Antibiothérapie des infections à sars-cov2 Quand? Quelles molecules? Pour quelles durée?

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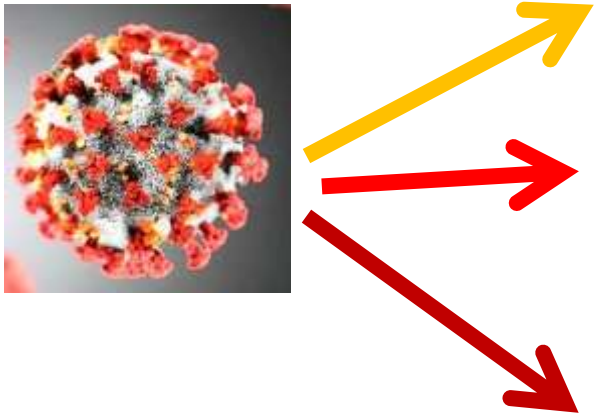
Hammamet ATR Dec 2021

COIs

- Grants: MSD, Pfizer, Thermofisher
- Adboards: Gilead, Pfizer, MSD, Paratek, Bayer, Medimmune, Nabriva
- Lectures: Pfizer, Merck, Biomerieux

PATHOPHYSIOLOGY

Altered immune response



- Pathologic immune response
  - Cytokine excess
  - Immunothrombosis
  - Excess mucus production
  - Altered IFN responses
  - T lymphocyte exhaustion
- ARDS per se
- Therapeutic strategies
  - Oxygenation
  - SILI/VILI
  - ECMO
  - Corticosteroids
  - IL6-ra, JAK ra
- Altered quality of care
  - Delayed ICU admission
  - Overcrowding/ heterogeneity of care
  - Cross transmission of pathogens

Covid pandemic:
ICU care outside the wall

Bichat hospital > 80 ICU beds and > 60 intermediate care beds

ICU in operative rooms
No single rooms
Incredible healthcare workload
(Prone position, extreme body weight)
Heterogeneity of healthcare personnel
Infection control measures not strictly followed?
Overuse of antimicrobials
Negative airway pressure in the rooms
Inappropriate use of gloves with high risk of cross transmission of MDR/XDR bacterias

Thrombosis of pulmonary arterioles

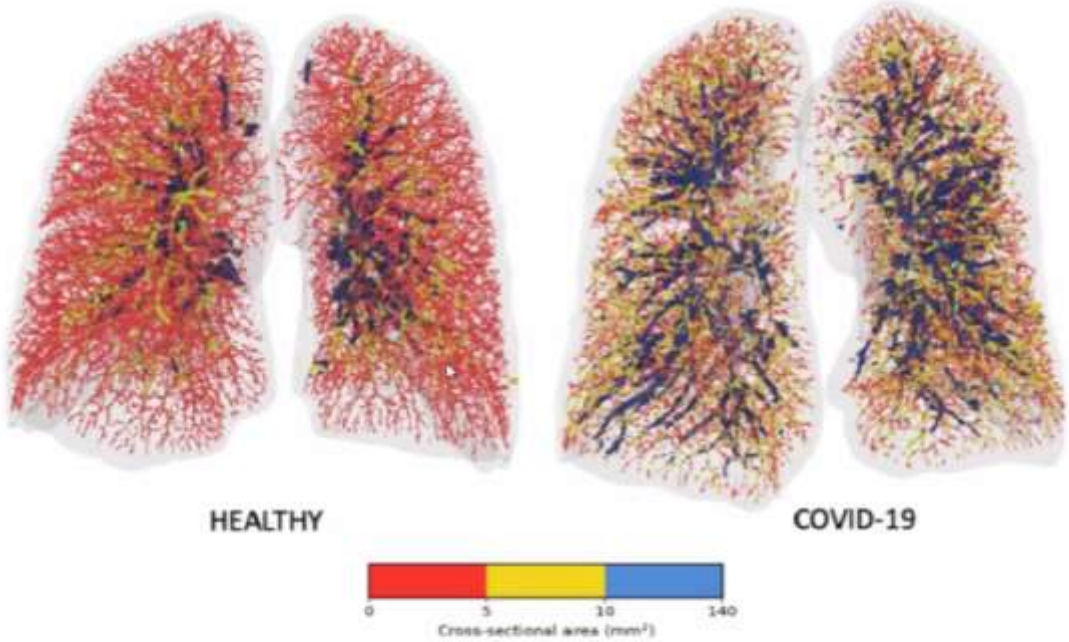


Figure 4: Visual representation of the blood vessels colored according to their size. Red denotes the small vessels, yellow the mid-size vessels and blue the larger vessels.

Lins Acta Radiol 2020

10 mantras for antibiotic therapy

1. **Treat only patients that are truly infected**
2. **Immediate adequate Abx is key – especially if septic shock, and patients with neutropenia**
3. ***You should know your ecology***
4. ***Previous colonization of the patient may help***
5. **NEVER start with antimicrobials that have already been used (Penem, CIP)**
6. **Severe ICU patients are at high risk of UNDERDOSAGE (PK optimisation and TDM++)**
7. **Prefer COMBO if you suspect MDR bacterias+++**
8. **Beware of OVERDOSING during the stabilization period**
9. **Limit the duration of antibiotic therapy if possible (decrease of antimicrobial use will decrease antimicrobial resistance)**
10. **Protect the other patients from cross colonization – Good hand hygiene**

PHASE INITIALE: CO INFECTIONS RARES: STRATÉGIE D'ÉPARGNE

Pulmonary Co-infections

- **Is rare**
  - Viral 10%, fungal 4%, bacterial 8 %
    - *Musuuza JS et al-PLoS One. 2021 May 6;16(5):e0251170*
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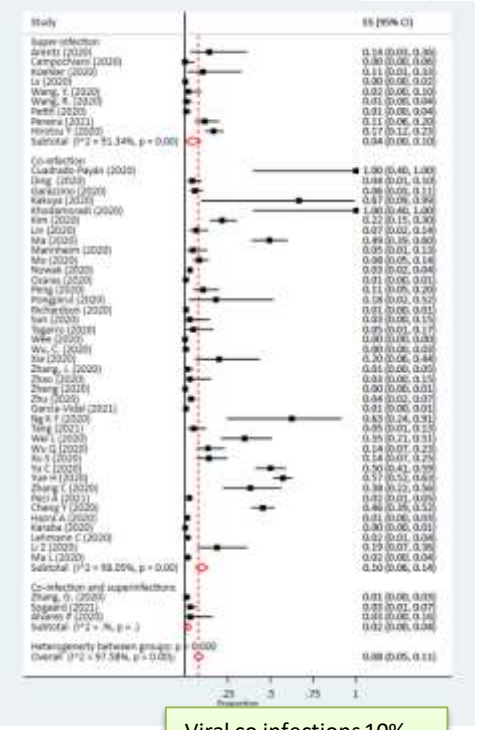
- Traditional biomarkers may be artificially masked by immunosuppressive agents
  - Corticosteroids
  - IL-6 receptor antagonists
- **Need for rapid diagnostic test**
- for identifying patients who may benefit from antibacterial agents.

Epidemio- General data

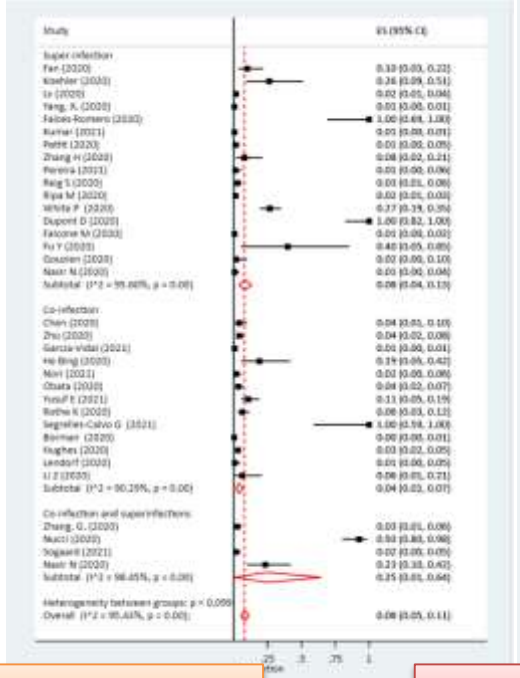
PLOS ONE

RESEARCH ARTICLE

Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis



Viral co infections 10%
Viral super infections 4%



Fungal co infections 4%
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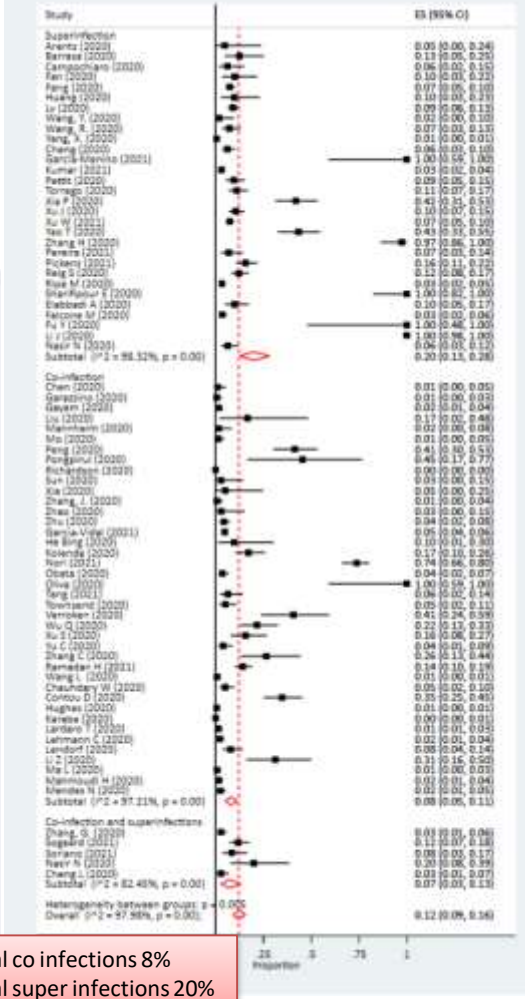


Bacterial co infections 8%
Bacterial super infections 20%

Musuuza JS et al-PLoS One. 2021 May 6;16(5):e0251170. doi: 10.1371/journal.pone.0251170. eCollection 2021.

Influenzae vs Sars-cov2: not really the same clinical picture…

36 ICUs international
Covid 19 respiratory infections within 72 hours

Co infections
8%
7 times less than influenzae

Table 2. Prevalence of early bacterial identification

	SARS-CoV-2 pneumonia	Influenza pneumonia	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	*p*-value*
Overall population	55/568 (9.7)	162/482 (33.6)	0.21 (0.15 to 0.30)	0.23 (0.16 to 0.33)	<0.0001
< 48h hospital stay†	29/359 (8.1)	129/341 (37.8)	0.14 (0.09 to 0.23)	0.15 (0.09 to 0.25)	<0.0001
at least 1 respiratory sample†	55/411 (13.4)	162/425 (38.1)	0.25 (0.17 to 0.36)	0.26 (0.18 to 0.39)	<0.0001

Values are as n/N (%). * adjusted for pre-specified confounders: simplified acute physiology score II, chronic obstructive pulmonary disease, chronic respiratory failure, immunosuppression, recent hospitalization and antibiotic treatment on ICU admission, and calculated after handling missing values on covariates by multiple imputation. † Sensitivity analyses were performed among patients intubated in the first 48h after hospital admission

Rouze A et al - Am J Respir Crit Care Med. 2021 May 26. doi: 10.1164/rccm.202101-0030OC

Influenzae vs Sars-cov2: not really the same clinical picture…

Co-infections/ early onset superinfections

S. Aureus

S pneumoniae

Enterobacterales (Susceptible/MDR)

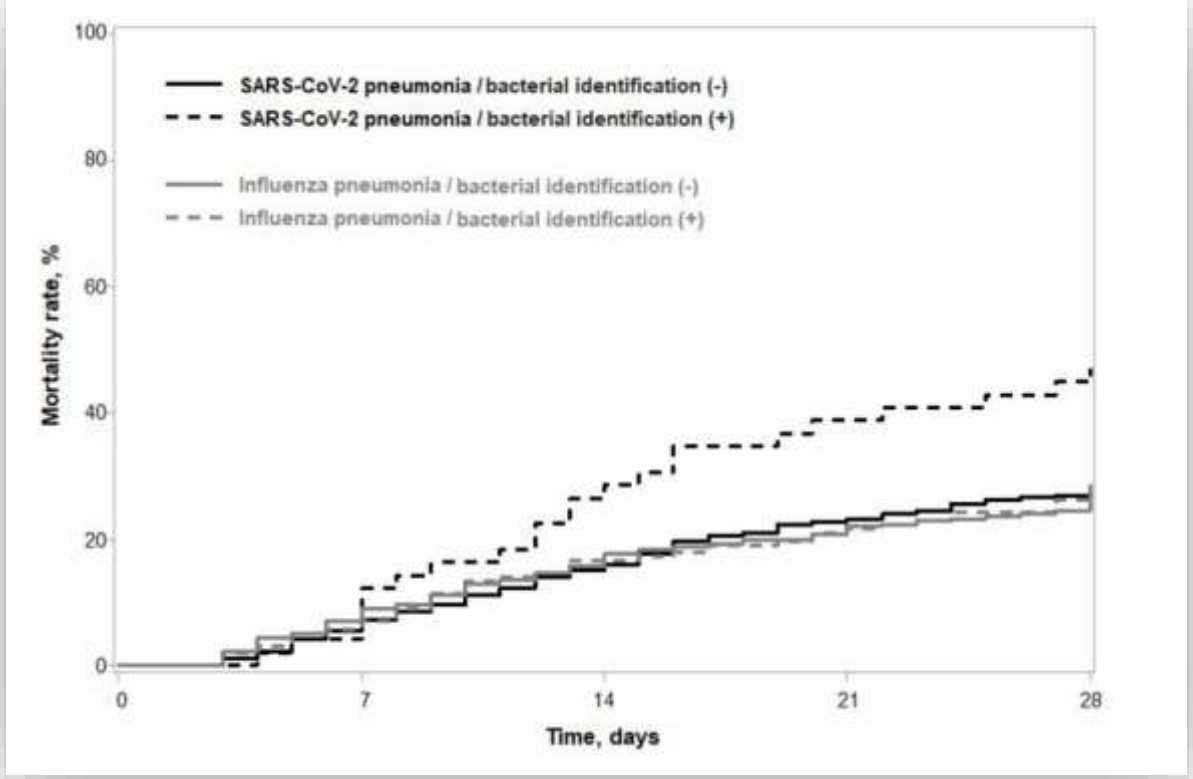
Table 3. Microbiological data

	SARS-CoV-2 pneumonia n = 55	Influenza pneumonia n = 162
Gram-positive cocci	32 (58.2)	116 (71.6)
Methicillin-sensitive *Staphylococcus aureus*	13 (23.6)	47 (29.0)
Methicillin-resistant *Staphylococcus aureus*	1 (1.8)	4 (2.5)
Staphylococcus other than aureus	1 (1.8)	2 (1.2)
Streptococcus pneumoniae	12 (21.8)	52 (32.1)
Other Streptococcus spp	4 (7.3)	10 (6.2)
Enterococcus spp	1 (1.8)	1 (0.6)
Gram-negative bacilli	23 (41.8)	45 (27.8)
Pseudomonas aeruginosa	6 (10.9)	10 (6.2)
Haemophilus influenzae	5 (9.1)	18 (11.1)
Moraxella catarrhalis	3 (5.5)	1 (0.6)
Enterobacter spp	2 (3.6)	1 (0.6)
Klebsiella pneumonia	2 (3.6)	3 (1.9)
Other Klebsiella spp	0 (0.0)	1 (0.6)
Serratia marcescens	2 (3.6)	0 (0.0)
Citrobacter spp	1 (1.8)	0 (0.0)
Proteus mirabilis	1 (1.8)	0 (0.0)
Acinetobacter baumannii	1 (1.8)	2 (1.2)
Escherichia coli	0 (0.0)	5 (3.1)
Morganella morganii	0 (0.0)	3 (1.9)
Stenotrophomonas maltophilia	0 (0.0)	1 (0.6)
Other	4 (7.3)	9 (5.6)
Polymicrobial	5 (9.1)	11 (6.8)
Multidrug-resistant isolates	3 (5.5)	6 (3.7)

Values are as n (%).
More than one bacteria can be identified for each patient.

Rouze A et al - Am J Respir Crit Care Med. 2021 May 26. doi: 10.1164/rccm.202101-0030OC

RTI within 72 hours of intubation



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ISARIC n=48765 patients (march-June 2020)

10% received CS

14%/ NIV/ 10% invasive ventilation

37% received Abx before admission

85% received Abx during hospital stay

Less than 10% with relevant microbiological informations (n=8649)

31.5% death

Russel (ISARIC) - Lancet Microbe 2021 Published **Online** June 2, 2021 https://doi.org/10.1016/ S2666-

La surconsommation des antibiotiques initiaux augmente le risque de surinfection tardive

Main characteristic of patients hospitalized for COVID-19 for ≥48 hours

Characteristic	No infection ($n = 917$)	Community-acquired co-infection ($n = 31$)		Hospital-acquired superinfection ($n = 43$)	
		Value	p[a]	Value	p[b]
Age (years)	61 (48–74)	63 (54.5–74)	0.671	67 (55.75–74.25)	0.006
Male sex	510 (55.6)	18 (58.1)	0.956	26 (60.5)	0.822
Comorbidities					
Hypertension	167 (18.2)	7 (22.6)	0.537	7 (16.3)	0.748
Diabetes mellitus	89 (9.7)	7 (22.6)	0.019	7 (16.3)	0.160
Chronic heart disease	122 (13.3)	9 (29)	0.013	7 (16.3)	0.576
Chronic lung disease	95 (10.4)	6 (19.4)	0.110	7 (16.3)	0.218
Chronic renal disease	47 (5.1)	8 (25.8)	<0.001	6 (14)	0.013
Cancer	77 (8.4)	1 (3.2)	0.259	8 (18.6)	0.021
Inflammatory markers at onset					
C-reactive protein	7.06 (3.31–13.29)	6.76 (3.20–9.79)	0.714	11.78 (5.55–17.87)	0.012
Ferritin	544 (249.5–1100)	208 (154–431.5)	0.042	797 (296–1743)	0.575
Lymphocyte count	0.9 (0.6–1.2)	0.8 (0.6–1.1)	0.892	0.783 (0.5–1.1)	0.088
Lactate dehydrogenase	287 (233–372)	264 (221–377.5)	0.477	311.5 (247.5–471–8)	0.193
Treatment at onset					
Lopinavir/ritonavir	732 (79.8)	27 (87.1)	0.227	35 (81.4)	0.802
Hydroxychloroquine	799 (87.1)	29 (93.5)	0.225	40 (93)	0.186
Azithromycin	751 (81.9)	26 (83.9)	0.779	36 (83.7)	0.761
Remdesivir	39 (4.3)	0 (0)	0.226	2 (4.7)	0.559
Ceftriaxone	528 (57.6)	24 (77.4)	0.028	32 (74.4)	0.029
Ceftaroline	26 (2.8)	2 (6.5)	0.232	5 (11.6)	0.001
Immunomodulatory treatment					
Tocilizumab	200 (21.8)	5 (16.1)	0.450	16 (37.2)	0.018
Methylprednisolone	238 (26)	9 (29)	0.701	25 (58.1)	<0.001
Dexamethasone	23 (2.5)	4 (12.9)	0.01	8 (18.6)	<0.001
Length of hospital stay	9 (5–15)	8 (4.5–11.5)	0.565	20 (11–27.75)	<0.001
ICU admission	109 (11.9)	8 (25.8)	0.02	29 (67.4)	<0.001
Length of ICU admission	3 (1–10)	3 (0–9)	0.888	5 (0.5–20)	0.095
Death	86 (9.4)	5 (16.1)	0.21	8 (18.6)	0.047

Carolina Garcia-Vidal, Clin Microbiol Infect 2020;

Reducing the use of empiric antibiotic therapy in COVID-19 on hospital admission

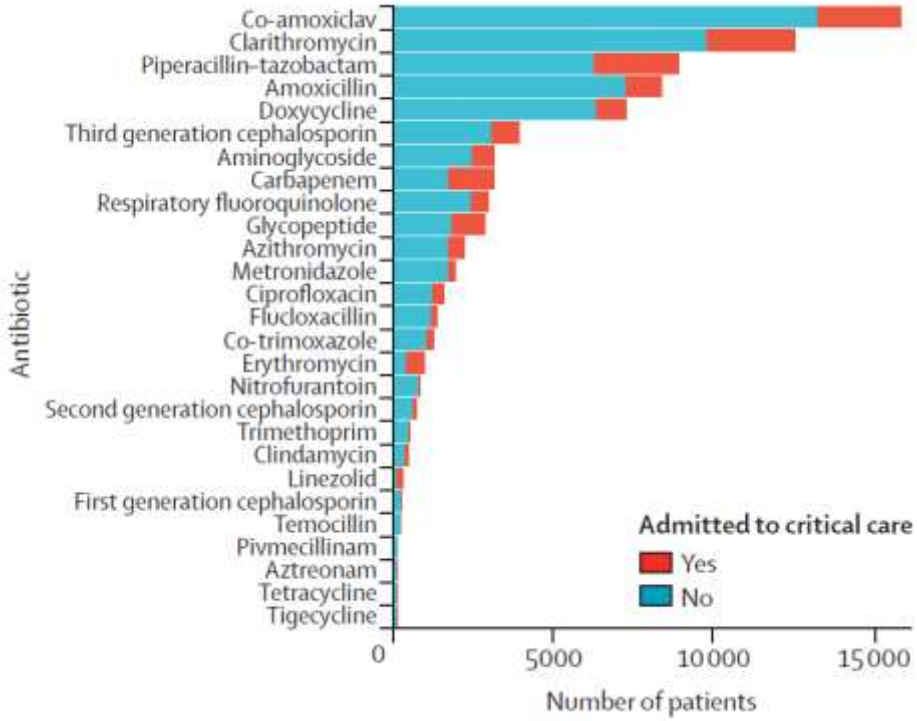
Guidelines:
AB if High fever, Xrays suggestive
Sample: FA/ Agu
AB stop if negative resuts
Stop azythro if Agu -

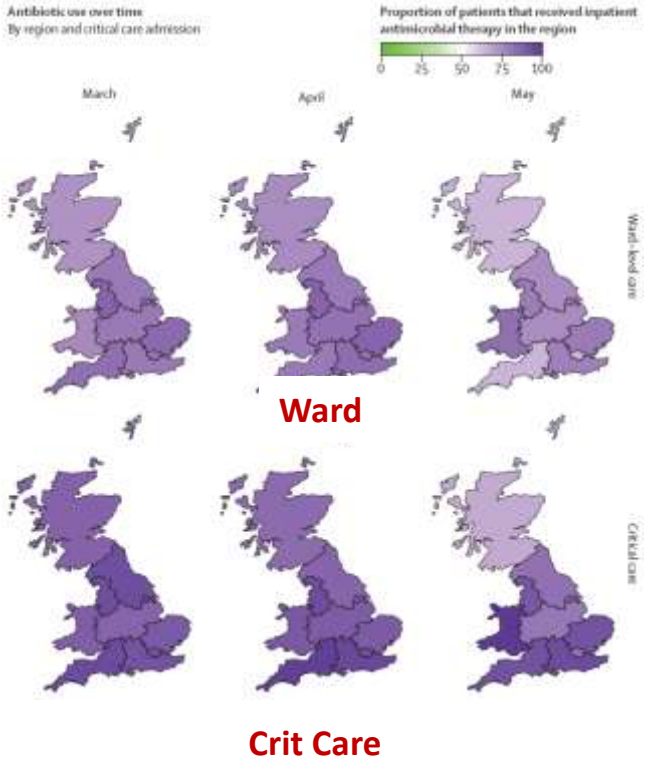
	Pre-Intervention (N = 76)	Post-Intervention (N = 170)	p-value
All antibiotics duration, median days (IQR)	2.3 (1, 3.9)	1 (0.5, 2.1)	< 0.001
Atypical coverage duration, median days (IQR)	3.8 (3, 4.1)	1 (0.4, 1.6)	< 0.001
Clostridioides difficile infection	1 (1)	2 (1)	> 0.99
Antibiotics re-initiated			
Any-indication	6 (8)	24 (14)	0.2
Bacterial pneumonia[a]	2 (2.6)	16 (9)	0.07
Readmission within 30 days			
All-cause	5 (7)	23 (13.5)	0.2
Bacterial pneumonia	1 (1.3)	3 (1.8)	> 0.99
Mortality (all-cause)	13 (17)	21 (12)	0.42
Length of stay, median (IQR)	7 (4, 13.2)	7 (4, 12)	0.5

Less antimicrobials, more bacteriological exams, similar outcome

Pettit et al. BMC Infectious Diseases (2021) 21:516 https://doi.org/10.1186/s12879-021-06219-z

Epidemio- AB use





Ward

Crit Care

Russel (ISARIC) - Lancet Microbe 2021 Published **Online** June 2, 2021 https://doi.org/10.1016/ S2666-

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Impact of rapid multiplex PCR on management of antibiotic therapy in COVID-19-positive patients hospitalized in intensive care unit

- 112 respiratory samples/ 67 ICU patients
- Biofire Filmarray™: Se 89.3%/ Sp 99.1%,
- Positive tests → AB start in 15% of episodes and de-escalation in 4%.
- When negative, 28% of episodes remained antibiotic-free (14% no initiation, 14% withdrawal).

Maataoui N et al- European Journal of Clinical Microbiology & Infectious Diseases 2021
https://doi.org/10.1007/s10096-021-04213-6

SURINFECTION TARDIVE, FREQUENTE, DIFFICILE A TRAITER

Epidemio- General data

PLOS ONE

RESEARCH ARTICLE

Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis

Late superinfections

A baumanii

MDR/XDR entrobacterales

P aeruginosa

Candida….

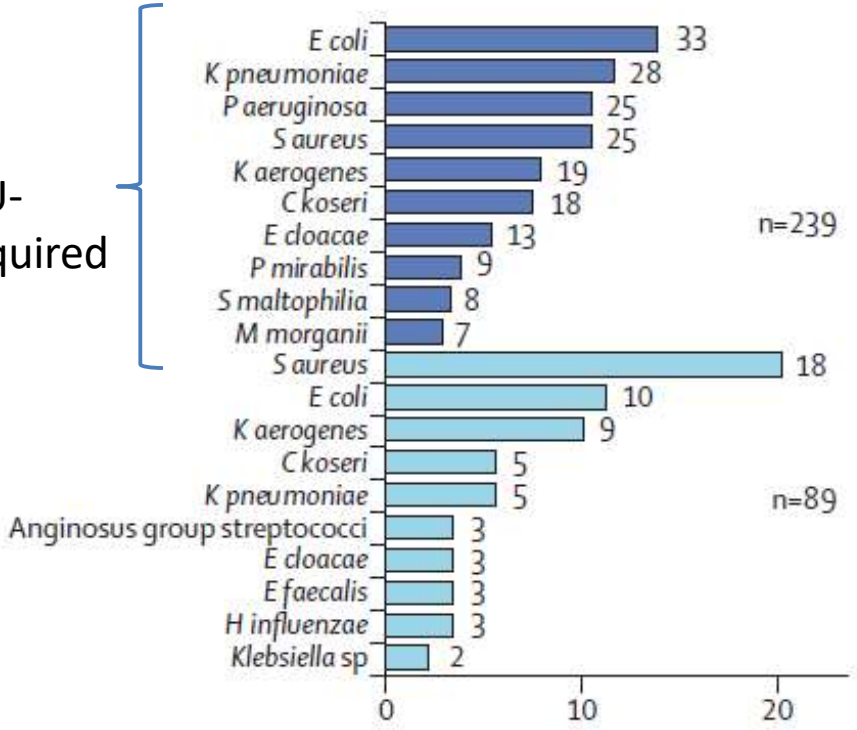
Table 2. All identified organisms as a proportion of total number of organisms per pathogen.

Pathogen type	Co-infection (N = 1910) No. (%)	Superinfection (N = 480) No. (%)
Bacteria		
Staphylococcus aureus	148 (7.7)	13 (2.7)
Haemophilus influenza	127 (6.6)	6 (1.3)
Mycoplasma pneumoniae	82 (4.3)	6 (1.3)
Acinetobacter spps	78 (4.1)	107 (22.3)
Escherichia coli	73 (3.8)	33 (6.9)
Stenotrophomonas maltophilia	10 (0.5)	18 (3.8)
Klebsiella pneumoniae	189 (9.9)	28 (5.8)
Streptococcus pneumoniae	156 (8.2)	4 (0.8)
Chlamydia pneumoniae	29 (1.5)	0 (0)
Bordetella	3 (0.2)	0 (0)
Moraxella catarrhalis	32 (1.7)	2 (0.4)
Pseudomonas	67 (3.5)	52 (10.8)
Enterococcus faecium	14 (0.7)	22 (4.6)
Viruses		
Non-SARS-CoV-2[a] coronavirus strains	38 (2.0)	9 (1.9)
Human influenza A	426 (22.3)	0 (0)
Human influenza B	73 (3.8)	0 (0)
Respiratory syncytial virus	72 (3.8)	2 (0.4)
Parainfluenza	17 (0.9)	0 (0)
Human metapneumovirus	20 (1.0)	9 (1.9)
Rhinovirus	68 (3.6)	11 (2.3)
Adenovirus	35 (1.8)	2 (0.4)
Fungi		
Mucor	6 (0.3)	1 (0.2)
Candida spp.	19 (1.0)	90 (18.8)
Aspergillus	128 (6.7)	65 (13.5)

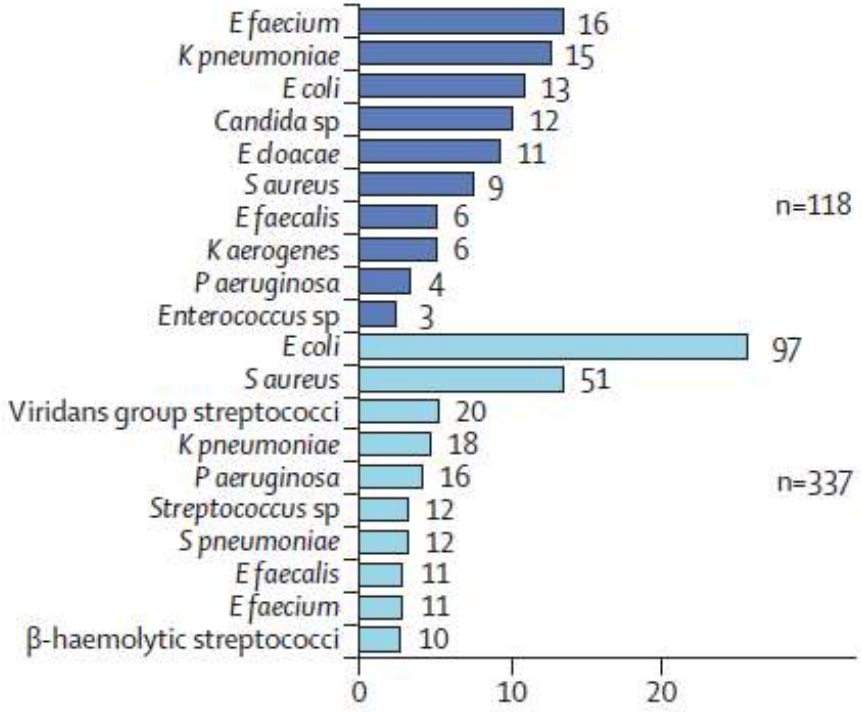
Musuuza JS et al-PLoS One. 2021 May 6;16(5):e0251170. doi: 10.1371/journal.pone.0251170. eCollection 2021.

Infections in critical care

ICU-acquired



Deep respiratory



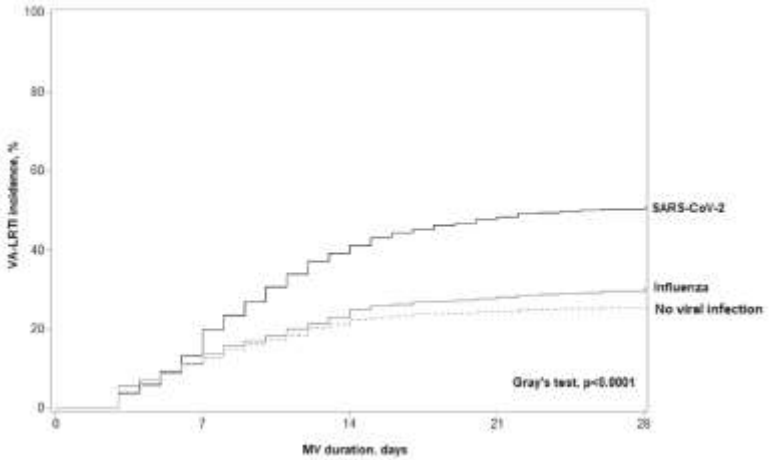
Blood

Russel (ISARIC) - Lancet Microbe 2021 Published **Online** June 2, 2021 https://doi.org/10.1016/ S2666-

MDR/XDR risk?

- Not different from other ICU patients
  - Of the same severity
  - If the HC workload is similar
  - In the same place
- But frequent long term ICU stay and AB exposure
  - MDR/XDR risk increased with duration of ICU stay

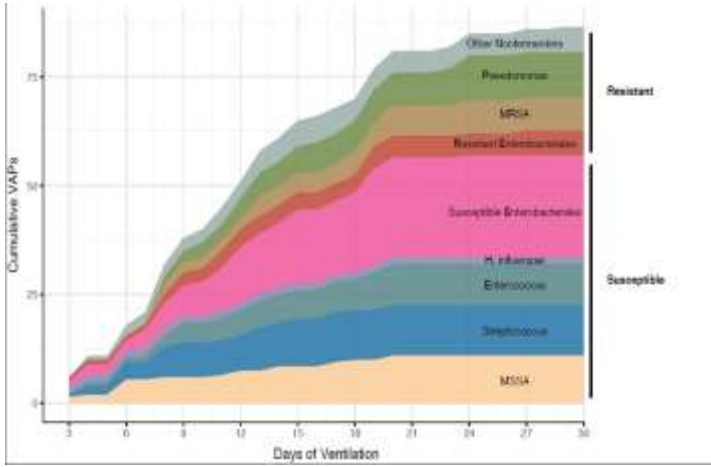
Sars-Cov2 is associated with a high risk of VAT/VAP



	SARS-CoV-2 (n = 568)	Influenza (n = 482)	No viral infection (n = 526)	p value[a]	Unadjusted SHR (95%CI)		Adjusted SHR (95%CI)[e]	
					SARS-CoV-2 vs. Influenza	SARS-CoV-2 vs. No viral infection	SARS-CoV-2 vs. Influenza	SARS-CoV-2 vs. No viral infection
VALRTI	287 (50.5)	146 (30.3)	133 (25.3)	<0.0001	1.87 (1.53–2.27)[b]	2.27 (1.84–2.79)[b]	1.60 (1.26–2.04)[b]	1.7 (1.2–2.39)[b]
VAT[c]	82 (14.4)	39 (8.1)	46 (8.8)	0.0001	1.83 (1.25–2.68)[b]	1.69 (1.18–2.43)[b]	1.50 (0.89–2.54)	1.25 (0.7–2.2)
VAP[d]	205 (36.1)	107 (22.2)	87 (16.5)	<0.0001	1.74 (1.38–2.2)[b]	2.38 (1.84–3.06)[b]	1.57 (1.2–2.04)[b]	1.84 (1.26–2.7)[b]

Rouze A et al - Intensive Care Med https://doi.org/10.1007/s00134-020-06323-9

BAL in sars-Cov2 MV patients



179 MV patients (monocenter)

Late BAL:
72 patients (44.4%) developed at least one VAP episode.
The incidence rate of VAP was 45.2/1000 ventilator days
Only 15/72 (20.8%) of initial VAPs were attributable to multidrug-resistant pathogens.

30/72 VAP with persisting pathogens

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Pickens CO et al- Am J Respir Crit Care Med . 2021 Aug 19. doi:

Critical Care

RESEARCH Open Access

Epidemiology and microbiology of ventilator-associated pneumonia in COVID-19 patients: a multicenter retrospective study in 188 patients in an un-inundated French region

188 patients
Retrospective multicenter
Rare Co-infections (25/188)
VAP 48.9% (39/1000 MV days)
Multiple episodes 19.7%

Risk factors of VAP (subdistribution hazard ratio)
Vasopressor support 1.94 [1.22–3.09], p = **0.005**
ECMO 3.09 [1.59, 6.03], p = **0.001**

Unusual rate of purulent pleurisis and abscess
Frequent BSI 15%

Table 3 List of co-infection-related isolates

Total number of isolates	25
Staphylococcus aureus—no. (%)	6 (24.0)
Enterobacteria—no. (%)	5 (20.0)
Streptococcus pneumoniae—no. (%)	3 (12.0)
Haemophilus influenzae—no. (%)	3 (12.0)
Other viruses—no. (%)	3 (12.0)
Other gram-negative bacteria—no. (%)	3 (12.0)
Other gram-positive bacteria—no. (%)	2 (8.0)

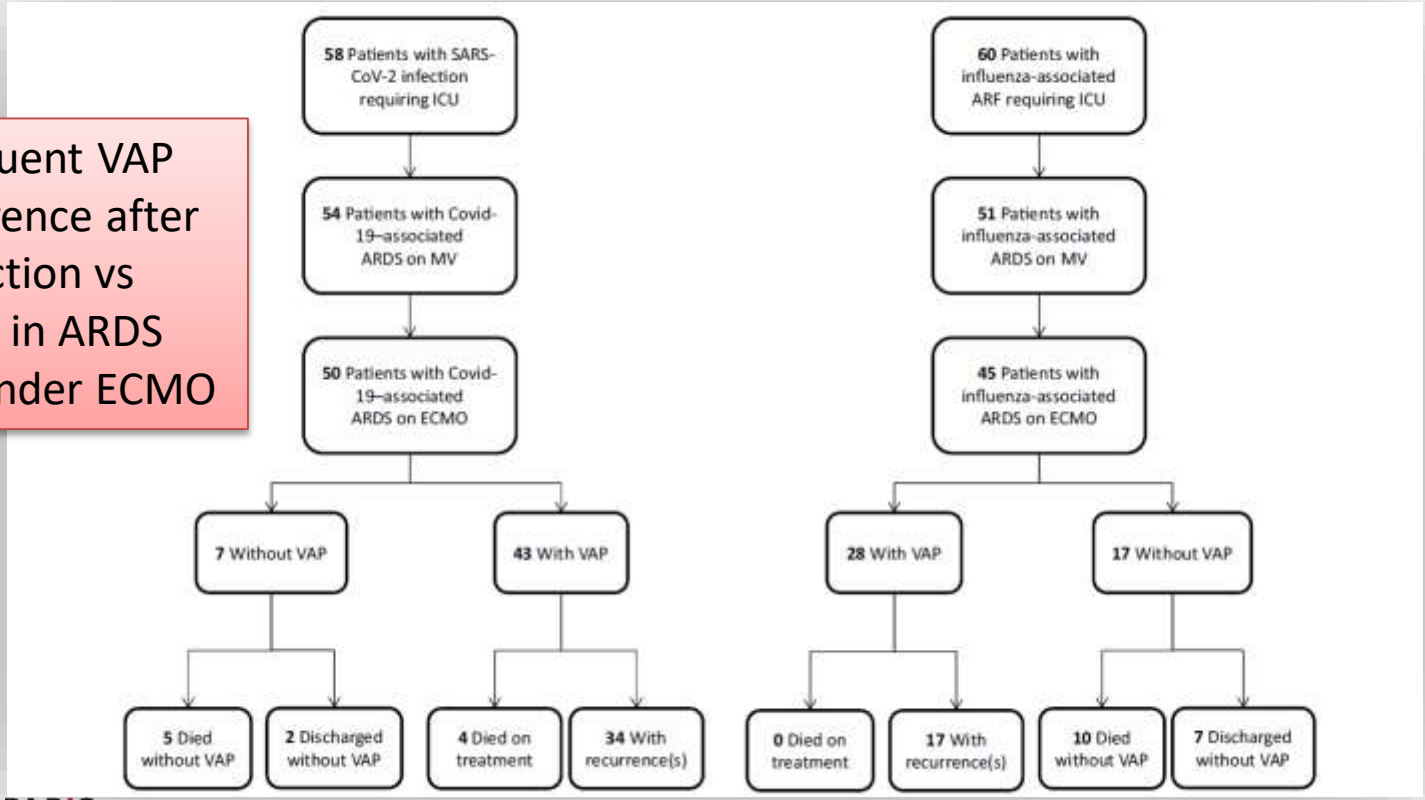
Table 4 List of ventilator-associated pneumonia-related isolates

VAP group	All	Early (< 5 days *)	Late (≥ 5 days *)	Mono-microbial	Poly-microbial
Headcount	143	14	129	86	55
Total number of isolates	205	17	188	86	119
Enterobacteria—no. (%)	102 (49.8)	6 (35.3)	96 (51.1)	38 (44.2)	64 (53.8)
Escherichia coli—no. (%)	26 (12.7)	3 (17.6)	23 (12.2)	11 (12.8)	15 (12.6)
Klebsiella pneumoniae—no. (%)	16 (7.8)	–	16 (8.5)	8 (9.3)	8 (6.7)
Serratia marcescens—no. (%)	12 (5.9)	–	12 (6.4)	6 (7.0)	6 (5.0)
Enterobacter cloacae—no. (%)	10 (4.9)	–	10 (5.3)	3 (3.5)	7 (5.9)
Pseudomonas aeruginosa—no. (%)	31 (15.1)	1 (5.9)	30 (16.0)	19 (22.1)	12 (10.1)
Stenotrophomonas maltophilia—no. (%)	8 (3.9)	–	8 (4.3)	4 (4.7)	4 (3.4)
Haemophilus—no. (%)	5 (2.4)	1 (5.9)	4 (2.1)	–	5 (4.2)
Staphylococcus aureus—no. (%)	28 (13.7)	4 (23.5)	24 (12.8)	15 (17.4)	13 (10.9)
Other Streptococci—no. (%)	5 (2.4)	2 (11.8)	3 (1.6)	1 (1.2)	4 (3.4)
Streptococcus agalactiae—no. (%)	2 (1.0)	1 (5.9)	1 (0.5)	–	2 (1.7)
Streptococcus pneumonia—no. (%)	2 (1.0)	1 (5.9)	1 (0.5)	1 (1.2)	1 (0.8)
Enterococcus faecium—no. (%)	1 (0.5)	–	1 (0.5)	–	1 (0.8)
Corynebacterium—no. (%)	1 (0.5)	–	1 (0.5)	–	1 (0.8)

Blonz *et al. Crit Care (2021) 25:72* https://doi.org/10.1186/s13054-021-03493-w

Sars-cov2 increases the risk of VAP recurrence

More frequent VAP and recurrence after covid infection vs influenzae in ARDS patients under ECMO



Luyt *et al. Ann. Intensive Care* (2020) 10:158
https://doi.org/10.1186/s13613-020-00775-4

Sars-cov2 increases the risk of VAP recurence

Table 3 Characteristics of recurrent VAP episodes in patients with Covid-19 or influenza ARDS

Characteristic	Episode 2		Episode 3		Episode 4	
	Covid-19	Influenza	Covid-19	Influenza	Covid-19	Influenza
Number of patients	34	17	20	8	11	3
Relapse	26 (76)	10 (59)	16 (76)	7 (78)	11 (100)	3 (100)
Days between end of treatment and relapse	2 (1–3)	3 (0–5)	2 (0–4)	3 (0–5)	0 (0–2)	8 (4–8)
Relapse before end of treatment	6 (23)	3 (30)	7 (44)	2 (29)	6 (55)	0
Superinfection	8 (24)	7 (41)	5 (24)	2 (22)	0	0
Days between end of treatment and superinfection	4 (0–8)	8 (7–11)	0 (0–0)	35 (23–48)	–	–
Superinfection before end of treatment	3 (38)	0	4 (100)	0	–	–
Pathogen responsible for VAP recurrence[a]						
Pseudomonas aeruginosa	19 (56)	11 (64)	12 (60)	7 (88)	8 (73)	3 (100)
Enterobacteriaceae	16 (47)	5 (29)	10 (50)	1 (13)	7 (64)	0
Inducible AmpC Enterobacteriaceae[b]	11 (32)	2 (12)	9 (45)	0	6 (55)	0
ESBL-producing Enterobacteriaceae	2 (6)	0	0	1 (13)	0	0
Stenotrophomonas maltophilia	2 (6)	0	1 (5)	0	1 (9)	0
Acinetobacter baumannii	0	1 (6)	0	0	0	0
Methicillin-resistant *Staphylococcus aureus*	1 (1)	0	0	0	0	0
Methicillin-susceptible *Staphylococcus aureus*	1 (1)	0	1 (5)	0	0	0
Enterococcus faecalis	1 (1)	0	4 (20)	0	0	0

The results are expressed as *n* (%) or median (IQR)

Luyt *et al. Ann. Intensive Care* (2020) 10:158
https://doi.org/10.1186/s13613-020-00775-4

Therapeutic failures in Sars-Cov2 associated superinfections?

- 50 first episodes of vHAP/VAP
- Clinical failure EOT 23 (46%)
- Microbiological failure EOT 36 (72%)
- 6 lung abcesses
- Recurrences 21 (42%)
- Superinfections 20 (40%)

Predictors of microbiological failure at EOT

Young age
Normal renal function baseline
Absence of diabetes/ hypertension
High Glomerular filtration
ECMO
VAP (21/33) vs vHAP

Micro-organisms

MSSA: 10/14
P aeruginosa 7/8
Other NF bacteria 4/4
Enterobacter sp 4/6

Suggestion to revisit and optimize antimicrobial therapy

Eve Garrigues et al MS in preparation

Intensive Care Med (2021) 47:180–187
https://doi.org/10.1007/s00134-021-06346-w

ORIGINAL

COVID-19 increased the risk of ICU-acquired bloodstream infections: a case–cohort study from the multicentric OUTCOMEREA network

Niccolò Buetti[1,11], Stéphane Ruckly[1], Etienne de Montmollin[1,9], Jean Reignier[2], Nicolas Terzi[3,4], Yves Cohen[5,6,7], Shidasp Shiami[8], Claire Dupuis[1,10] and Jean-François Timsit[1,9*]

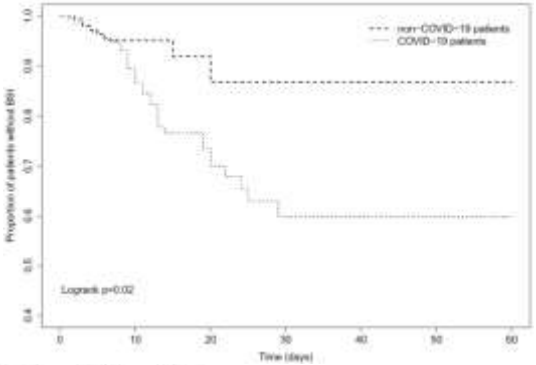


Table 2 Outcomes in the matched population

	Non-COVID-19 (*n* = 235)	COVID-19 (*n* = 235)	*p* value
Length of stay ICU, mean days [IQR]	6 [4; 11]	9 [5; 20]	< 0.0001
ICU-BSI, *n* (%)	8 (3.4)	35 (14.9)	< 0.0001
Time between ICU admission and BSI, median days [IQR]	6.5 [5; 12.5]	12 [9; 16]	0.086[§]
Mortality day-60, *n* (%)	38 (16.2)	84 (35.7)	< 0.0001
Mortality day-60 among BSIs, *n* (%)	2 (25.0)	25 (71.4)	0.037[§]

Groups were compared using McNemar, Bowker and Wilcoxon signed rank test, as appropriate

ICU intensive care unit, *BSI* bloodstream infection

§ Wilcoxon or Fisher tests, as appropriate

Among COVID-19 patients (*n = 235), 21 and 9 patients* received anakinra and tocilizumab, respectively

Fine and Gray model on risk of ICU acquired BSI

- Tocilizumab or anakinra: sHR 3.20, 95% CI 1.31–7.81, p = 0.011)

- Ankinra: sHR 2.54, 95% CI 0.96–6.73, p = 0.061
- Tocilizumab: sHR 2.87, 95% CI 1.06–7.77, p = 0.038.

- Corticosteroids (1st 2 days): sHR 0.85, 95% CI 0.39–1.84, p = 0.67)

OUTCOMEREA network: Buetti N et al- Intensive Care Med (2021) 47:180–187

Table 3 Distribution of microorganisms in ICU bloodstream infections (BSI, $n=48$) and sources of infection ($n=46$) among COVID-19 and non-COVID-19 patients

	Non-COVID-19	COVID-19
Microorganisms identified (n = 48)*		
Coagulase-negative Staphylococci	2 (22.2)	14 (35.9)
Staphylococcus aureus	1 (11.1)	3 (7.7)
Enterococcus spp	0 (0)	4 (10.3)
Other Gram-positive	3 (33.3)	3 (7.7)
Enterobacterales	2 (22.2)	5 (12.8)
Pseudomonas aeruginosa	1 (11.1)	5 (12.8)
Anaerobic bacteria	0 (0)	1 (2.6)
Candida albicans	0 (0)	4 (10.3)
Source of infection (n = 46)*		
Intra-abdominal	1 (12.5)	1 (2.6)
Skin/soft tissue	0 (0)	2 (5.3)
CRBSI	2 (25)	8 (21.1)
Pulmonary	3 (37.5)	8 (21.1)
Urinary tract	0 (0)	1 (2.6)
Unknown	2 (25)	18 (47.4)

OUTCOMEREA network: Buetti N et al- Intensive Care Med (2021) 47:180–187

Beware of therapeutic failure and PK in Sars-Cov2 patients

- MDR and XDR bacteria
  - Ask for MIC, resistance mechanisms
  - Role of Combo?
- « Not fully » predictable dosage using PK models
- Increase in the Vd (sepsis/morbid obesity)
  - Low plasma concentration
  - ECMO
- Glomerular hyperfiltration
  - Low plasma concentrations
  - Decrease of Time above the MIC
  - Variability of clearance
- Decrease in lung diffusion
  - Microthrombi
  - pulmonary infarction

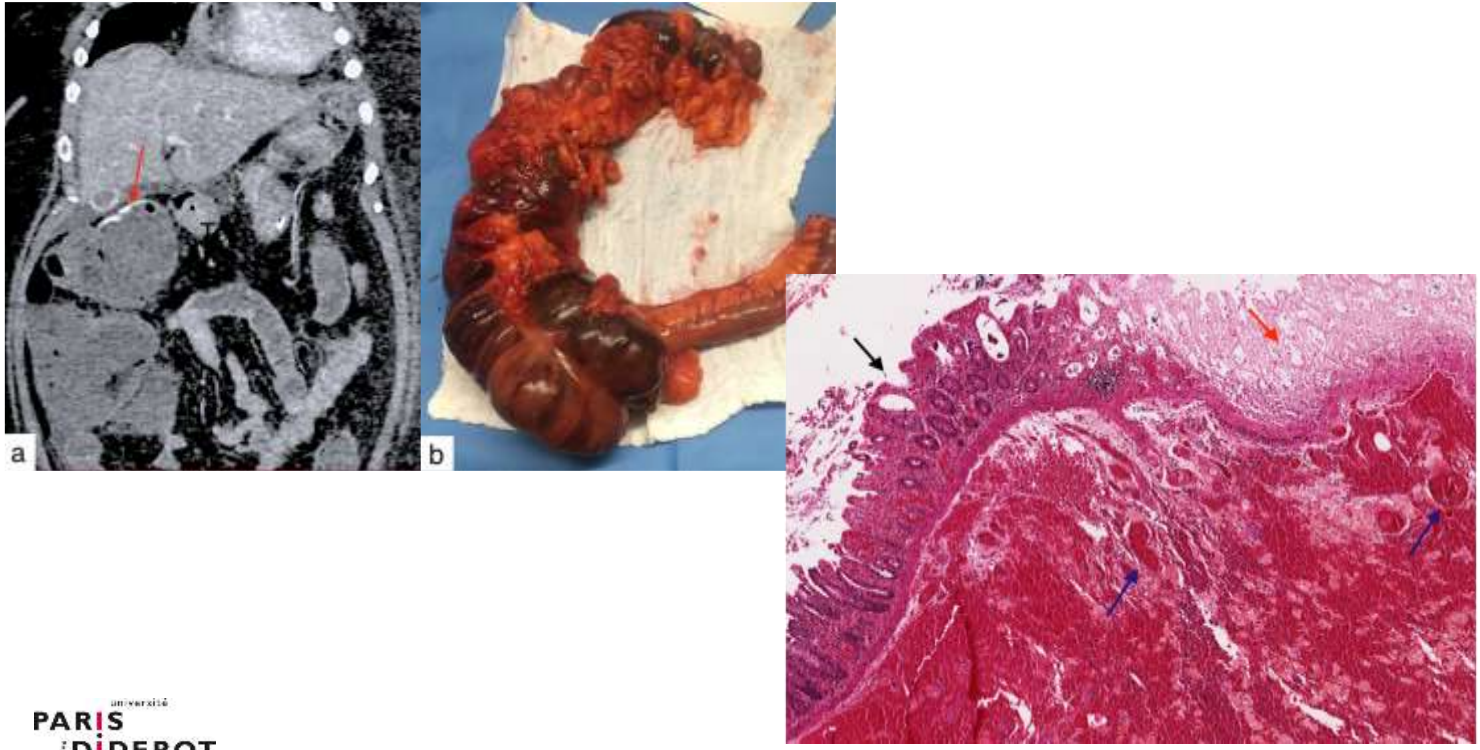
Individualized therapy

Loading dose
(Prolonged) Combo
Adapted duration of Tt

Initial and repeated TDM++++

FIEVRE/CHOC INEXPLIQUÉE : Y PENSER

Mesenteric ischemia at day 15 of Sars-Cov2 ARDS

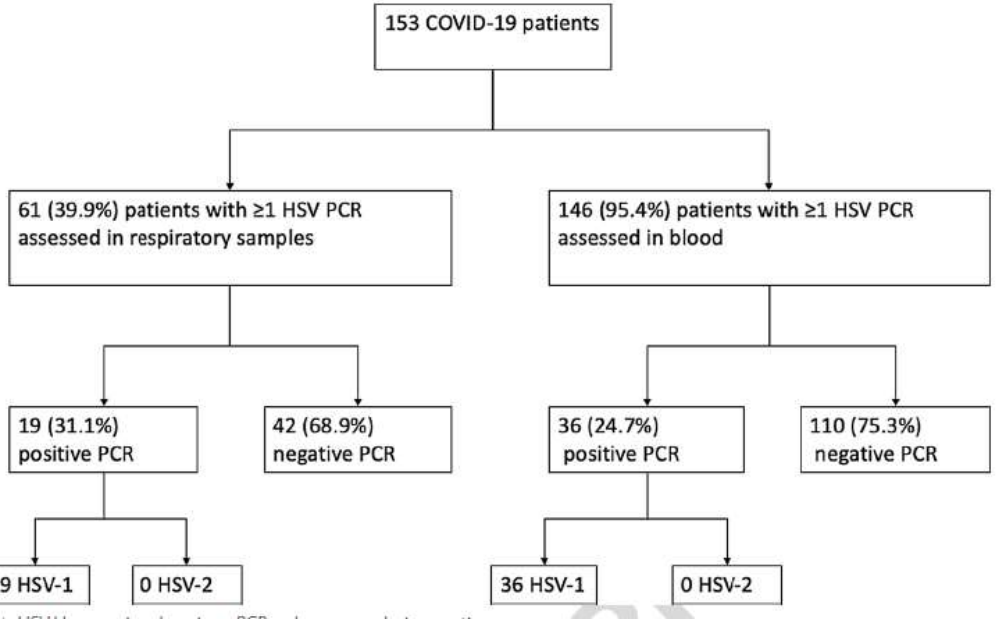


RESEARCH Open Access

HSV-1 reactivation is associated with an increased risk of mortality and pneumonia in critically ill COVID-19 patients

Antoine Meyer[1,2], Niccolò Buetti[1,3*], Nadira Houhou-Fidouh[2], Juliette Patrier[2], Moustafa Abdel-Nabey[2], Pierre Jaquet[2], Simona Presente[2], Tiphaine Girard[2], Faiza Sayagh[2], Stephane Ruckly[1,2], Paul-Henri Wicky[1], Etienne de Montmollin[1,2], Lila Bouadma[1,2], Romain Sonneville[2,4], Diane Descamps[2] and Jean-Francois Timsit[1,2]

Risque de DC X 2.05
Risque de HAP/VAP X 2.38
Surtout pcr-HSV sg



Crit care 2021 in press

Infection et sars-cov2
« first: do not harm… »

- Stratégie précocemment documentée
- Bactéries variables en fonction de l'ecosysteme…
- Si ca n'est pas le poumon…pensez tube digestif, catheters….
- Optimisation initiale des doses
- Attention aux toxicités
- Bithérapie et Durée individualisée
- ATTENTION particulière à la transmission croisée des BMR/BHR
- En dehors des bactéries….HSV…, Champignons, activation macrophagique, effet rebond à l'arrêt des corticoïdes, insuffisance surrénale, ……

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