Antimicrobial stewardship nel paziente COVID

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Conflicts of interest

- Investigator-initiated grants (Pfizer, Gilead Italia, Shionogi)
- Personal fees for speaker/consultant (Pfizer, Tillotts Pharma)

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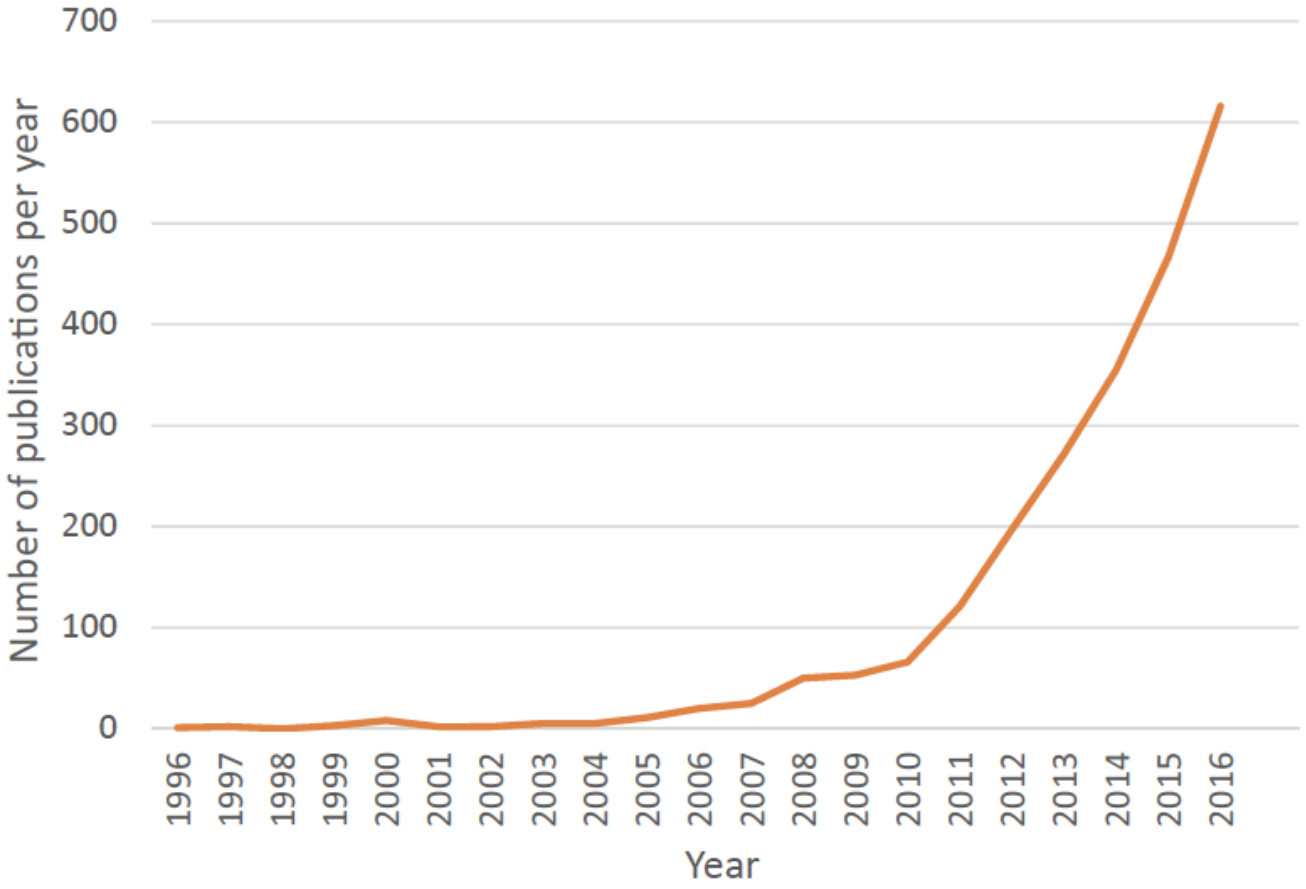

Fig. 1. Pubmed citations on antimicrobial or antibiotic stewardship over the past 20 years.

Dyar et al. Clin Microbiol Infect 2017

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Previous definitions of antimicrobial stewardship

Table 1
Descriptions of antimicrobial stewardship from the literature

Types of description of antimicrobial stewardship	Examples from the literature
Descriptions of activities	Antimicrobial stewardship includes optimal selection, dose and duration of treatment, as well as control of antibiotic use [9]
	Antimicrobial stewardship refers to the responsible use of antimicrobials by healthcare professionals, and more specifically, to selection of the most appropriate antibiotic, duration, dose and route of administration for a given patient with a demonstrated or suspected infection [36]
Descriptions of goals	The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms, and the emergence of resistance [15]
As a programme or set of interventions	Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy and route of administration [16,37]
	Antimicrobial stewardship is defined as interventions to improve the appropriate use of antimicrobials through promotion of optimal agent selection, dosing, duration and route of administration [38]
	Antimicrobial stewardship refers to a programme or series of interventions to monitor and direct antimicrobial use at a healthcare institution, so providing a standard, evidence-based approach to judicious antimicrobial use [1]
	A programme that supports selection, dosing, routes of administration and duration of antimicrobial therapy [39]
As an approach or method	Antimicrobial stewardship refers to the multifaceted approach (including policies, guidelines, surveillance, prevalence reports, education and audit of practice) that healthcare organizations have adopted to optimize prescribing [40]
	Antimicrobial stewardship is a method of overseeing antimicrobial use in healthcare facilities to ensure that every patient requiring antimicrobial therapy receives optimal therapy [22]
As a means to tackle resistance	Antimicrobial stewardship is a key component of a multifaceted approach to preventing the emergence of antimicrobial resistance [41]
	A proposed solution to the combined problems of increasing antibiotic resistance, the dwindling number of antimicrobial agents, and the suboptimal use of antibiotics in clinical practice is the strategy of antimicrobial stewardship [38]
	A critical mission of preservation of antimicrobial utility [39]
As responsible use	Antimicrobial stewardship programmes are a set of interventions that aim to ensure the judicious use of antimicrobials by preventing their unnecessary use, and by providing targeted and limited therapy in situations where they are wanted [42]
	[Stewardship] refers to how the judicious use of antibiotics can maximize both their current effects and the chances of their being available for future generations [18]
Descriptions of good stewardship	Good antimicrobial stewardship is the optimal selection, dose, and duration of an antimicrobial that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance. Good antimicrobial stewardship is akin to motherhood and apple pie [24]
	Good antimicrobial stewardship involves selecting an appropriate drug and optimizing its dose and duration to cure an infection while minimizing toxicity and conditions for selection of resistant bacterial strains [41]

Antimicrobial Stewardship

- Antimicrobial stewardship is defined as a coherent set of actions designed to use antimicrobials responsibly [Dyar et al. Clin Microbiol Infect 2017]

- These include optimal selection, duration, and dose of treatment, and control of antimicrobial use [Barlam et al. Clin Infect Dis 2016]

Antimicrobial stewardship and COVID-19

2020

early 2021

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Heterogeneity of prevalence/incidence of infections across studies

- Small sample sizes
- Different diagnostic approaches
- Reduced diagnostic approaches
- Unusual clinical presentation (anti-inflammatory agents)
- Early death from COVID-19 as a competing event
- Different measure (prevalence, incidence)

Personal view

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Balancing evidence and frontline experience in the early phases of the COVID-19 pandemic: current position of the Italian Society of anti-infective therapy (SITA) and the Italian Society of Pulmonology (SIP)

Matteo Bassetti • Daniele Roberto Giacobbe • Stefano Aliberti • Emanuela Barisione • Stefano Centanni • Francesco Giuseppe De Rosa • Fabiano Di Marco • Andrea Gori • Guido Granata • Malgorzata Mikulska • Nicola Petrosillo • Luca Richeldi • Pierachille Santus • Carlo Tascini • Antonio Vena • Pierluigi Viale • Francesco Blasi •

CMI CLINICAL MICROBIOLOGY AND INFECTION

- It might be prudent to consider empiric antibiotic treatment in critically ill patients with pneumonia due to COVID-19 in whom bacterial infection cannot be excluded.
- This suggestion is based on the fact that bacterial coinfection:
  - is common in patients with viral pneumonia
  - can be associated with a substantial risk of delaying appropriate treatment, thereby potentially increasing mortality.

Bassetti et al. Clin Microbiol Infect 2020

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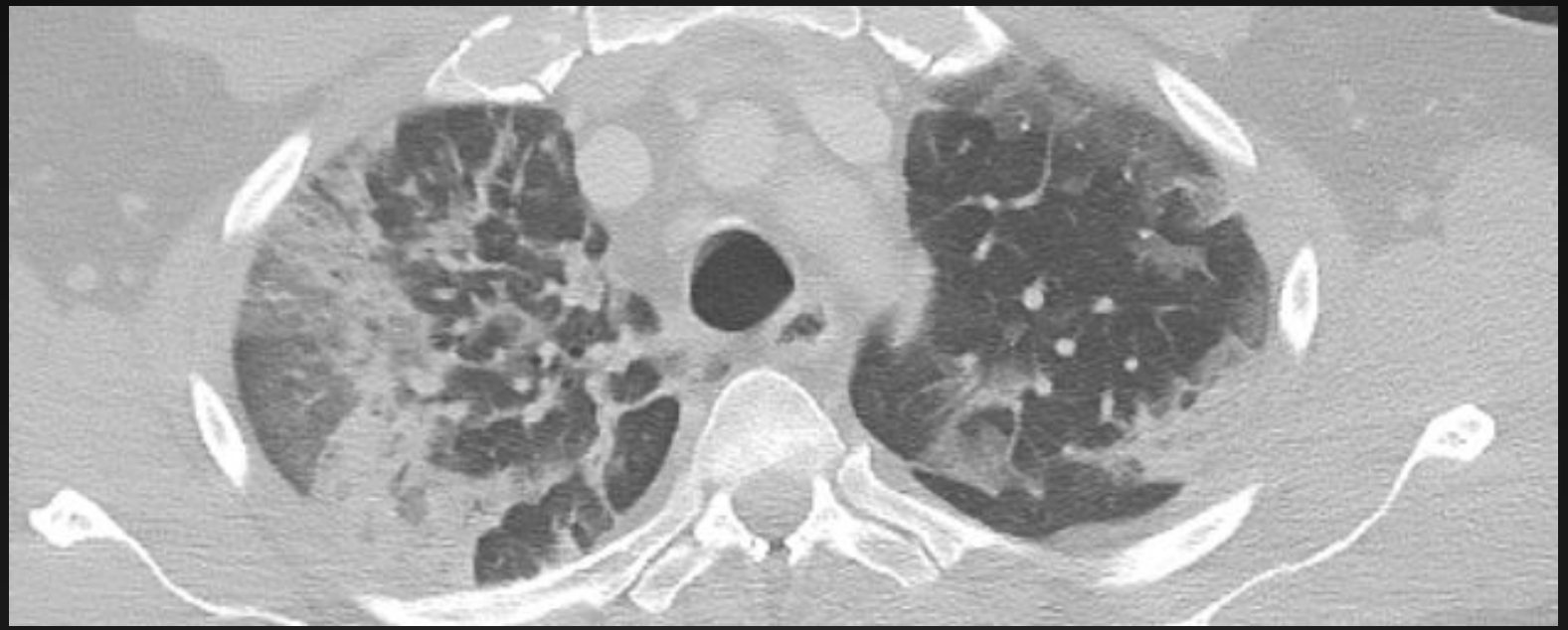

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THE LANCET
Volume 395, Issue 10223, 15–21 February 2020, Pages 507-513

Articles

Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study

Prof Nanshan Chen MD [a, †], Prof Min Zhou MD [e, f, †], Xuan Dong PhD [a, †], Prof Jieming Qu MD [e, f, †], Fengyun Gong MD [b], Yang Han PhD [c, i], Prof Yang Qiu PhD [i], Jingli Wang MD [b], Ying Liu MD [d], Yuan Wei MD [a], Jia'an Xia MD [a], Ting Yu MD [a], Prof Xinxin Zhang MD [g, h], Prof Li Zhang MD [a]

THE LANCET
Volume 395, Issue 10223, 15–21 February 2020, Pages 497-506

Articles

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Prof Chaolin Huang MD [a*], Yeming Wang MD [b, e, f*], Prof Xingwang Li MD [g*], Prof Lili Ren PhD [h*], Prof Jianping Zhao MD [j*], Yi Hu MD [k*], Prof Li Zhang MD [a], Guohui Fan MS [b, c, e], Jiuyang Xu MDc [l], Xiaoying Gu PhD [b, c, e], Prof Zhenshun Cheng MD [m], Ting Yu MD [a], Jiaan Xia MD [a], Yuan Wei MD [a], Prof Wenjuan Wu MD [a], Prof Xuelei Xie MD [a], Wen Yin MD [k], Hui Li MD [b, e, f] ... Prof Bin Cao MD [b, e, f, p, †]

- According to first reports prevalence of co-infection/superinfection only 1-10%

Intensive Care Med (2020) 46:846–848
https://doi.org/10.1007/s00134-020-05991-x

LETTER

Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China

Qiurong Ruan[1,2], Kun Yang[3], Wenxia Wang[4], Lingyu Jiang[5] and Jianxin Song[4*]

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Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

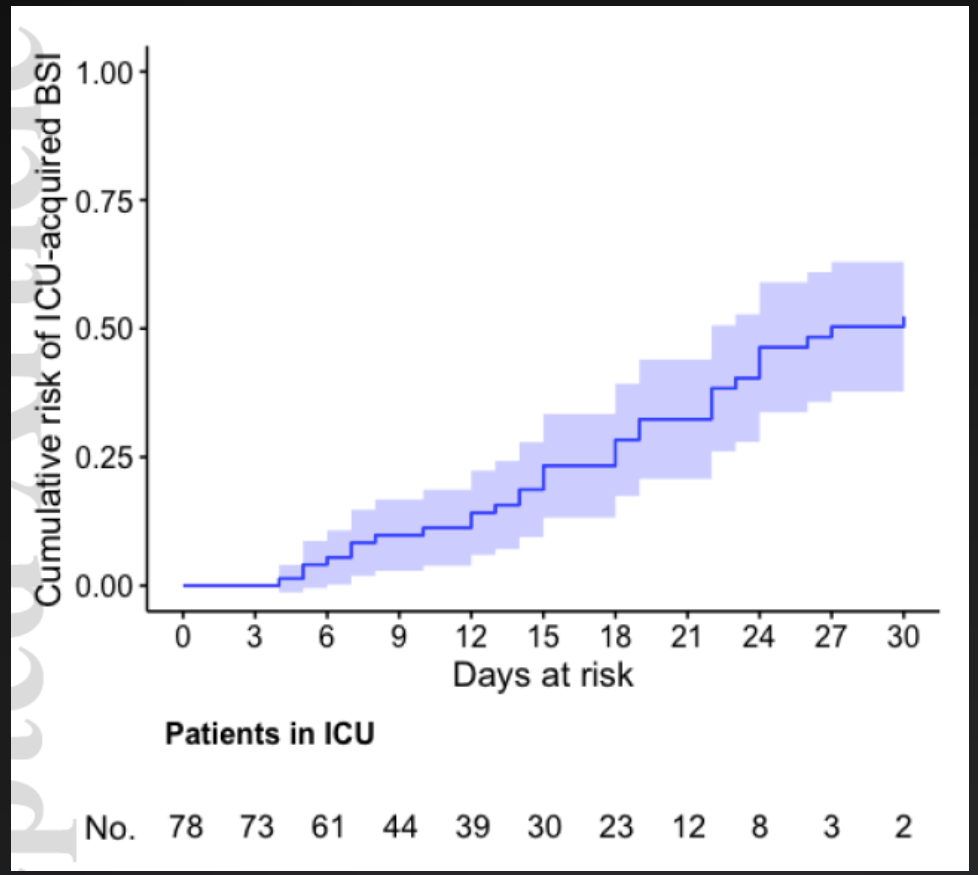
Fei Zhou, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao*

Lancet 2020

- High prevalence of secondary infections
- 50% in non-survivors
- 1% in-survivors
- Likely key contribution to mortality

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Treatments*				
Antibiotics	181 (95%)	53 (98%)	128 (93%)	0·15
Antiviral treatment	41 (21%)	12 (22%)	29 (21%)	0·87
Corticosteroids	57 (30%)	26 (48%)	31 (23%)	0·0005
Intravenous immunoglobin	46 (24%)	36 (67%)	10 (7%)	<0·0001
High-flow nasal cannula oxygen therapy	41 (21%)	33 (61%)	8 (6%)	<0·0001
Non-invasive mechanical ventilation	26 (14%)	24 (44%)	2 (1%)	<0·0001
Invasive mechanical ventilation	32 (17%)	31 (57%)	1 (1%)	<0·0001
ECMO	3 (2%)	3 (6%)	0	0·0054
Renal replacement therapy	10 (5%)	10 (19%)	0	<0·0001
Outcomes				
Sepsis	112 (59%)	54 (100%)	58 (42%)	<0·0001
Respiratory failure	103 (54%)	53 (98%)	50 (36%)	<0·0001
ARDS	59 (31%)	50 (93%)	9 (7%)	<0·0001
Heart failure	44 (23%)	28 (52%)	16 (12%)	<0·0001
Septic shock	38 (20%)	38 (70%)	0	<0·0001
Coagulopathy	37 (19%)	27 (50%)	10 (7%)	<0·0001
Acute cardiac injury	33 (17%)	32 (59%)	1 (1%)	<0·0001
Acute kidney injury	28 (15%)	27 (50%)	1 (1%)	<0·0001
Secondary infection	28 (15%)	27 (50%)	1 (1%)	<0·0001

Bloodstream infections in critically ill patients with COVID-19



Giacobbe et al. Eur J Clin Invest 2020

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Patient characteristics, clinical course and factors associated to ICU mortality in critically ill patients infected with SARS-CoV-2 in Spain: A prospective, cohort, multicentre study

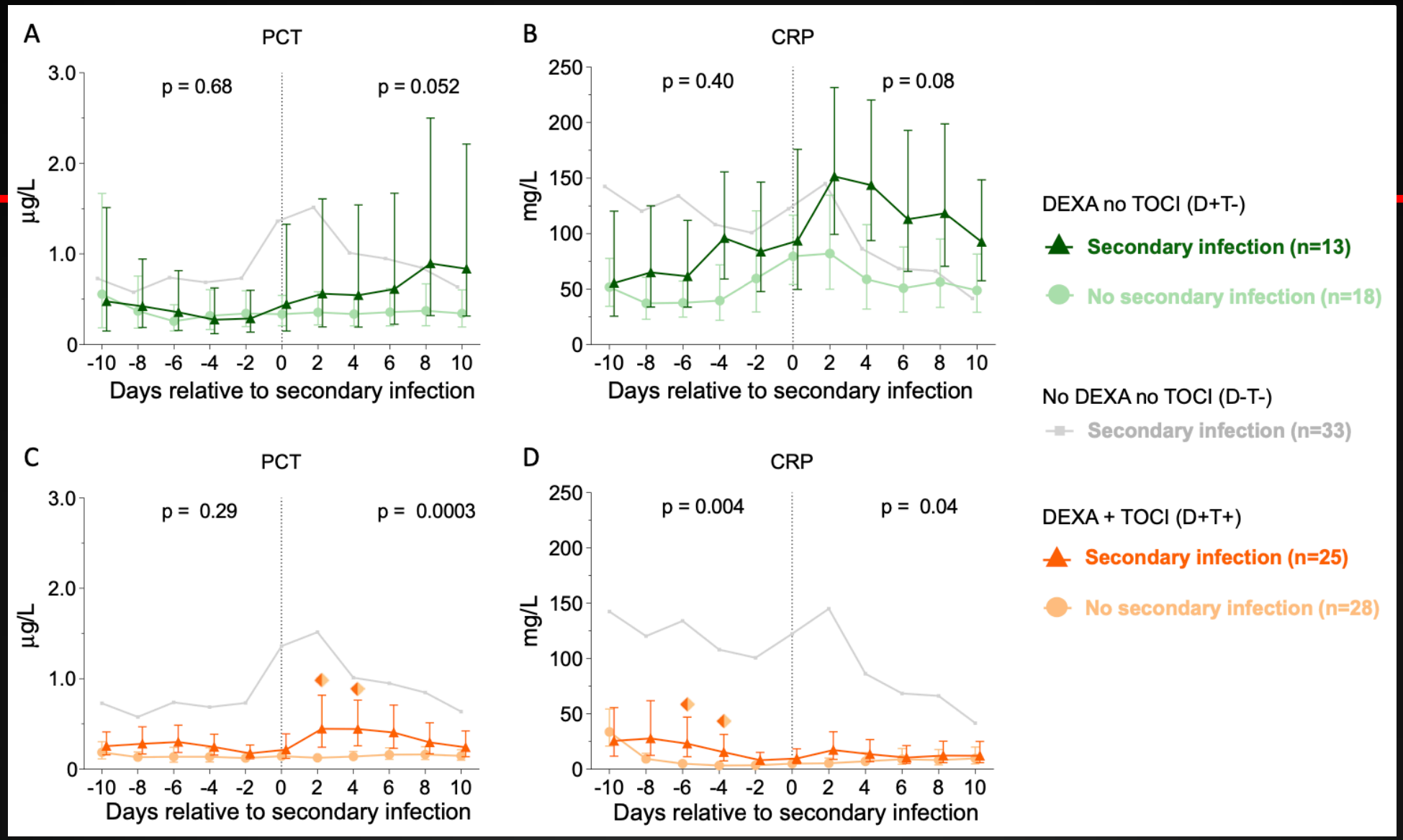
- 661 ICU patients
- Mortality 31%
- Respiratory superinfections and BSI > 25% of the population
- Septic shock associated with increased mortality

Ferrando et al. Rev Esp Anestesiol Reanim 2020

TABLE 2 Characteristics of 45 ICU-acquired BSI episodes in 31 critically ill patients with COVID-19

	Total no of episodes (n = 45)	Episodes in patients treated with tocilizumab (n = 16)	Episodes in patients treated with steroid (n = 12)	Episodes in patients treated with tocilizumab and steroid (n = 7)	Episodes in patients treated with neither tocilizumab nor steroid (n = 10)
Fever (temperature > 37.3°C), n (%)	24 (53)	6 (38)	5 (42)	4 (57)	9 (90)
Laboratory results					
Blood neutrophil count, cell × 10^{-3}/mm^3	10.8 (8.1-14.8)	8.9 (5.5-14.7)	13.4 (8.6-16.0)	12.4 (8.7-16.0)	10.4 (6.4-14.5)
Blood platelet count, cell × 10^{-3}/mm^3	247 (192-332)	234 (191-355)	260 (188-445)	208 (190-300)	244 (184-294)
Serum lactate, mmol/L	1.2 (0.8-1.6)	1.3 (1.0-2.1)	1.2 (0.8-1.5)	1.2 (0.7-1.4)	1.1 (0.6-1.3)
Serum fibrinogen, g/L	4.3 (2.7-6.5)	2.8 (2.2-3.1)	5.9 (4.3-8.0)	4.4 (2.1-5.4)	6.5 (4.3-9.2)
Serum C-reactive protein, mg/L	44.6 (11.3-137.0)	20.6 (8.4-33.6)	105.2 (54.0-164.0)	43.7 (2.9-120.0)	169.0 (70.4-194.0)
Serum procalcitonin	0.3 (0.1-1.2)	0.1 (0.0-0.3)	0.9 (0.2-2.3)	0.1 (0.1-0.2)	1.2 (0.4-1.9)

Giacobbe et al. Eur J Clin Invest 2020



Kooistra et al. Crit Care 2021

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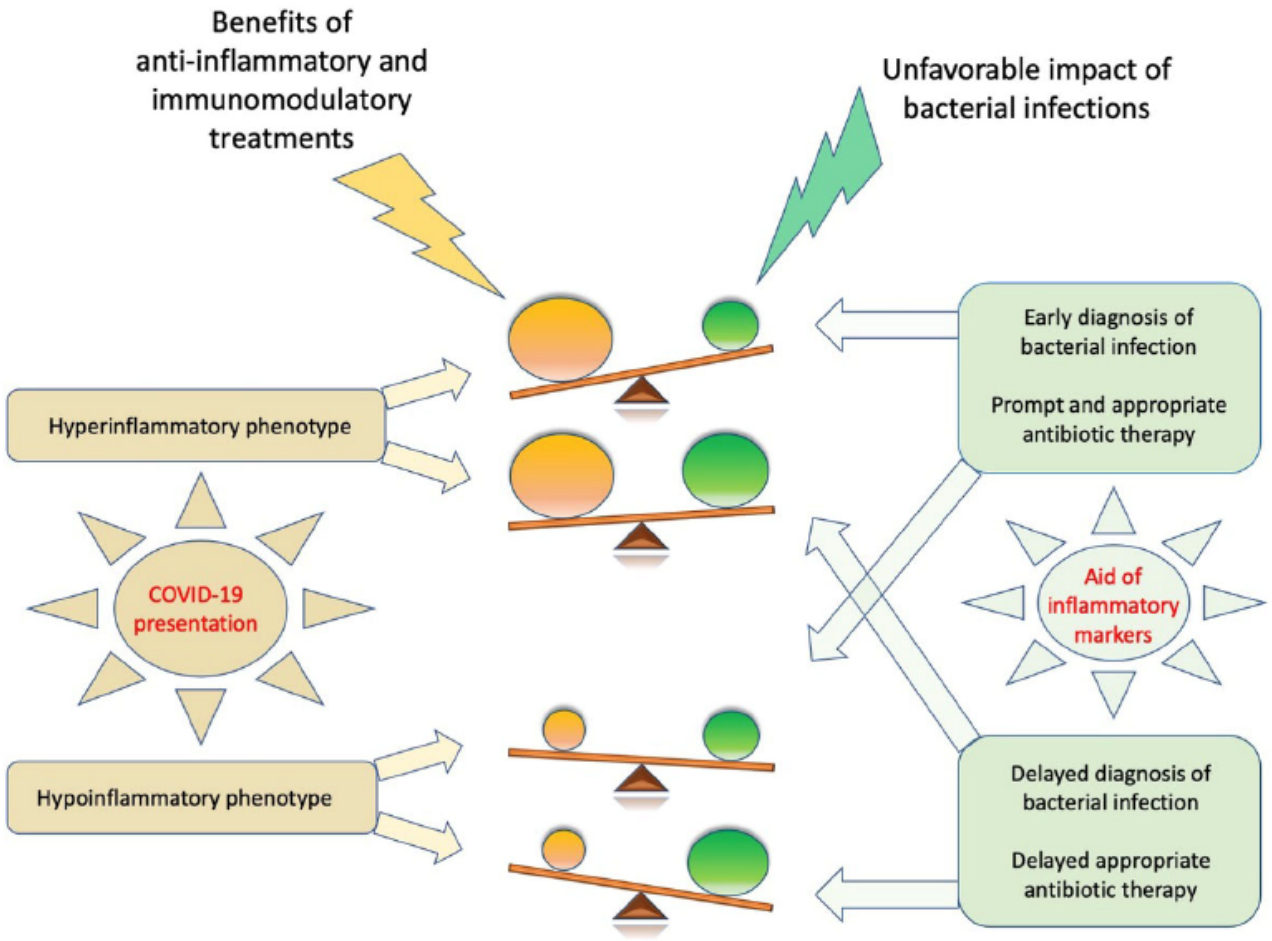

Fig. 1. Complex balance between the effects of anti-inflammatory/immunomodulatory agents for the treatment of COVID-19 and the possible unfavorable impact of bacterial infections.

Giacobbe et al. ***Front Biosci (Landmark Ed.)*** 2021

Research needs

Table 1
Research needs regarding COVID-19 and antibiotic steward

Research need	Study design	Challenges	Comment
(1) Establish the exact incidence of bacterial co-infection and superinfection at the different phases of the disease	Observational cohort study or in the context of randomized controlled trials assessing other interventions	Adequate diagnostics of lower respiratory tract infections require bronchoalveolar lavage (BAL) which may be difficult to perform (risk of respiratory deterioration, risk of exposure for healthcare personnel, resource constraints) Limited availability of bacteriological tests in the context of the pandemic)	• Ideally combined with (2)
(2) Assess the diagnostic performance of biomarkers to rule out/rule in bacterial superinfection	Observational cohort study or in the context of randomized controlled trials assessing other interventions	The reference standard (presence or absence of bacterial super-/co-infection) may be difficult to ascertain and may have suboptimal accuracy by itself: see (1)	• Ideally combined with (1) • Ideally studies should assess more than one biomarker
(3) Better understand the contribution of infection versus immune response in the different phases of COVID (first days after start of symptoms versus second week)	Observational cohort study or in the context of randomized controlled trials (e.g. of immune-modulating interventions such as steroids or IL-6 or IL-1 inhibitors)	See (1). Obtaining BAL samples may be challenging	
(4) Assess the impact of the COVID pandemic on antibiotic use and resistance in all settings (community, nursing homes, hospitals)	National, regional, local surveillance of antibiotic use and resistance based on established networks	Many confounding factors besides antibiotic use need to be taken into account (e.g. overcrowding of hospitals)	

Huttner et al. Clin Microbiol Infect 2020

Measuring ASP

- ASP intervention → similar/improved clinical outcomes

- If similar clinical outcomes → reduction in antibiotic use, reduction in antibiotic-related complications

STUDY PROTOCOL

Efficacy and safety of antimicrobial stewardship prospective audit and feedback in patients hospitalized with COVID-19: A protocol for a pragmatic clinical trial

Justin Z. Chen[1‡*], Holly L. Hoang[1‡], Maryna Yaskina[2], Dima Kabbani[1], Karen E. Doucette[1], Stephanie W. Smith[1], Cecilia Lau[3], Jackson Stewart[3], Karen Zurek[4], Morgan Schultz[4], Carlos Cervera[1]

1 Division of Infectious Diseases, Department of Medicine, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada, **2** Women and Children's Health Research Institute, University of Alberta, Edmonton, Alberta, Canada, **3** Pharmacy Services, Alberta Health Services, Edmonton, Alberta, Canada, **4** Pharmacy Services, Covenant Health, Edmonton, Alberta, Canada

Chen et al. PLoS ONE 2022; 17(3): e0265493

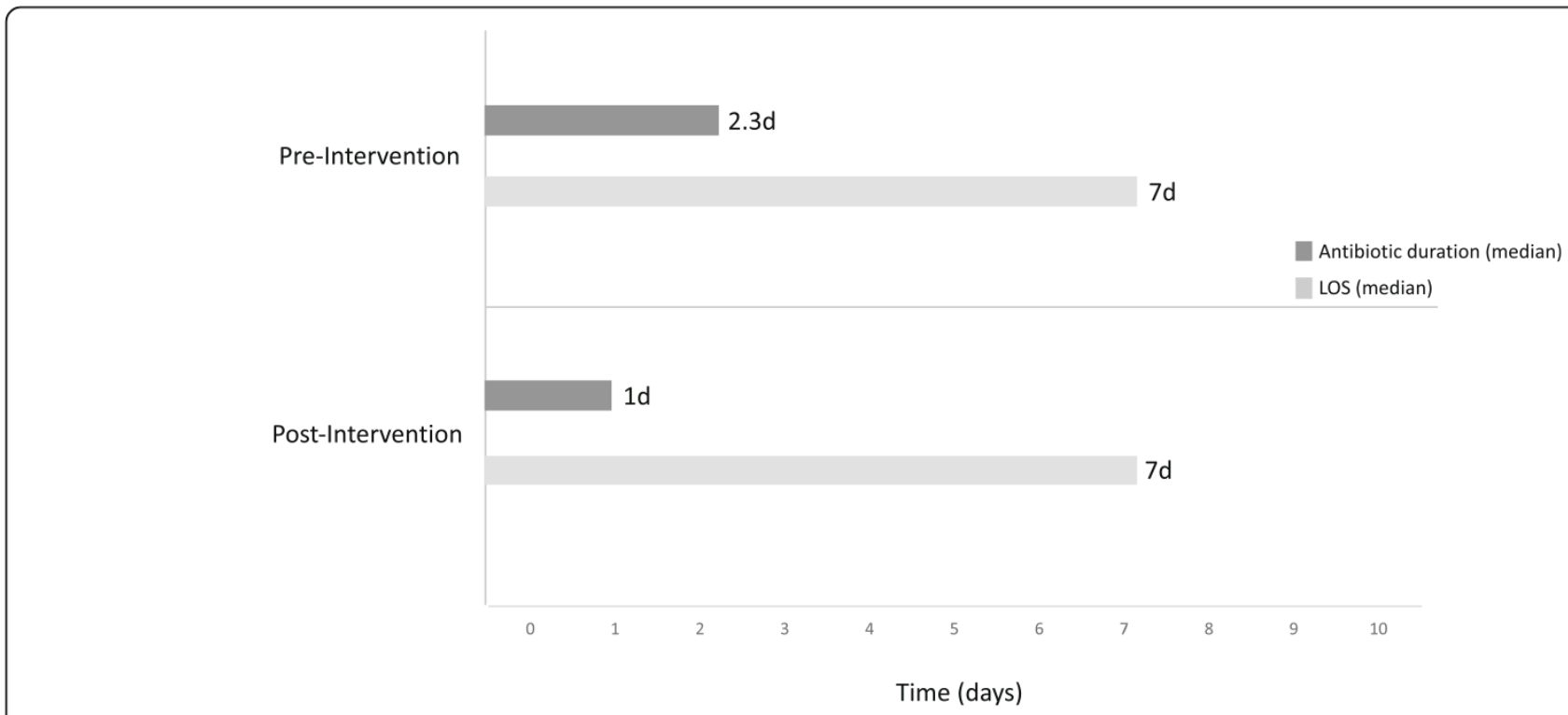

Fig. 1 Antibiotic duration and length of stay pre- and post-intervention

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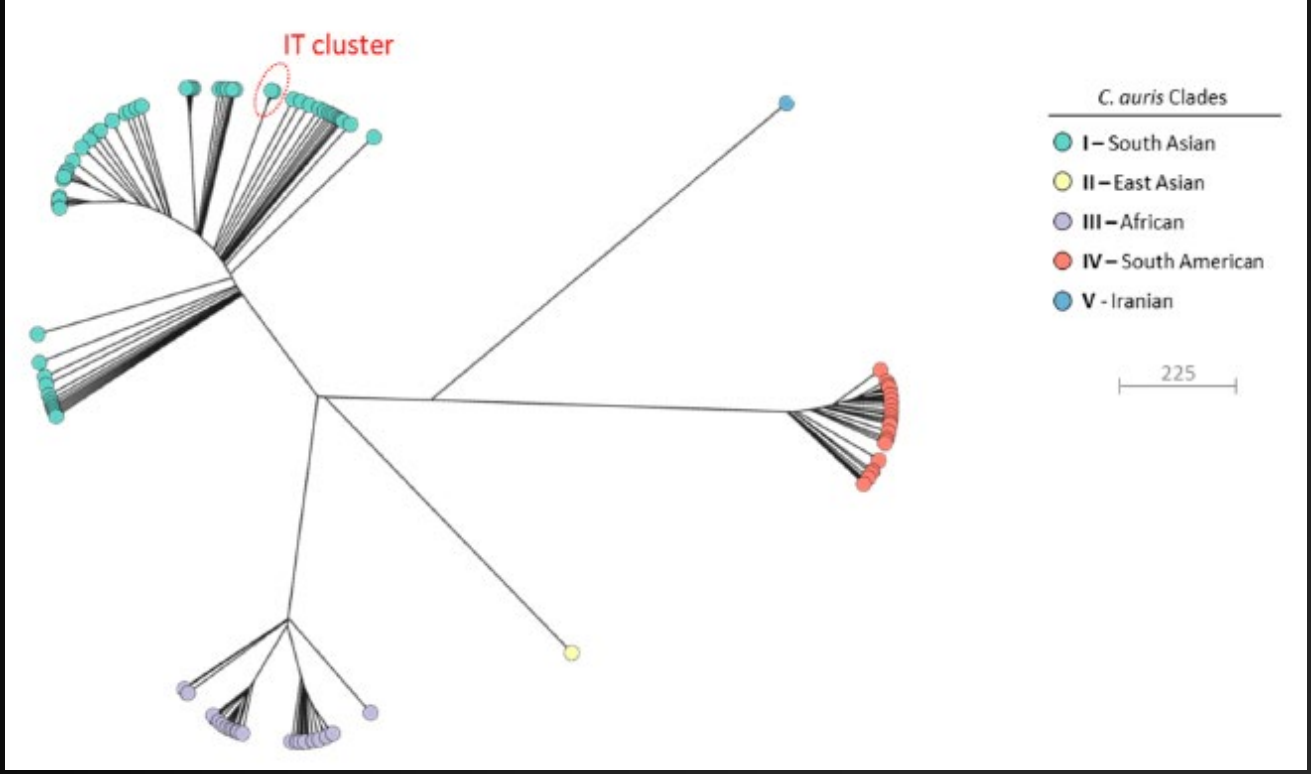
Molecular Epidemiological Investigation of a Nosocomial Cluster of *C. auris*: Evidence of Recent Emergence in Italy and Ease of Transmission during the COVID-19 Pandemic

Vincenzo Di Pilato [1,*], Giulia Codda [1], Lorenzo Ball [1,2], Daniele Roberto Giacobbe [3,4], Edward Willison [5], Malgorzata Mikulska [3,4], Laura Magnasco [3,4], Francesca Crea [5], Antonio Vena [3], Paolo Pelosi [1,2], Matteo Bassetti [3,4] and Anna Marchese [1,5]



Di Pilato et al. J Fungi 2021

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Morbidity and Mortality Weekly Report

Candida auris Outbreak in a COVID-19 Specialty Care Unit — Florida, July–August 2020

Christopher Prestel, MD[1,2]; Erica Anderson, MPH[2]; Kaitlin Forsberg, MPH[3]; Meghan Lyman, MD[3]; Marie A. de Perio, MD[4,5]; David Kuhar, MD[1]; Kendra Edwards[6]; Maria Rivera, MPH[2]; Alicia Shugart, MA[1]; Maroya Walters, PhD[1]; Nychie Q. Dotson, PhD[2]

Clinical Infectious Diseases

CORRESPONDENCE

***Candida auris*: A Latent Threat to Critically Ill Patients With Coronavirus Disease 2019**

ELSEVIER

Contents lists available at ScienceDirect

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journal homepage: www.clinicalmicrobiologyandinfection.com

CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID

Letter to the Editor

Outbreak of *Candida auris* infection in a COVID-19 hospital in Mexico

Hiram Villanueva-Lozano [1,*], Rogelio de J. Treviño-Rangel [1,*], Gloria M. González [1,*], María Teresa Ramírez-Elizondo [2,3], Reynaldo Lara-Medrano [2], Mary Cruz Aleman-Bocanegra [2], Claudia E. Guajardo-Lara [4], Natalia Gaona-Chávez [2], Fernando Castilleja-Leal [3], Guillermo Torre-Amione [3], Michel F. Martínez-Reséndez [2,3,*]

Rodriguez et al. Clin Infect Dis 2021; Prestel et al. MMWR 2021; Villanueva-Lozano et al. Clin Microbiol Infect 2021

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Infect Dis Ther (2021) 10:1837–1885
https://doi.org/10.1007/s40121-021-00487-7

GUIDELINES

Clinical Management of Adult Patients with COVID-19 Outside Intensive Care Units: Guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)

Matteo Bassetti · Daniele Roberto Giacobbe · Paolo Bruzzi · Emanuela Barisione · Stefano Centanni · Nadia Castaldo · Silvia Corcione · Francesco Giuseppe De Rosa · Fabiano Di Marco · Andrea Gori · Andrea Gramegna · Guido Granata · Angelo Gratarola · Alberto Enrico Maraolo · Malgorzata Mikulska · Andrea Lombardi · Federico Pea · Nicola Petrosillo · Dejan Radovanovic · Pierachille Santus · Alessio Signori · Emanuela Sozio · Elena Tagliabue · Carlo Tascini · Carlo Vancheri · Antonio Vena · Pierluigi Viale · Francesco Blasi on behalf of the Italian Society of Anti-infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)

Question 6 *Should antibiotics be administered to inpatients with COVID-19?*

We recommend against the routine use of antibiotics in hospitalized patients with COVID-19 without proven bacterial infection—*strong recommendation, moderate certainty of evidence (for azithromycin); weak recommendation, very low certainty of evidence (for antibiotics in general)*

We recommend collection of respiratory specimens for culture or molecular detection of respiratory pathogens, blood cultures, and urinary antigens for *Streptococcus pneumoniae* and *Legionella* spp. in hospitalized patients with COVID-19 and suspected bacterial pneumonia—*best practice recommendation (based on expert opinion only)*

Empirical antibiotic treatment of suspected bacterial pneumonia alongside proper diagnostic procedures, should be considered in patients with COVID-19 with evidence of consolidative radiological lesions—*best practice recommendation (based on expert opinion only)*

In the case of empirical antibiotic treatment, selection of agents to be administered should follow standard practice for the treatment of bacterial pneumonia—*best practice recommendation (based on expert opinion only)*

Antimicrobial stewardship and COVID-19

late 2021

2022

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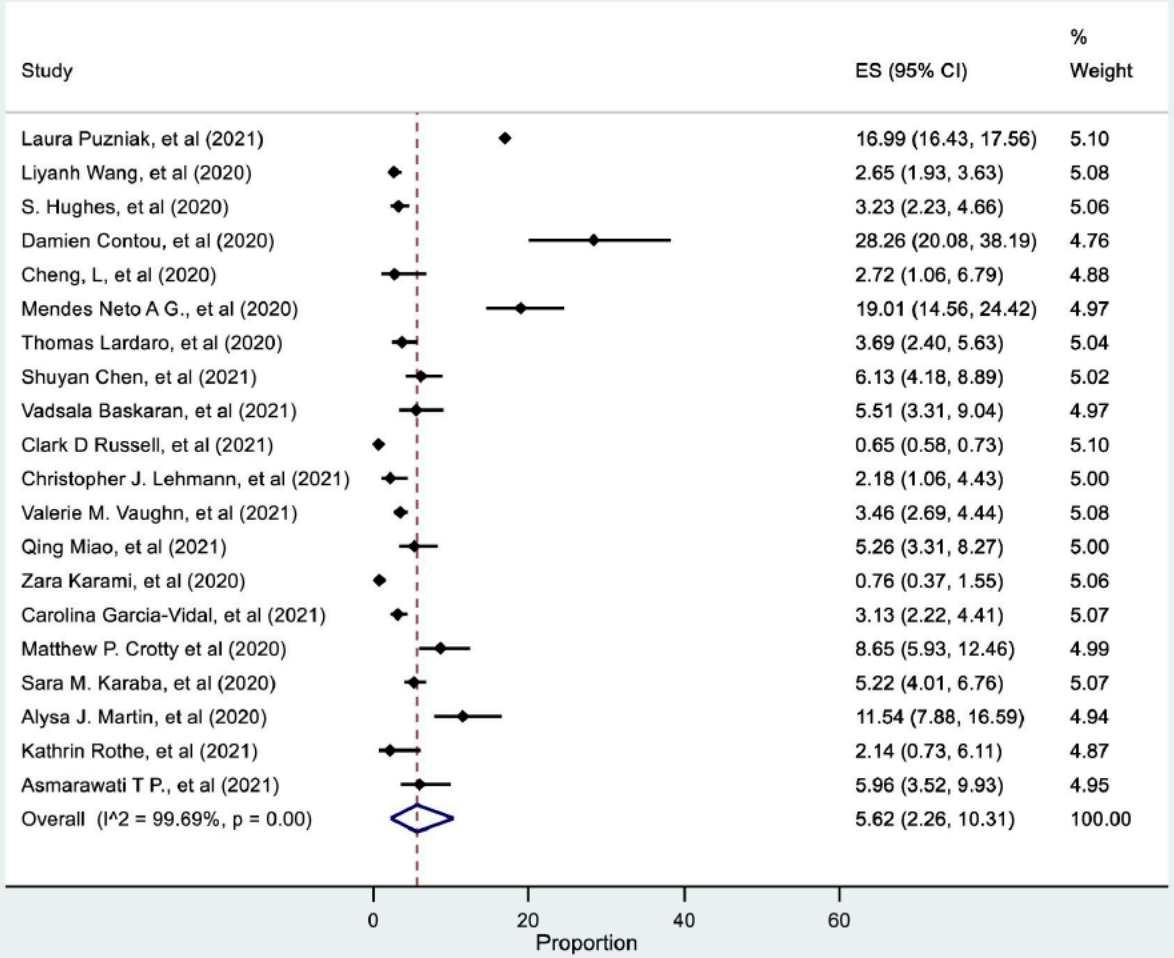
Prevalence of Bacterial Coinfection



Alshaikh F et al. PLoS ONE 2022; 17(8): e0272375

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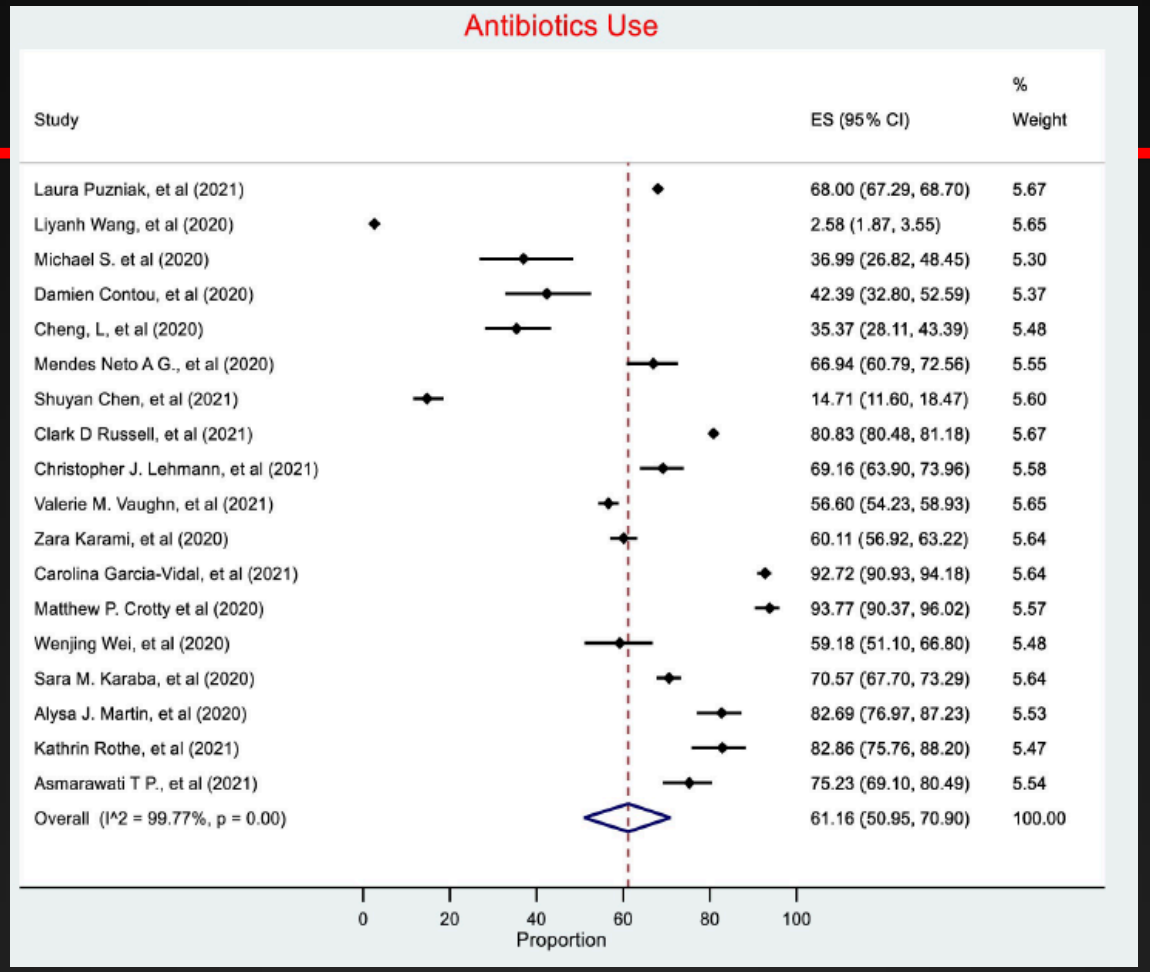

Alshaikh F et al. PLoS ONE 2022; 17(8): e0272375

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Antimicrobial stewardship and COVID-19 now

- Completely changed landscape → need to change approach
- The change also involves studies on ASP in COVID-19 patients
- Possible long-term consequences of excessive antibiotic use in 2020 and early 2021

Personal view

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Thank you

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