medical conditions at a	
"Classic underlying disease"[b]	18 (32%)
Underlying condition, yes	46 (81%)
Types of conditions[c]	
Cancer	
Neutropenia	
Diabetes	
Transplantation	
Underlying lung disease	
Immunosuppressant use at admis	
Immunosuppressed host (based on condition and/ or medication use) at admission	20 (35%)
Influenza-related data at admission	
Type	
A	
B	
Receipt of anti-influenza treatmen	
Hospitalization data	
Lymphopenia (<1000 cells/μL)	
Steroid use, yes	
Aspergillus data	
Days from influenza to *Aspergillus* diagnosis	6 (0–32)[a]
Sites of Aspergillosis[c]	
Lung	57 (100%)
Tracheobronchitis	9 (16%)
Systemic	6 (11%)

Species	
	40 (70%)
	1 (2%)
	1 (2%)
	1 (2%)
	1 (2%)
	13 (23%)
Type of diagnostic specimen	
Bronchoscopy culture	27 (47%)
	22 (39%)
	21 (37%)
	28 (49%)
	4 (7%)
	1 (2%)
Proven	21 (37%)
Probable	14 (25%)
Possible	22 (39%)
	53 (93%)
	38 (67%)
	11 (19%)
Not reported	8 (14%)
Characteristic	Number (%)[a] or Median (Range)
ECMO	12 (21%)
Mortality	26 (46%)

流感起病1周内出现

缺乏经典的宿主因素

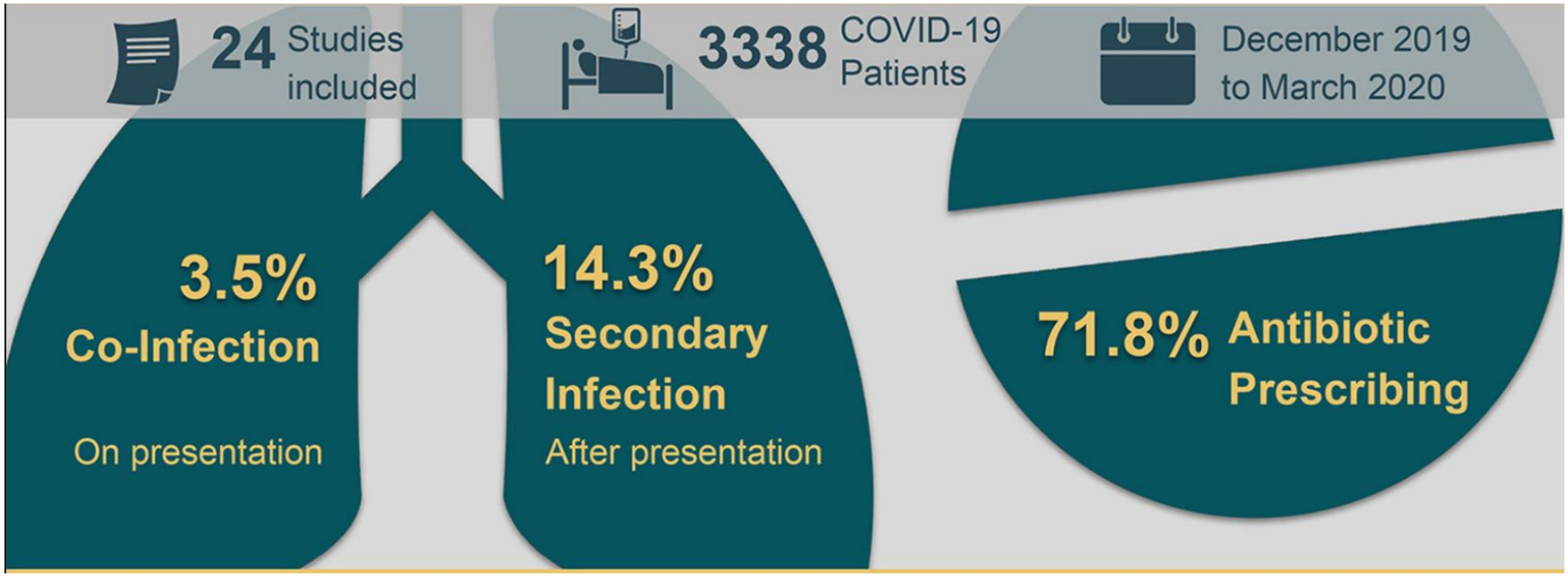
多数合并有至少1种内科疾病

重视重症甲流后合并感染

- 糖皮质激素应用
  - 流感患者中糖皮质激素与抗病毒药物常联合应用
    - 抑制流感后炎症反应对肺实质造成的损伤
  - 18-69%重症H1N1流感病毒性肺炎患者有糖皮质激素应用史
  - IPA者入ICU前应用糖皮质激素者明显高于非IPA者
    - 7/9 (78 %) versus 7/31 (23 %), p = 0.002
  - H1N1相关ARDS在病程早期应用糖皮质激素
    - 与高ICU病死率、高住院病死率及高混合感染风险

Intensive Care Med (2012) 38:1761–1768

重视COVID-19救治过程中继发感染



- 混合感染或继发感染比例高：细菌、真菌、TB
- 糖皮质激素应用对继发感染的影响仍有争议

Clin Microbiol Infect 2020;26(12):1622-1629.

认识不同宿主合并重症CAP的病原学特点

要点一： 免疫抑制患者要特别警惕机会致病菌感染

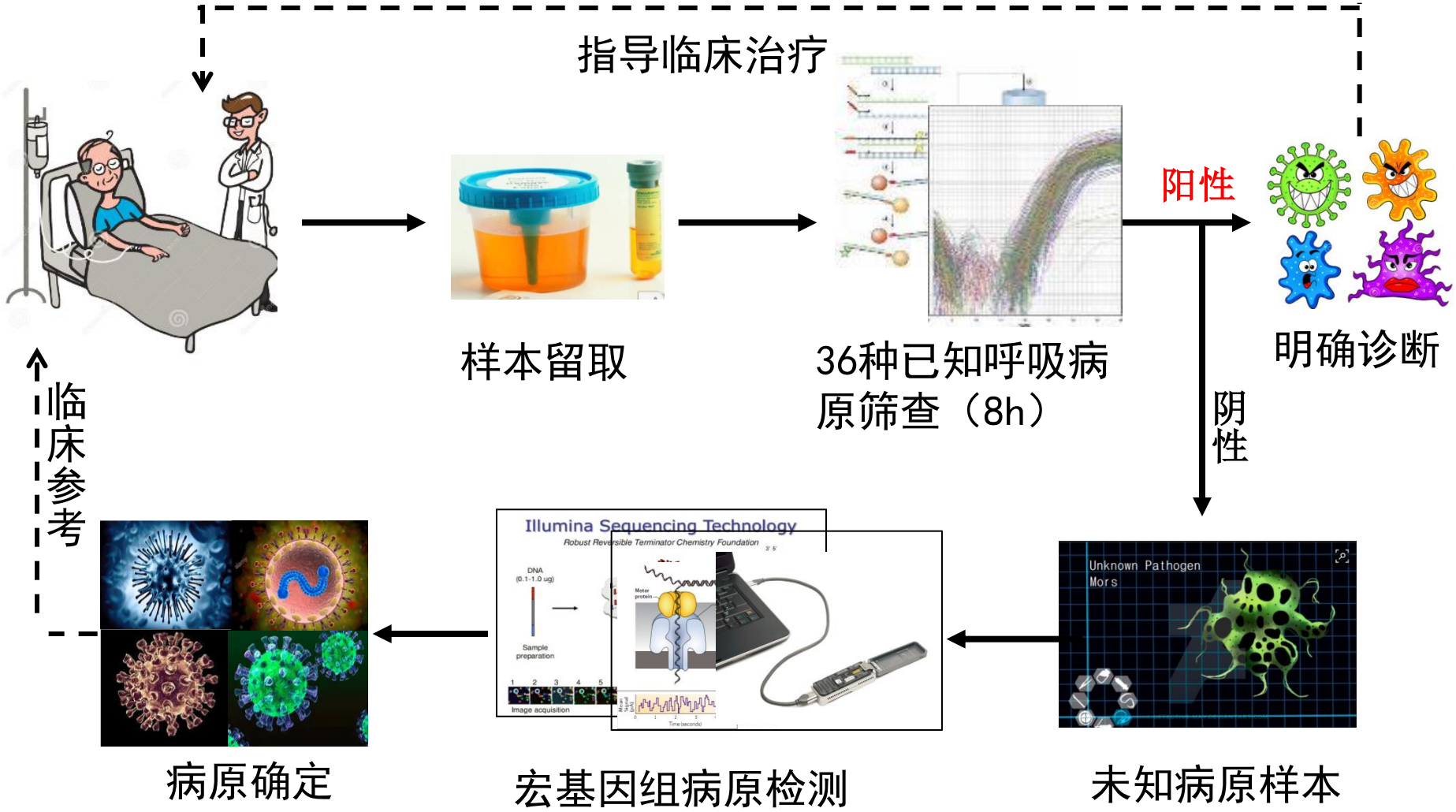
要点二： 多为混合感染

要点三： 在免疫缺陷宿主病情常快速进展

要点四： 谨慎使用糖皮质激素

经验性抗感染和最终明确诊断需要多科室共同努力

研发快速广覆盖的病原检测技术



—— 实现病原检测的实时化，减少抗生素不合理应用

无反应性肺炎（nonresponding CAP）

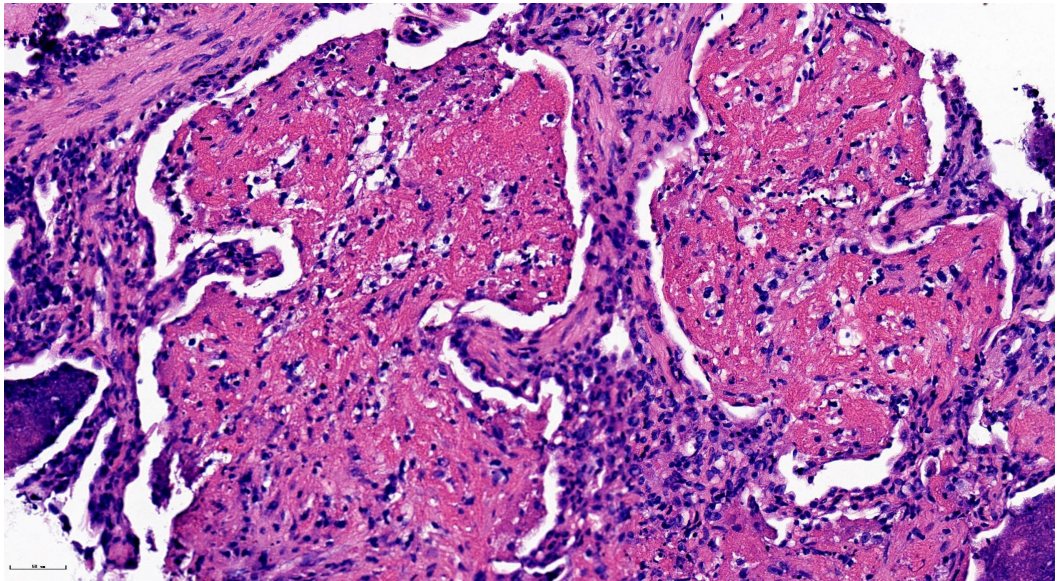
- CAP 治疗失败或无反应性 CAP：指经过初始抗感染治疗后，患者临床症状无好转或恶化，导致感染播散，出现并发症甚至死亡
- 指南推荐如果初始治疗 72h 后病情无改善，可考虑为无反应性 CAP

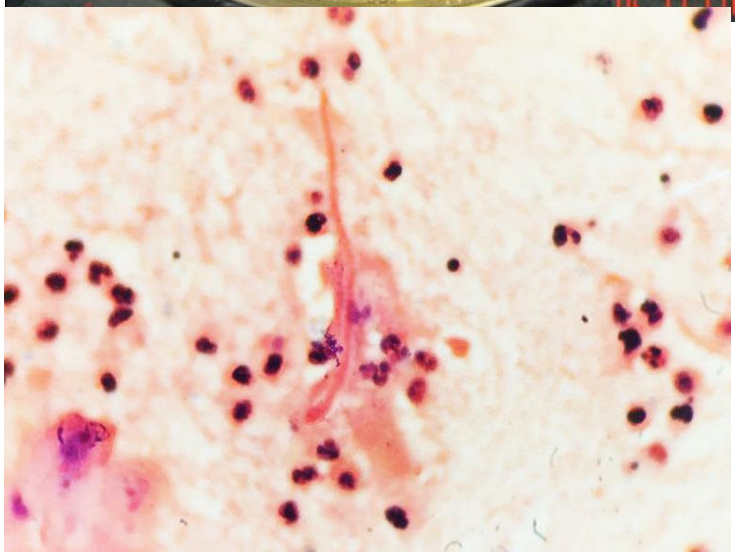
Causes of treatment failure in communityacquired pneumonia	
Infectious	• Resistant microorganisms: ○ *Pseudomonas aeruginosa* ○ MRSA ○ Beta-lactamase producing *Enterobacteriaceae* • Unusual microorganisms ○ *Mycobacterium tuberculosis* ○ *Nocardia* spp ○ Fungi (Aspergillus spp, Histoplasma, Coccidioides) ○ *Pneumocystis jirovecii* ○ Hantavirus • Nosocomial pneumonia ○ *Pseudomonas aeruginosa* ○ MRSA ○ *Acinetobacter baumanii* ○ Anaerobes • Complications of pneumonia ○ Empyema ○ Abscess or necrotizing pneumonia ○ Metastatic infection: endocarditis, meningitis, arthritis
Noninfectious	• Neoplasms • Pulmonary edema • Pulmonary embolism • Pulmonary hemorrhage • Cryptogenic organizing pneumonia • Eosinophilic pneumonia • Acute respiratory distress syndrome • Sarcoidosis • Vasculitis

Infect Dis Clin N Am 27 (2013) 189–203

感染 Vs 非感染

- 诊疗方案差异极大
  - 抗生素 Vs 激素/化疗
  - 广谱抗生素大量使用
  - 筛选出多重耐药菌
  - 延误治疗时机



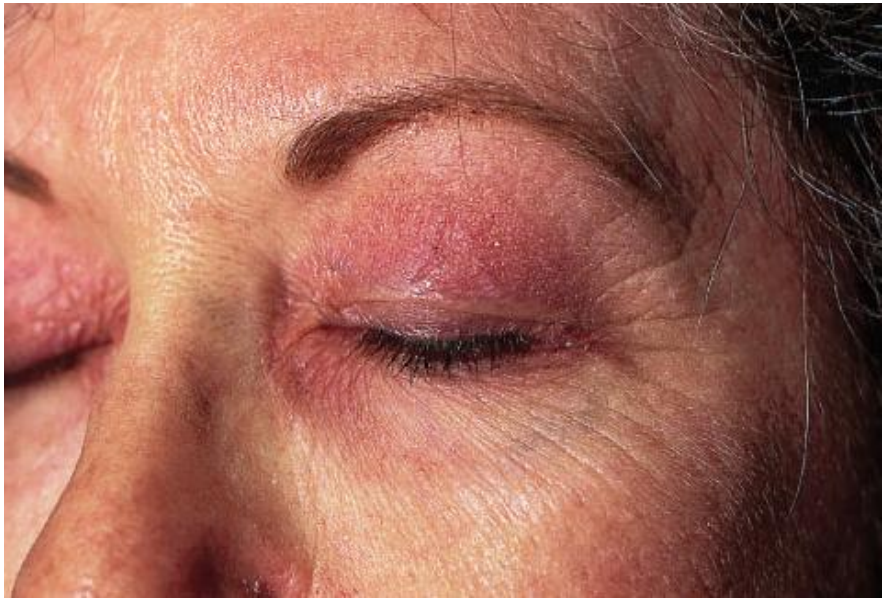


CASE

- 59/F，入院时间 2017-8-16
- 主诉：咳嗽10天，发热3天，呼吸困难1天
- ABG（经鼻高流量吸氧 70%）：pH 7.43，pCO2 36.2mmHg，pO2 78.9mmHg，Lac 0.7mmol/L
- 初始治疗：头孢吡污、舒普深、莫西沙星等抗感染治疗，效果不佳

皮肌炎（dermatomyositis，DM）

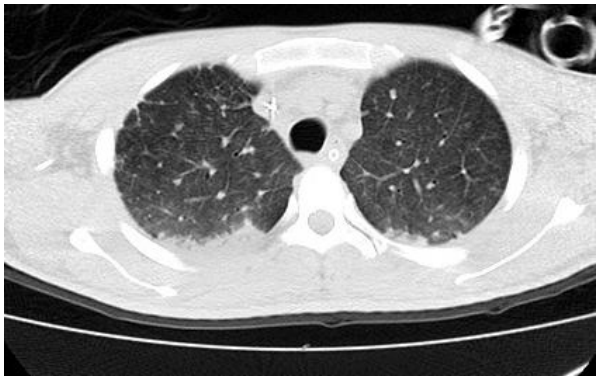
- 一种累及皮肤和肌肉的炎症性结缔组织病
- 多见于40-60岁
- 特征性皮损：**Gottron 征**、**向阳疹**、**技工手**
- 肌酶（CK、LDH、AST）升高
- 特异性抗体：**抗Mi-2抗体**、**抗Jo-1抗体**、**抗 MDA-5抗体**
- 肺受累：间质性肺疾病，发生率约40%，可急性加重导致 ARDS

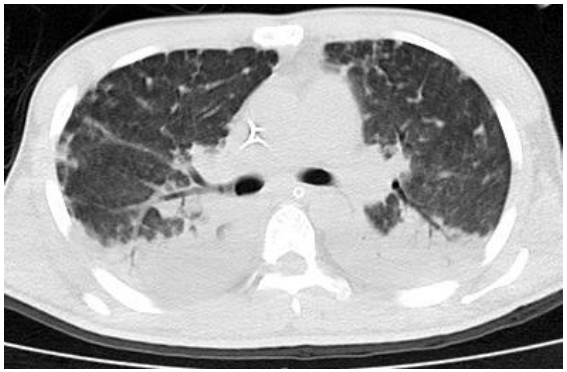


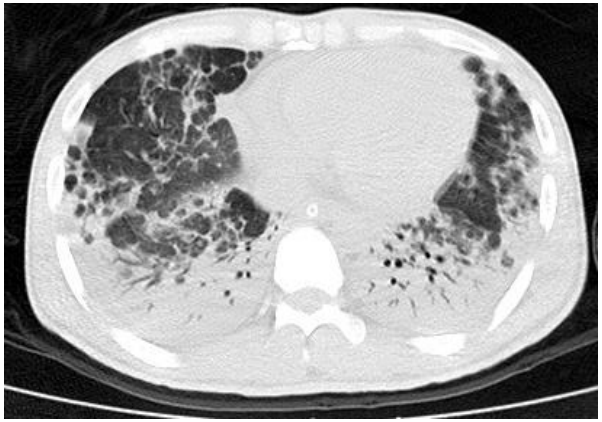
CASE

- 霍**，25/M，入院时间：2018-4-23
- 主诉：咽痛13天，发热伴呼吸困难11天
- 查体：双侧扁桃体Ⅰ°肿大，咽后壁、双侧扁桃体可见大量脓苔及伪膜
- 胸部 CT：双肺散在磨玻璃影，以中外带分布为主
- 外院先后予头孢曲松、美罗培南、奥司他韦、莫西沙星、替考拉宁、替考拉宁等药物抗感染治疗效果不佳
- 呼吸困难进行性加重，2天前气管插管

入院影像学







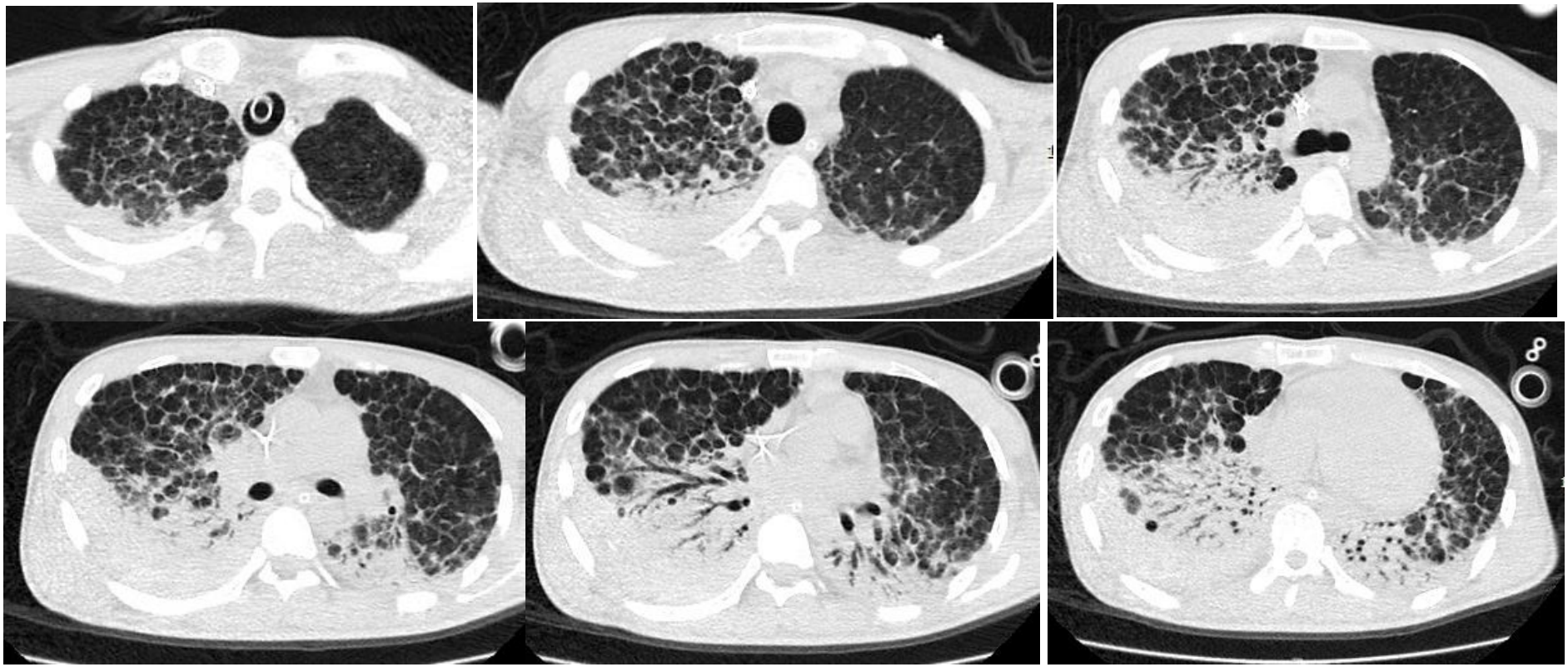
入院后诊疗

- ABG（PCV，PC 15，PEEP 14，FiO2 1.0）：pH 7.48，pCO2 38.9mmHg，pO2 65.7mmHg
- 入院第2天建立VV-ECMO 支持治疗
- 入院第3天，超声引导下经皮肺穿刺活检

肺组织实变，较多淋巴细胞及组织细胞浸润，散在少量中性粒细胞，小血管及纤维母细胞增生，肺泡减少。考虑 AIP，COP 不除外

治疗及转归

- 甲强龙500mg*3d→240mg*3d→120mg*5d→80mg…
- 患者肺部病变没有改善，最终因脓毒性休克死亡
- 最终诊断：**急性间质性肺炎**



小 结

- 重症CAP的理性治疗在于充分治疗的同时避免过度诊疗
- 重症CAP抗感染治疗的选择应综合评估患者病情严重程度、病原倾向性、耐药危险因素以及特殊人群特点，有针对性的选择抗感染策略
- 重症病原学检测应有针对性，根据检测方法特点合理安排
- 尽早进行抗感染治疗应建立在对CAP的充分鉴别基础上，避免不必要的抗菌药物使用
- 抗感染疗程和出院时间点的判断可依据达临床稳定标准，避免ICU内停留导致的HAP等并发症