COVID-19

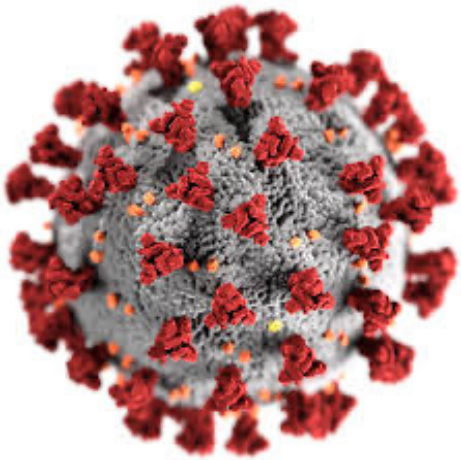
Nosocomial and (co)infections

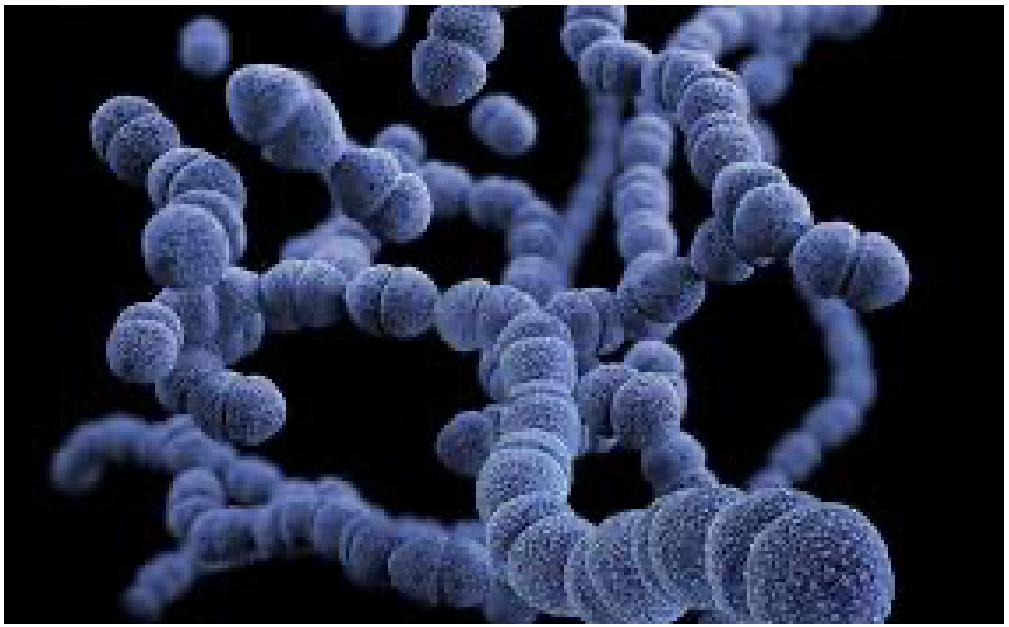
Jeroen Schouten

14th July 2020

Center for Infectious Diseases
Radboudumc

Bacterial co-infections and SARS-CoV-2





How frequent are superinfections?

the challenges

- Even in “normal” CAP the detection of a likely pathogen is rare
  - 853/2259 (38%) patients in an active population-based surveillance in 5 US hospitals pathogen detected
  - 247/2259 (11%) likely bacterial pathogen identified

- Invasive diagnostic procedures such as bronchoalveolar lavage are difficult during the COVID-19 pandemic
  - Risk of deterioration or patients with respiratory failure
  - Strained personnel resources
  - Concerns about risk of exposure of healthcare personnel

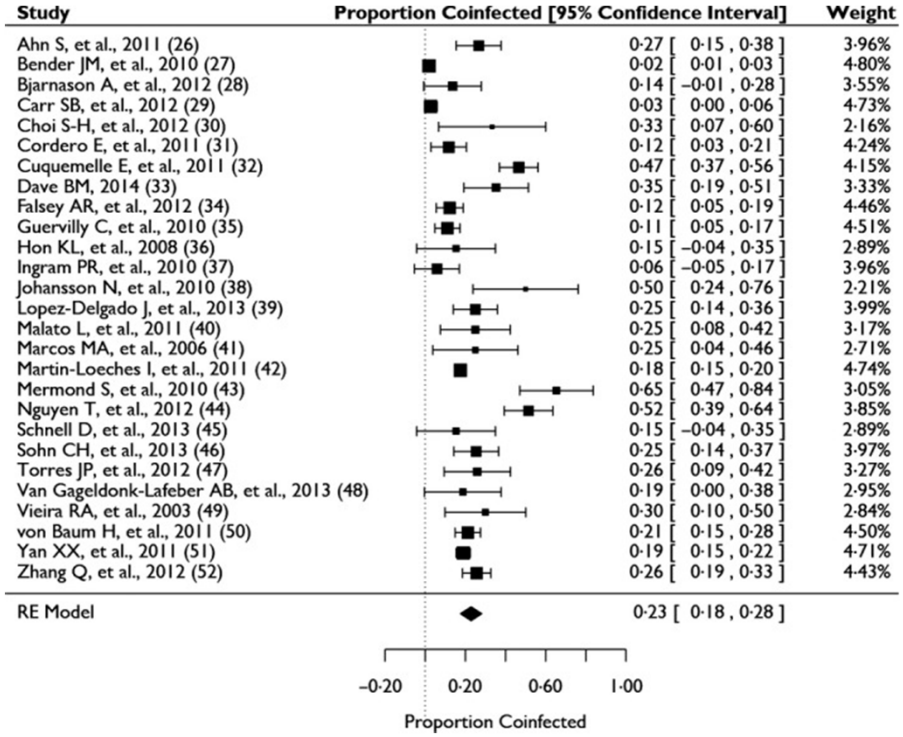
- Shortages of diagnostic tests may be an issue
  - e.g. urinary antigens, blood culures

Jain et al. N Engl J Med. 2015 Jul 30;373(5):415-27.

The frequency of bacterial superinfection in influenza

- Systematic review
  - All patients with laboratory confirmed influenza
  - All tested for “an array of common bacterial species”
- Coinfection range 2% to 65%
  - 11% - 35% for the studies with the least heterogeneity
- Probably an overestimation
  - All studies focused on hospitalized patients
  - About 50% of ICU patients

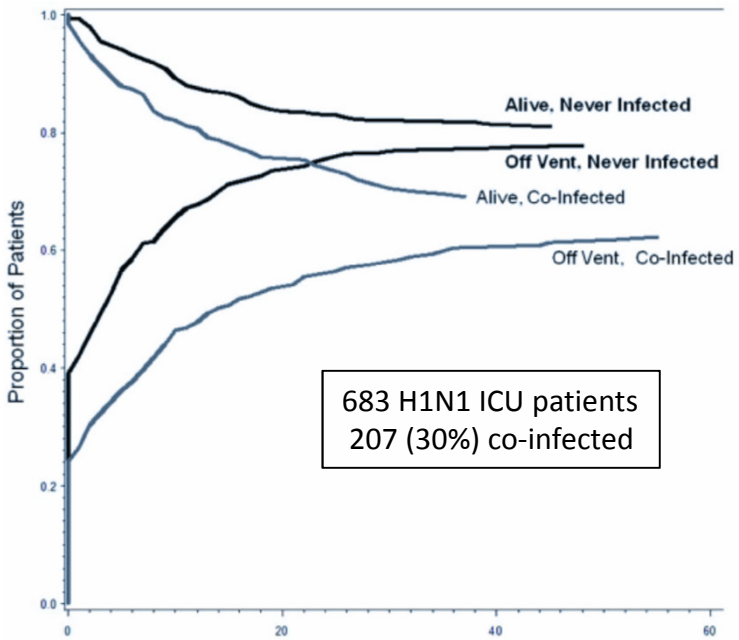
27 studies including 3215 participants



Klein et al. Influenza Other Respir Viruses. 2016 Sep;10(5):394-403.

The frequency of bacterial superinfection in influenza

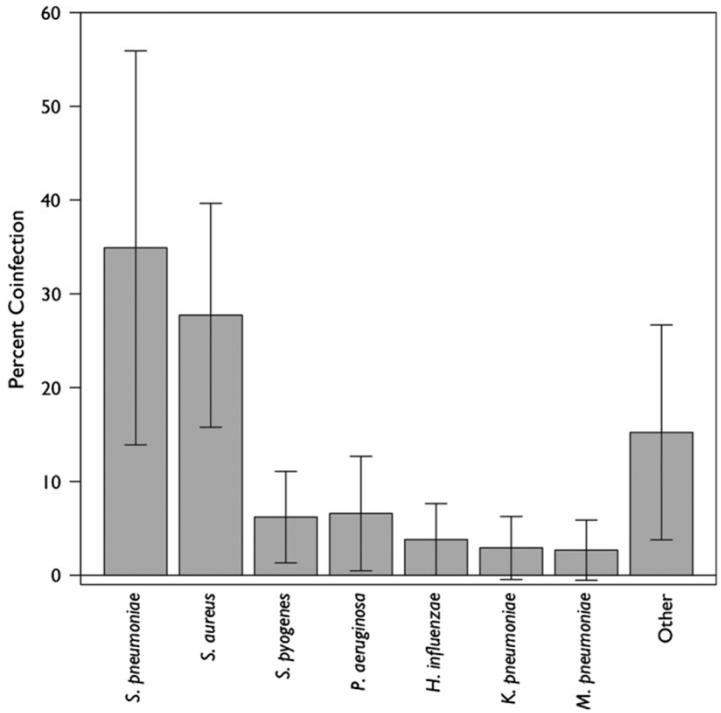
35 ICU in United States



683 H1N1 ICU patients
207 (30%) co-infected

Rice et al. CCM 2012

27 studies including 3215 participants



Klein et al. Influenza Other Respir Viruses. 2016

Clinical Infectious Diseases

IDSA GUIDELINE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza[a]

- "Clinicians should also consider that a positive influenza test result **does not exclude bacterial coinfection**, and evaluation of the potential need for antibiotics, especially in patients with pneumonia, should be considered."

IDSA Influenza Clinical Guidelines 2018

Bacterial co-infections in Coronavirus infections

- Rapid (systematic) review of the literature: 18 articles identified
  - SARS-CoV-2 9/18 (50%)
  - SARS-CoV- 1 5/18 (28%)
  - MERS 1/18 (6%)
  - Other Coronaviruses 3/18 (17%)

- Setting (ICU versus non-ICU) often not defined

- **1450 of 2010 patients (*72%* !) received antibiotics**

Rawson et al. Clin Infect Dis . 2020 May 2

Bacterial co-infections in Coronavirus infections

- **SARS-CoV-2**
  - 62/806 (8%) of bacterial/fungal co-infection
  - 11% for Coronaviruses other than SARS-CoV-2

- **CAVE:**
  - Different settings (China, US,…) with different epidemiology and different infection control standards
  - Setting (ICU versus non-ICU) often not defined
  - Type of infection often not specified (pulmonary versus extra-pulmonary)
  - Sampling not standardized
  - Few atypical pathogens

Rawson et al. Clin Infect Dis . 2020 May 2;ciaa530.

Bacterial co-infections and SARS-CoV-2

- Seems to be less frequent than in severe influenza
- Atypical pathogens seem uncommon
  - Universal atypical coverage probably not warranted if antibiotic treatment deemed necessarry
- Better studies are needed…

Bacterial co-infections and SARS-CoV-2

Admissions ICU Radboudumc (76 COVID patients)

- Total 48 episodes of nosocomial infections
- 43% has at least 1 episode of nosocomial infection (VAP/HAP, bacteremia, CLABSI,…)
- 75% of all bacterial infections occur > 9 days after admission

Bacterial co-infections and SARS-CoV-2

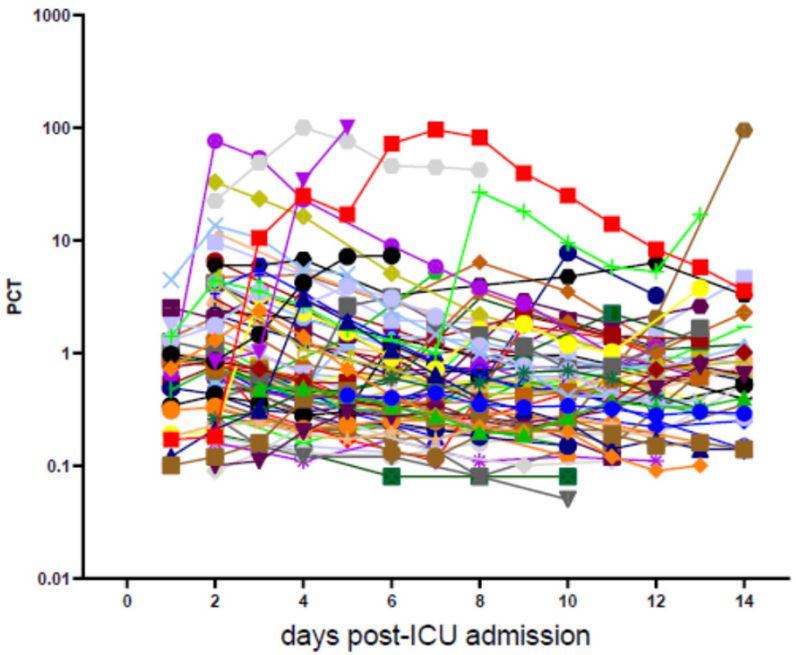
- Role CRP and PCT unclear (NEJM, Guan 2020)
  CRP > 10 mg/dl 481/793 (60,7%)
  PCT > 0,5 ng/ml 35/633 (5,5%)

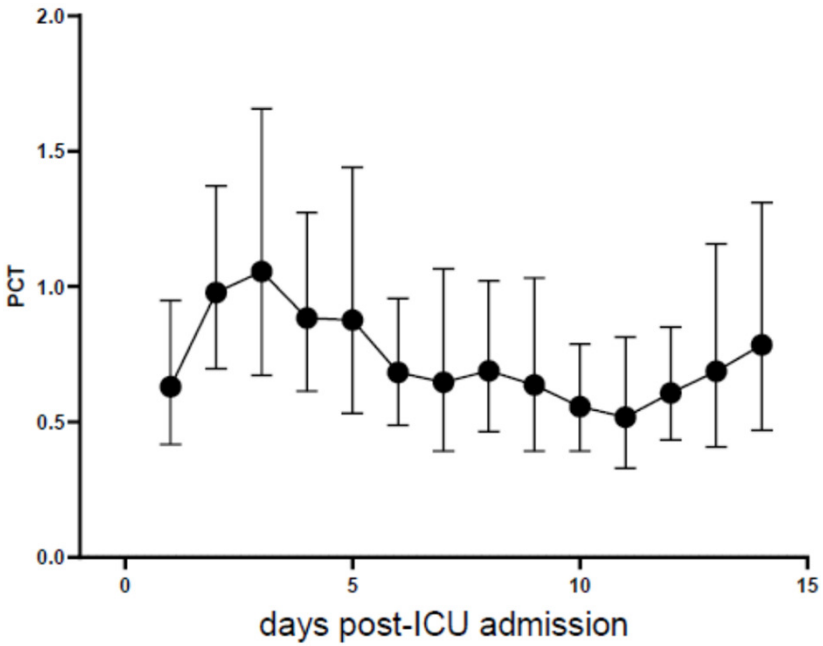
N	Zhang 140	Huang 41	Chen 99	Xu 62	Liu 12	Wang 34 [5]	Chen 29	Chen 9 [6]
N sev.	58	13	17	1	6	0	14	0
%CRP↑	91	NA	86	NA	83	3	93	75
%PCT↑	35	8	6	11	8	3	0	NA

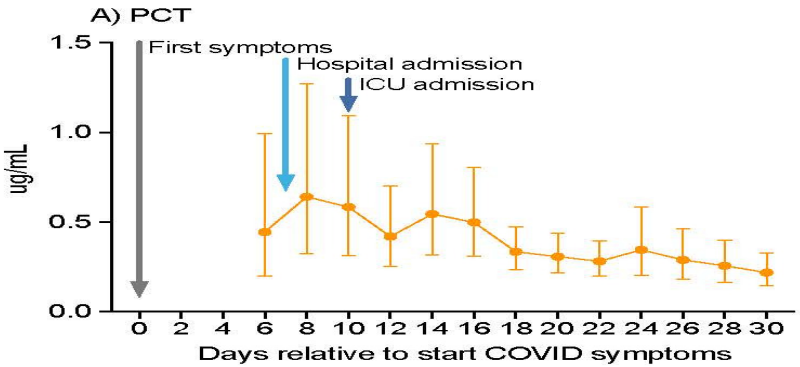
	Secondary infection (n=33)	No secondary infection (n=33)	p-value
Sex			
Male, n (%)	26 (79%)	23 (70%)	0.57
Female, n (%)	7 (21%)	10 (30%)	
Age, years	67 [60-73]	65 [56-70]	0.17
BMI, kg/m²	27.6 [25.4-31.1]	27.7 [24.3-30.7]	0.40
APACHE II	15 [13-19]	15 [10-19]	0.77
Days between covid symptoms and hospital admission (median [IQR]	7 [4-10]	7 [5-11]	0.72
Days between covid symptoms and ICU admission (median [IQR])	10 [7-13]	10 [6-14]	0.96
Day infection from start hospital admission (median [IQR])	15 [12-21]	NA	
Day infection from start ICU admission (median [IQR])	13 [8-19]	NA	
Medical history, n (%)			
Cardiovascular insufficiency	9 (27%)	9 (27%)	1.00
Hypertension	17 (52%)	16 (48%)	1.00
Respiratory insufficiency	2 (6%)	3 (9%)	1.00
Renal insufficiency	0 (0%)	1 (3%)	1.00
Metastatic neoplasm	2 (6%)	3 (9%)	1.00
Immunological insufficiency	0 (0%)	1 (3%)	1.00
COPD	3 (9%)	3 (9%)	1.00
Diabetes	11 (33%)	4 (12%)	0.08
Hematologic malignancy	0 (0%)	1 (3%)	1.00

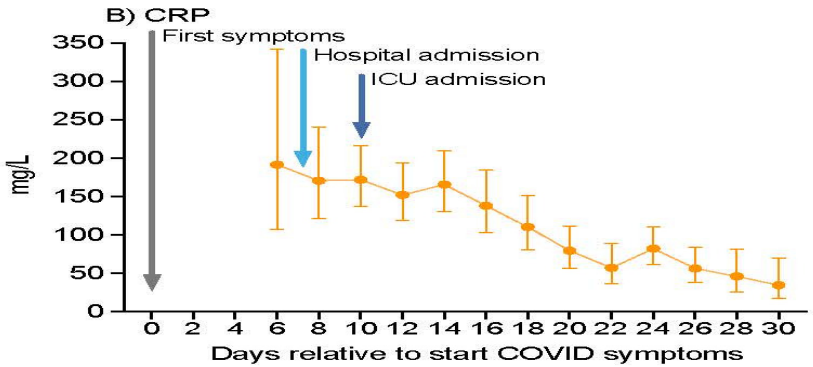
Bacterial co-infections and SARS-CoV-2

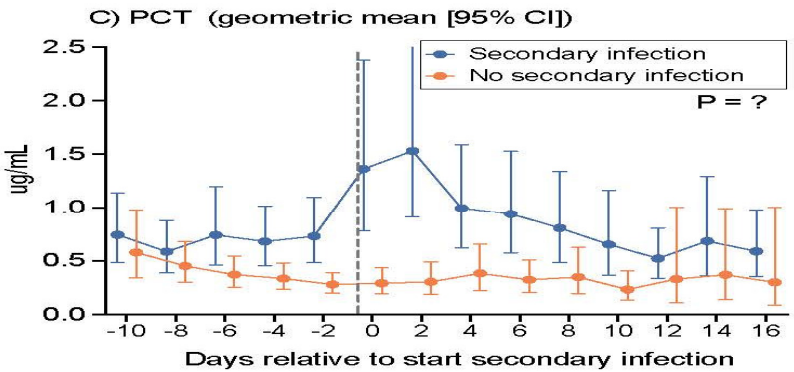
Admissions ICU Radboudumc (76 COVID patients)

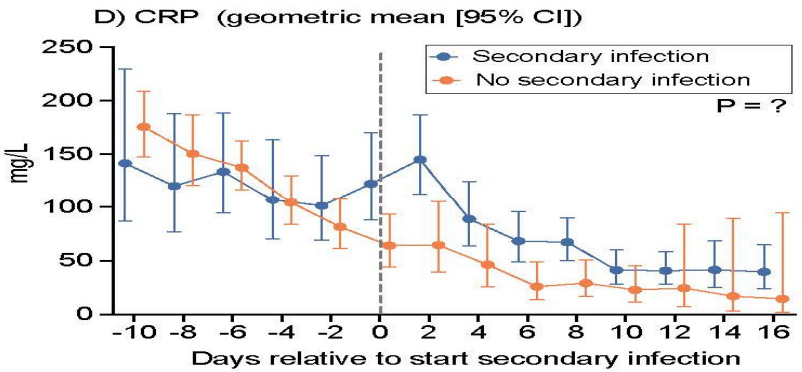


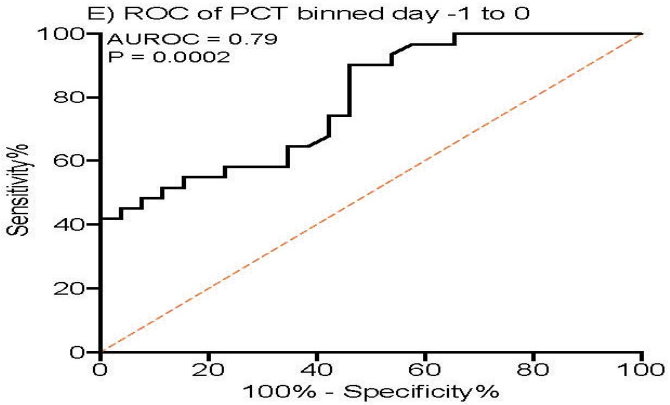


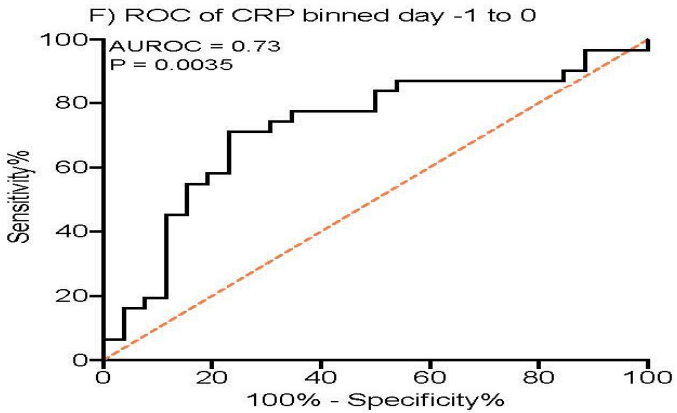

A) PCT
First symptoms
Hospital admission
ICU admission
ug/mL
1.5
1.0
0.5
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Days relative to start COVID symptoms


B) CRP
First symptoms
Hospital admission
ICU admission
mg/L
350
300
250
200
150
100
50
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Days relative to start COVID symptoms


C) PCT (geometric mean [95% CI])
Secondary infection
No secondary infection
P = ?
ug/mL
2.5
2.0
1.5
1.0
0.5
0.0
-10 -8 -6 -4 -2 0 2 4 6 8 10 12 14 16
Days relative to start secondary infection


D) CRP (geometric mean [95% CI])
Secondary infection
No secondary infection
P = ?
mg/L
250
200
150
100
50
0
-10 -8 -6 -4 -2 0 2 4 6 8 10 12 14 16
Days relative to start secondary infection


E) ROC of PCT binned day -1 to 0
AUROC = 0.79
P = 0.0002
Sensitivity%
100
80
60
40
20
0
0 20 40 60 80 100
100% - Specificity%


F) ROC of CRP binned day -1 to 0
AUROC = 0.73
P = 0.0035
Sensitivity%
100
80
60
40
20
0
0 20 40 60 80 100
100% - Specificity%

Fungal co-infections

> Mycoses. 2020 Apr 27. doi: 10.1111/myc.13096. Online ahead of print.

COVID-19 Associated Pulmonary Aspergillosis

Philipp Koehler [1 2], Oliver A Cornely [1 2 3 4], Bernd W Böttiger [5], Fabian Dusse [5], Dennis A Eichenauer [1], Frieder Fuchs [6], Michael Hallek [1], Norma Jung [1], Florian Klein [7], Thorsten Persigehl [8], Jan Rybniker [1], Matthias Kochanek [1], Boris Böll [1], Alexander Shimabukuro-Vornhagen [1]

Affiliations + expand

PMID: 32339350 DOI: 10.1111/myc.13096 Add to Library Get PDF

Abstract

Objectives: Patients with acute respiratory distress syndrome (ARDS) due to viral infection are at risk for secondary complications like invasive aspergillosis. Our study evaluates Coronavirus disease 19 (COVID-19) associated invasive aspergillosis at a single center in Cologne, Germany.

Methods: A retrospective chart review of all patients with COVID-19 ARDS admitted to the medical or surgical intensive care unit at the University Hospital of Cologne, Germany.

Results: COVID-19 associated invasive pulmonary aspergillosis was found in five of 19 consecutive critically ill patients with moderate to severe ARDS.

Conclusion: Clinicians caring for patients with ARDS due to COVID-19 should consider invasive pulmonary aspergillosis and subject respiratory samples to comprehensive analysis to detect co-infection.

Keywords: Aspergillus; ECMO; ICU; SARS-CoV-2; isavuconazole; voriconazole.

Li and Xia

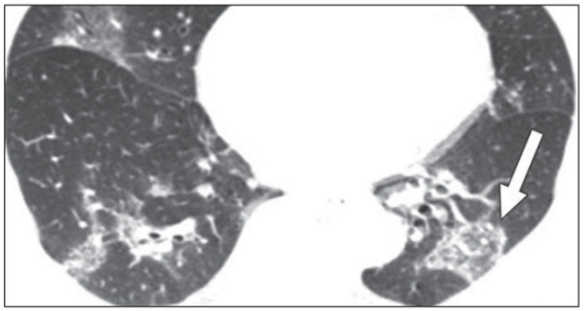


Fig. 4—68-year-old man with coronavirus disease (COVID-19). Transverse CT scan shows "reversed halo" sign in left lower lobe (*arrow*).

https://www.aspergillus.org.uk/blog/invasive-aspergillosis-covid-19-patients

Fungal co-infections: CAPA

Diagnosing COVID-19-associated pulmonary aspergillosis

Lancet Microbe 2020
Published Online
May 8, 2020
https://doi.org/10.1016/
S2666-5247(20)30027-6

There is increasing concern that patients with coronavirus disease 2019 (COVID-19) might be at risk of developing invasive pulmonary aspergillosis co-infection.[1] In a cohort of 221 patients with COVID-19 in China, fungal infections were diagnosed in seven individuals, all of whom were admitted to the intensive care unit (ICU).[2] However, causative fungal pathogens were in ICUs. A retrospective multicentre cohort study showed that influenza infection was an independent risk factor for invasive pulmonary aspergillosis.[6] In addition to local erosion of the epithelial barrier of the respiratory tract, influenza virus can exhibit a direct immunomodulatory effect through suppression of the NADPH oxidase complex.[9] Suppression of the NADPH

COVID-19 Associated Pulmonary Aspergillosis

Andreas L.E. van Arkel[1,2], Tom A. Rijpstra[3], Huub N.A. Belderbos[4], Peter van Wijngaarden[5],

Paul E. Verweij[6,7], and Robbert G. Bentvelsen[1,8]

Fungal co-infections…

Patient	Sex, age in years	Medical history	Days post symptom onset to onset CAPA	APACHE-II at ICU admission	Days post ICU admission to onset CAPA	Bronchoscopy findings	Microbiological findings (days post symptom onset of sample acquisition)	CAPA classification [8]	Outcome (days post symptom onset)
1	Male, 83	Cardiomyopathy Prednisolon 0·13 mg/kg/day for 28 days pre-admission	10 days	16	3 days	Not performed	Tracheal aspirate cultured *Aspergillus fumigatus* (day 7) Serum GM index 0·4 (day 8)	Possible	Died (day 12)
2	Male, 67	COPD Gold III Post RTx NSCLC 2014 Prednisolon 0·37 mg/kg/day for 2 days pre-admission	10 days	16	3 days	Not performed	Tracheal aspirate cultured *Aspergillus fumigatus* (day 5)	Possible	Died (day 11)
3	Male, 75	COPD Gold IIa	8 days	15	5 days	Mucoid white sputum left bronchus	BAL cultured *Aspergillus fumigatus* (day 8) BAL GM index 4·0 (day 8)	Probable	Died (day 12)
4	Male, 43	None	21 days	10	14 days	Unrevealing	BAL GM index 3·8 (day 18) Serum GM index 0·1 (day 16)	Probable	Survived
5	Male, 57	Bronchial asthma Fluticason 1·94 mcg/kg/day for 1 month pre-admission	13 days	15	5 days	Unrevealing	BAL cultured *Aspergillus fumigatus* (day 11) BAL GM index 1·6 (day 11) Serum GM index 0·1 (day 13)	Probable	Died (day 20)
6	Male, 58	None	42 days	15	28 days	Not performed	Sputum cultured *Aspergillus* (day 36, 40, 43, 47, and 50)	Possible	Survived
Median			11·5 days	15	5 days				12 days

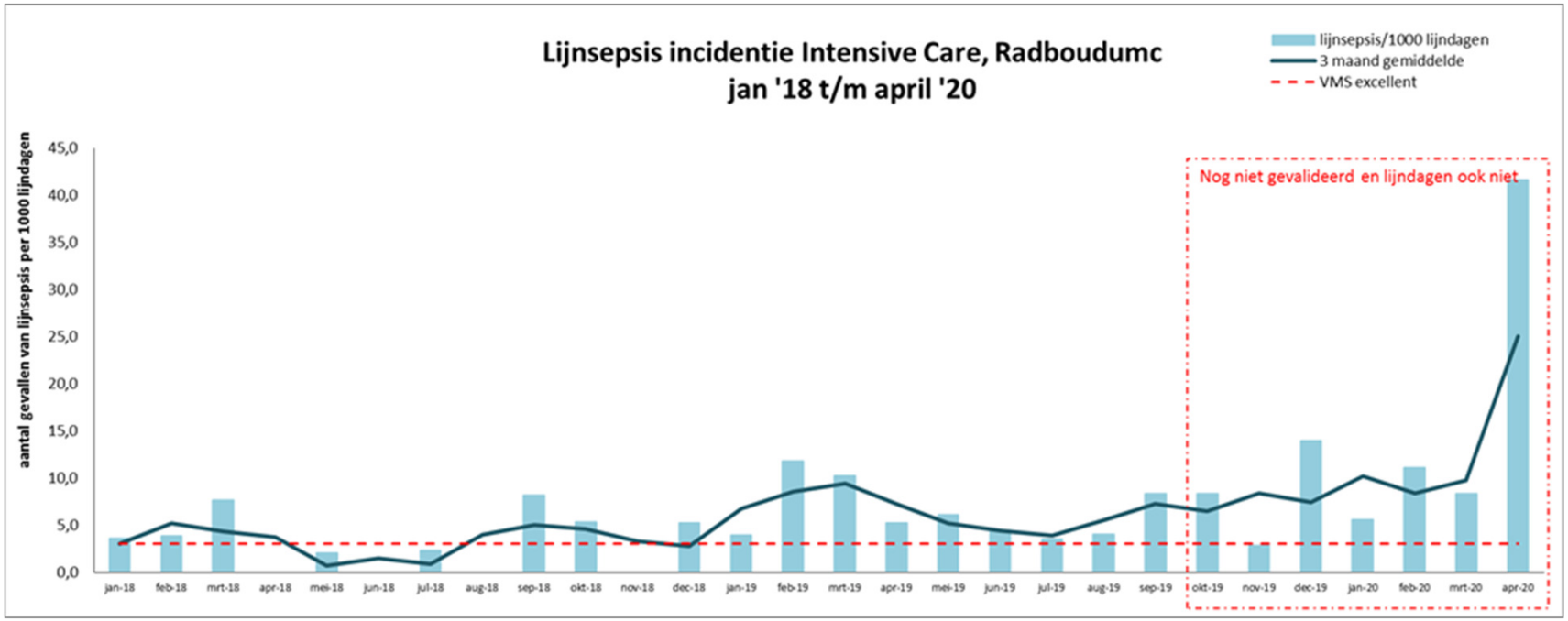
Fungal co-infections…

- Ong 20% incidentie beschreven in populatie Amphia Breda
- Incidentie wisselend beschreven wereldwijd
- Hoge geassocieerde mortaliteit

Echter..

- Twijfelachtige diagnostiek: maar in 3 van 6 patiënten pos BAL GM
- Onduidelijkheid over definitie van CAPA
- Waarde van Aspergillus antigen in BAL en serum twijfelachtig
- Geen typische patroon van aantasting IAPA

Central venous catheter infections…



Central venous catheter infections…

Opvallende toename in centrale lijn infecties tijdens COVID-19.
Mogelijke oorzaken:

- Nurse-bed ratio van 1:1 naar 1:3-4
- Moeizame insertie
- Buik positionering (moeizame verzorging)
- Lijnverzorging afgeschaald van 96 uur naar 1 week
- Dagelijkse check minder
- Langer in situ laten van lijnen
- Mondverzorging terug geschaald
- Lijnen afgedopt (+ taurolock)wegens tekort aen spuitenpompen
- ? Meer geïnfecteerde thrombose

Samenvattend

- Geen aanwijzingen voor co-infecties /superinfecties bij COVID
- Wel veel (late) nososcomiale infecties (bacteriemieën, CVC infecties, VAP)
- PCT ws. van weinig waarde
- Bij bewezen COVID-19 brede antibacteriële dekking ws. niet nodig
- Cave: veranderende epidemiologie eind 2020 (klassieke CAP, influenza)
- CAPA nog onduidelijk ziektebeeld
- Let op voor lijninfecties!
- Pas zoveel mogelijk standaard diagnostiek toe (ook BAL kan veilig!)

Vragen en suggesties

- Welke empirische antibiotische therapie geven jullie
- Eigen ervaringen met nosocomiale / lijninfecties?
- Wat doen jullie bij een positieve Aspergillus kweek?