Relazioni tra COVID-19, uso di antibiotici e infezioni da multiresitenti

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COVID-19 e la trasformazione del sistema per contrastare l'infezione

Webinar
12 giugno 2020
ore 14:30 - 18:00

Riflessioni preliminari

- La concitazione pandemica non ha giovato all'appropriatezza delle scelte assistenziali e terapeutiche
- Aree di degenza COVID-19 gestite da specialisti diversi (internisti, pneumologi, altri)
- Aree di terapia intensiva ricavate da spazi non dedicati ed armate con personale a volte "inesperto"
- Coinvolgimento assistenziale di personale "esterno"
- Netto aumento del carico di lavoro e del rischio infettivo per il personale di assistenza
- Infezioni COVID-19 nel personale di assistenza (medici, infermieri)

Riflessioni preliminari

- **Calo di attenzione nei confronti dell'Infection Control**
- **Iniziale utilizzo di antimicrobici a largo spettro nella ipotesi di polmonite non esclusivamente virale**
- Attrazione nei confronti dei macrolidi e della doxiciclina nell'ipotesi di un effetto sinergico anti-SARS-CoV2
- Disarmo rapido ed esteso dell'ospedale No-COVID
- Calo drammatico dell'offerta generale e specialistica, anche ambulatoriale
- Utenza diffidente che rimanda l'accesso in ospedale
- Potenziali danni per le patologie tempo-dipendenti
- Potenziali danni per il trattamento delle patologie croniche

Problematiche specifiche

- Rapporto tra COVID-19 ed infezioni batteriche
- Patogeni comunitari e nosocomiali (MDR)
- Co-infezioni e superinfezioni
- Setting infezioni: degenza ordinaria od ICU
- Terapia antibiotica empirica (per il COVID-19, per le infezioni batteriche) in ospedale ed a domicilio
- Raccomandazioni terapeutiche esistenti
- Infection control e sorveglianza microbiologica
- Programmi di AS mirati
- Linee-guida per la terapia antimicrobica

SARS-CoV-2, bacterial co-infections, and AMR: the deadly trio in COVID-19?

- There is extensive clinical evidence, supported by animal models, demonstrating that **respiratory viral infections predispose patients to bacterial co-infections and superinfections.**
- **Most fatalities in the 1918 influenza pandemic were indeed due to subsequent bacterial infection**
- Similar observations were made during the last influenza pandemics**: the 1957 H2N2, the 1968- 969 H3N2 and the 2009-10 H1N1**

Jose A. Bengoechea, Connor G. Bamford EMBO Mol Med doi: 10.15252/emmm 202012560

Is there a case to consider co-infections in COVID-19?

- COPD is one of comorbidities associated with severe COVID-19
- **COPD pts are colonized by bacterial pathogens** making it likely that SARS-CoV-2 infection occurs in patients already colonized
- **The possibility exists that severe COVID-19 pts could be subsequently or co-incidentally infected by bacteria.**
- The median hospital stage of COVID-19 pts is 7 days but can reach up to 14 days or even longer and **the risk of HAP increases significantly the longer the hospitalization period.**
- **More than 90% of HAP are associated with MV** often used in COVID-19 pts admitted in the ICU.

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COVID-19 therapies and bacterial co-infections.

- **Drugs modulating the immune response may increase the risk of potentially fatal secondary bacterial respiratory infections.**
- There is a significant increase of bacterial pneumonia in COPD pts treated with glucocorticoids
- There is the need to consider **the impact of any intervention targeting inflammatory responses on secondary infections**
- Careful considerations should also be taken for recombinant cytokine therapy, such as **treatment with type I or III IFNs, which could promote bacterial super-infection and associated pathology.**

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COVID-19 and AMR

- **ICUs are epicentres for AMR development.**
- SARSCoV- 2 is transmitting in hospitals also MDR bacteria, leading to an increase in the mortality due the limited arsenal of antibiotics
- In addition to the direct impact in the health care setting, **the transmission of AMR to the environment should not be forgotten.**
- The increased levels of antimicrobials released in waste water from hospitals will affect levels of antimicrobials in the environment, affecting the **level of resistance in both animals (both wildlife and feed animals) and in farming and natural systems.**

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COVID-19 and AMR

- **The need for antibiotic treatment should be rapidly evaluated and stopped if not necessary.**
- The microbiology lab should suggest the most suitable based on the microorganism and the resistance pattern.
- Some of hand sanitizers and antibacterial soaps may content **additional chemicals** that may fuel bacterial AMR
- Bacteria exploit efflux pumps to develop resistance against disinfectants, and these same efflux pumps contribute to AMR.
- It is essential that the public adhere to the manufacturer's instructions for proper use to avoid the selection of bacteria with increased tolerance/resistance to antimicrobials.

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Co-infections in people with COVID-19: a systematic review and meta-analysis

- Thirty studies including 3834 patients were included.
- **Overall, 7% of hospital COVID-19 pts had a bacterial co-infection**
- **A higher proportion of ICU pts had bacterial co-infections than pts in mixed ward setting (14% versus 4%).**
- The commonest bacteria were ***Mycoplasma pneumoniae, Pseudomonas aeruginosa and Haemophilus influenzae***.
- The proportion with a viral co-infection was 3%, with RSV and influenza A the commonest
- Three studies reported fungal co-infections.
- **Conclusions**: **A low proportion of COVID-19 patients have a bacterial co-infection**. **These findings do not support the routine use of antibiotics in the management of COVID-19** .

L. Lansbury , B. Lim , V. Baskaran , WS. Lim: Journal of Infection (2020), doi: https://doi.org/10.1016/j.jinf.2020.05.046

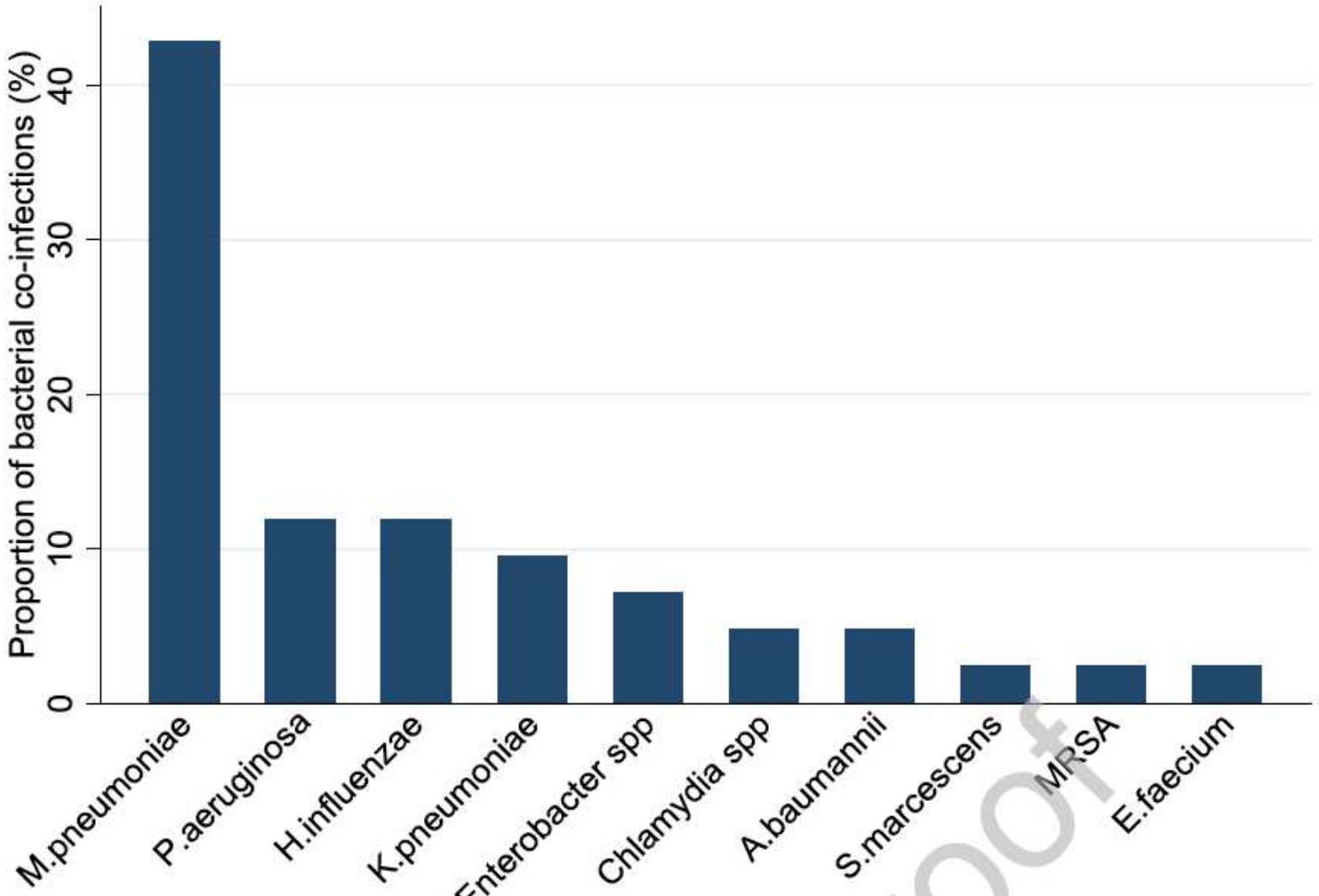

Figure 4 Bacterial pathogens detected in COVID-19 patients, as a proportion (%) of the total number of detections (n=27)

L. Lansbury , B. Lim , V. Baskaran , WS. Lim: Journal of Infection (2020), doi: https://doi.org/10.1016/j.jinf.2020.05.046

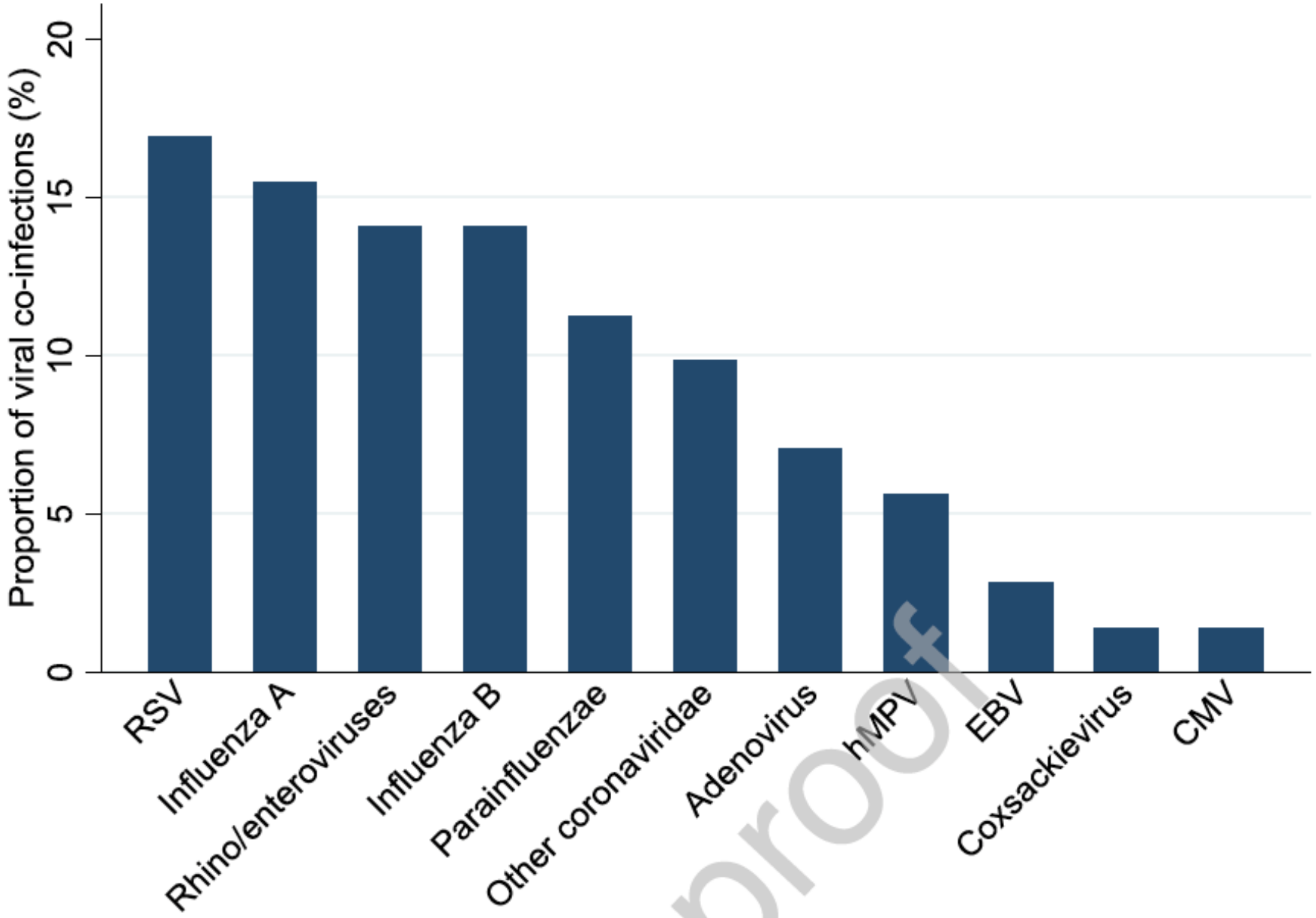

Figure 5 Viral pathogens as a proportion (%) of the total number of viral detections (n=71)

Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing

- Nine studies were identified
- **For COVID-19, 62/806 (8%) patients were reported as experiencing bacterial/fungal co-infection during hospital admission.**
- Despite a paucity of evidence for bacterial coinfection in COVID-19 **1450/2010 (72%) of pts reported received antimicrobial therapy.**
- No antimicrobial stewardship interventions were described.
- **Conclusions:** Despite frequent prescription of broad-spectrum empirical antimicrobials in COVID-19, **there is a paucity of data to support the association with respiratory bacterial/fungal co-infection.**

TM Rawson et al. CID 2020

Co-infections among patients with COVID-19: The need for combination therapy with non-anti-SARS-CoV-2 agents?

- The prevalence of co-infection was variable among COVID-19 patients however, it could be up to 50% among non-survivors.
- **Co-pathogens included bacteria, such as *S. pneumoniae, S. aureus, K. pneumoniae, M. pneumoniae, C. pneumonia, L. pneumophila and A. baumannii; Candida species and Aspergillus flavus***
- Viruses such as influenza, coronavirus, rhinovirus/enterovirus, parainfluenza, metapneumovirus, influenza B virus, and HIV.
- Influenza A was one of the most common co-infective viruses, which may have caused initial false negative results of RT-PCR for SARS-CoV-2.

Journal of Microbiology, Immunology and Infection, https://doi.org/10.1016/j.jmii.2020.05.013

Co-infections among patients with COVID-19: The need for combination therapy with non-anti-SARS-CoV-2 agents?

- Laboratory and imaging findings alone cannot help distinguish co-infection from SARS-CoV-2 infection.
- **Newly developed syndromic multiplex panels that incorporate SARS-CoV-2 may facilitate the early detection of coinfection among COVID-19 patients.**
- **Clinicians cannot rule out SARS-CoV-2 infection by ruling in other respiratory pathogens through old syndromic multiplex panels at this stage of the COVID-19 pandemic.**
- **After recognizing the possible pathogens causing co-infection among COVID-19 patients, appropriate antimicrobial agents can be recommended.**

Journal of Microbiology, Immunology and Infection, https://doi.org/10.1016/j.jmii.2020.05.013

Table 3 Summary of recommendations on the use of non-anti-SARS-CoV-2 agents for the treatment of COVID-19.

Recommendation	Anti-bacterial agent	Anti-fungal agent	Anti-non-SARS-CoV-2 antiviral agent	Comments
National Institutes of Health[42]	Insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication			For critically ill patients
Infectious Diseases Society of America[43]	N/A	N/A	N/A	No
Surviving Sepsis Campaign[44]	Daily assessment for de-escalation and re-evaluation of the duration of therapy after initiating empiric antimicrobials, and spectrum of coverage based on the microbiology results and the patient's clinical status			In mechanically ventilated patients with COVID-19 and respiratory failure, empiric antimicrobials/ antibacterial agents were suggested.
Canada[46]	Empirical antibiotic should be based on the clinical diagnosis, local epidemiology, and susceptibility data.	N/A	Empiric therapy with a neuraminidase inhibitor should be considered for the treatment of influenza virus infection in patients with or at risk for severe disease under influenza endemic.	Empiric antimicrobials should be used in the treatment of all likely pathogens causing severe acute respiratory infection and sepsis within 1 h of initial patient assessment for COVID-19 patients with sepsis.

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Recommendation	Anti-bacterial agent	Anti-fungal agent	Anti-non-SARS-CoV-2 antiviral agent	Comments
Unites Kingdom[48]	An oral antibiotic is indicated in the following scenarios: (1) The likely cause is bacterial (2) It is unclear whether the cause is bacterial or viral and symptoms are more concerning (3) They are at high risk of complications Doxycycline is used as first-line treatment, whereas amoxicillin is used as alternative treatment.	N/A	N/A	Antibiotics are not used as treatment for or to prevent pneumonia if the infection is likely caused by SARS-CoV-2 and symptoms are mild. Dual antibiotics are not routinely used.
China[49]	Mild patients use antibiotics, such as amoxicillin, azithromycin, or fluoroquinolones, as treatment against CAP; severe patients use empirical antibiotics to treat all possible pathogens.	NA	NA	Blind or inappropriate use of antibacterial drugs should be avoided.

Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing

- Concerns associated with the potential of sudden cardiac arrest secondary to QT prolongation associated with many of the agents used for atypical infection: **macrolides, tetracyclines, and quinolones**.
- **Macrolides have also been associated with potential antiviral effect in combination with hydroxychloroquine, but also have a potential synergistic effect on QT prolongation.**
- Very few atypical bacterial co-infections have been identified in reports of COVID-19 cases to date.
- Therefore, the potential unintended consequences of prolonged macrolide use must be weighed against potential likelihood of atypical bacterial co-infection within COVID-19 cohorts.

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Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing

- Further concern for **COVID-19 pts cared for in ICU** is the potential **increased rate of nosocomial infection**.
- **A large proportion of reported bacterial co-infections appear to be HCA, including CVC-related blood stream infections, and ventilator associated pneumonia.**
- Guidelines must focus on maintenance of good **infection control, antimicrobial stewardship, and robust surveillance for HCAIs and antimicrobial resistance.**
- A**ccess to core antimicrobials** must also be a primary goal.
- Potential stewardship interventions to support reduced antimicrobial prescribing during the COVID-19 pandemic urgently require consideration.

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Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing

- **Traditional markers used to support antimicrobial decisions,** such as vital signs, blood tests like white cell count and C-reactive protein, and imaging **tend to be abnormal in SARS-COV-2 infection.**
- This makes decision making surrounding the requirement for empiric antibacterial cover challenging.
- With fears surrounding prolonged patient contact and aerosol generation, the number of patients undergoing routine microbiological investigation may be reduced (i.e. BAL).
- **One potential solution to support antimicrobial prescribing in COVID-19 is the use of bacterial specific biomarkers, such as procalcitonin.**

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Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing

- Procalcitonin differentiate between bacterial and viral infection and supports early cessation of antibiotics in confirmed bacterial infection with no effect on patient mortality.
- **Procalcitonin use has been reported in the COVID-19 literature and may be an important tool to support reducing antimicrobial use.**
- The use of **clinical decision support systems** may facilitate decision making, especially when **linked with A.I.**
- **ID team** responsible for co-ordinating stewardship programs must continue to provide support to clinical teams managing COVID-19 patients to ensure **regular review and cessation of antimicrobial therapy.**

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Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing

- A**ppropriate microbiological sampling** prior to **commencement of antimicrobial therapy** should be encouraged
- Shortages of key antimicrobials being a concern, **judicious use will be vital to ensure access to therapy by those with confirmed bacterial infection.**
- Guidelines and stewardship programs should reflect the growing body of evidence supporting short-course antimicrobial therapy, early oral antibiotic switch and treatment de-escalation

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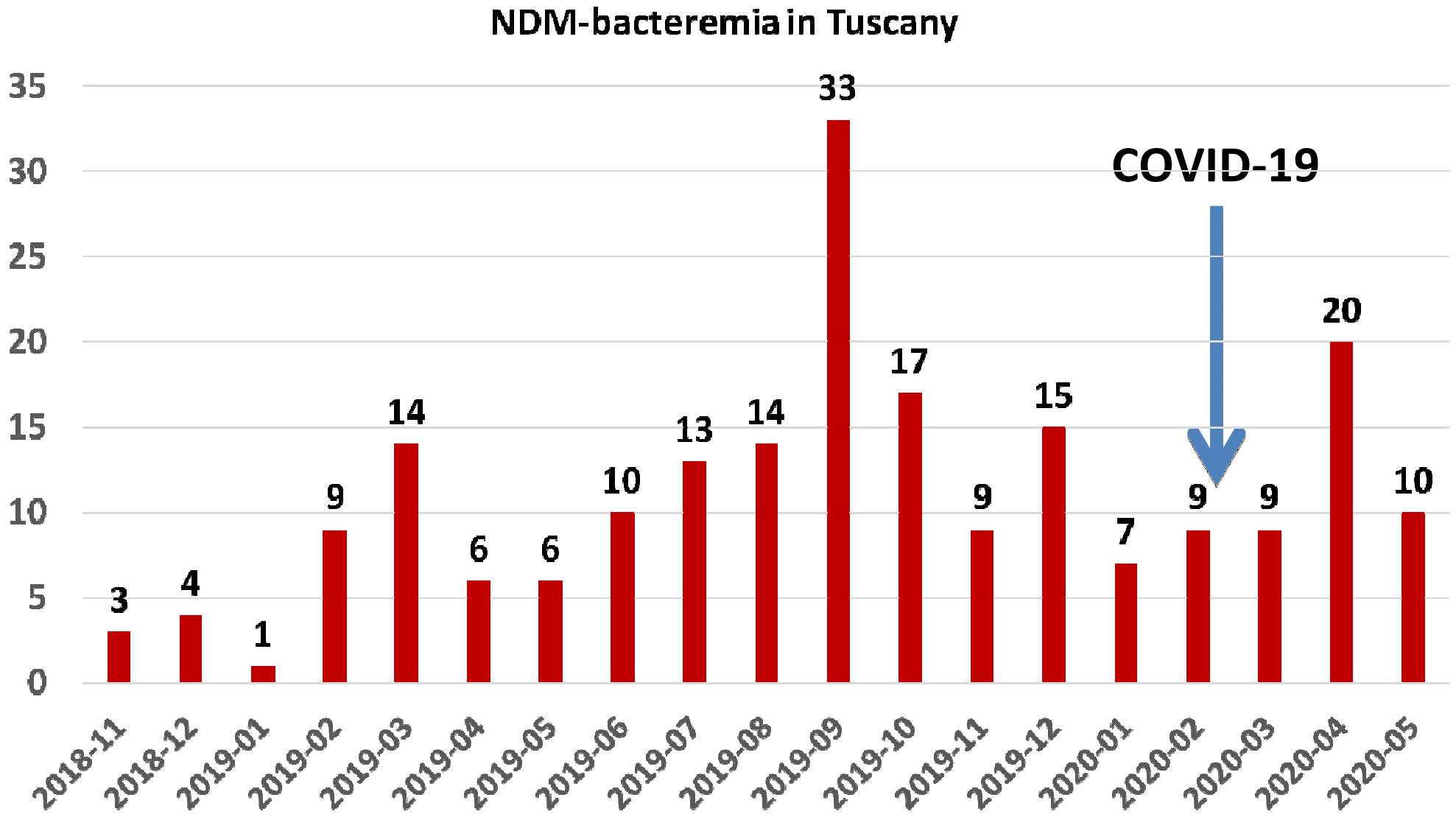
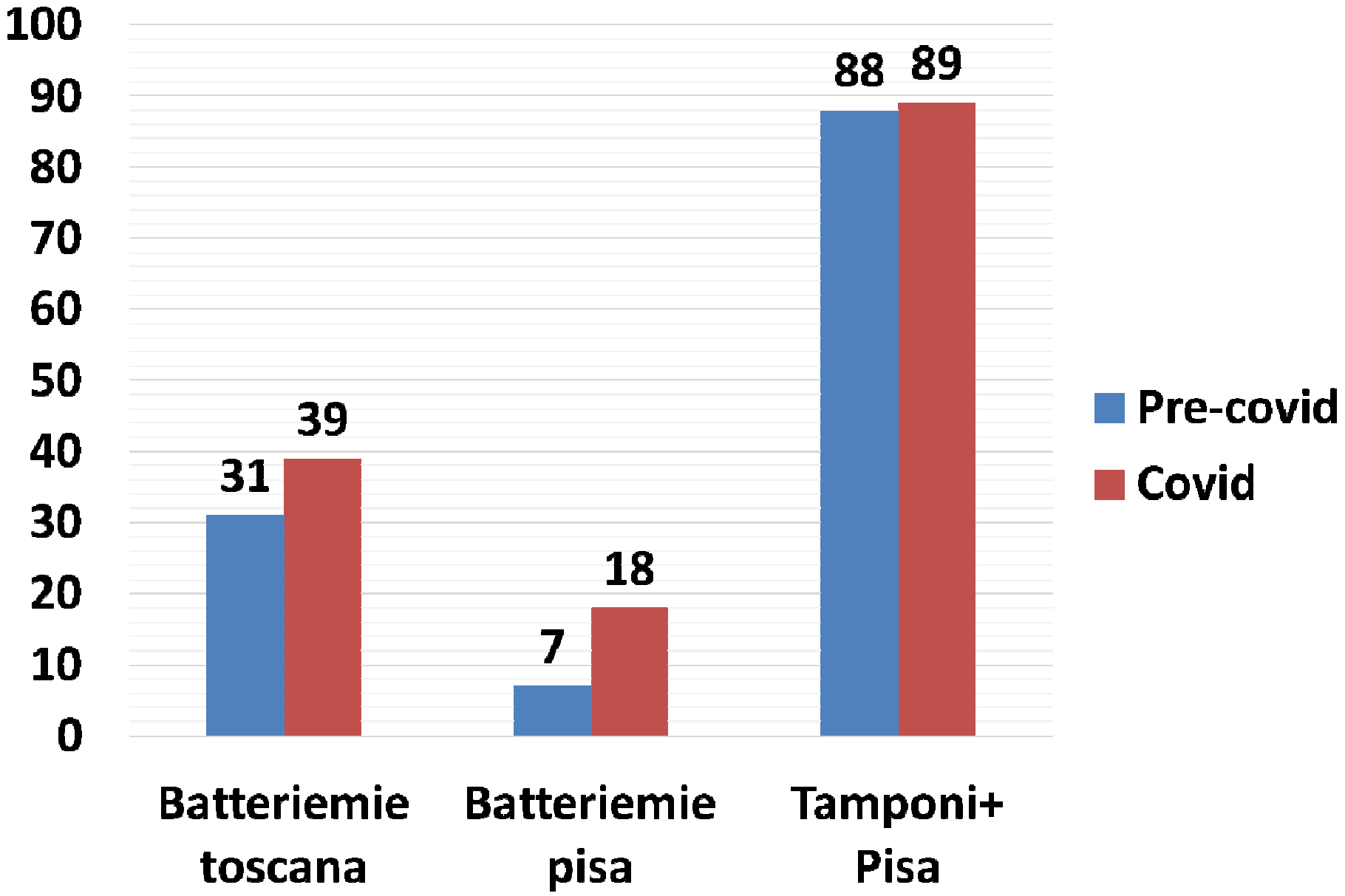
NDM-producing Klebsiella pneumoniae the Tuscany epidemic

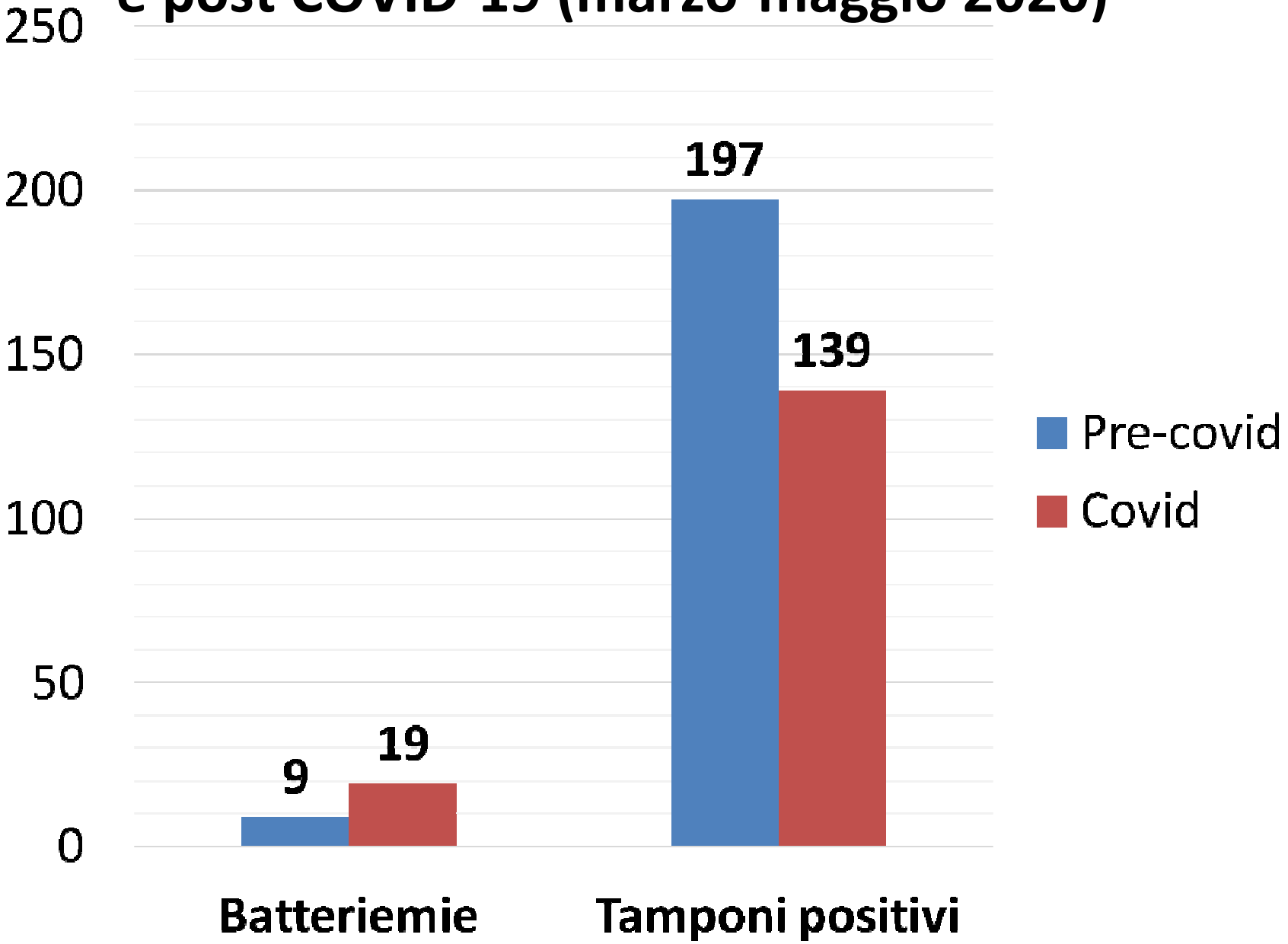


210 episodes from November 2018 to May 2020

Epidemiologia NDM pre-(dic. 2019-feb. 2020) e post COVID-19 (marzo-maggio 2020)



Epidemiologia CRE* pre-(dic. 2019-feb. 2020) e post COVID-19 (marzo-maggio 2020)



*CRE: NDM + KPC + OXA + IMP + VIM

CONSUMO ANTIBIOTICI AOUP

ATC	Gen-Mag 2020	Gen-Mag 2019	Diff. Valore	% Diff. Valore
A07AA12CA-FIDAXOMICINA 200 mg ORALE SOLIDO	€ 19.099	€ 15.518	€ 3.581	23%
J01 - ANTIBATTERICI PER USO SISTEMICO	€ 1.004.492	€ 1.126.024	-€ 121.532	-11%
J02 - ANTIMICOTICI PER USO SISTEMICO	€ 203.146	€ 316.283	-€ 113.137	-36%
J06BB21-BEZLOTOXUMAB	€ 0	€ 5.623	-€ 5.623	-100%
Somma:	**€ 1.226.738**	**€ 1.463.448**	**-€ 236.711**	**-16%**

OBIETTIVI APPROPRIATEZZA

ATC	Grammi Gen-Mag 2020	Grammi Gen-Mag 2019	Diff. Grammi	% Diff. Grammi	Gen-Mag 2020 Valore	Gen-Mag 2019 Valore	Diff. Valore	% Diff. Valore
CARBAPENEMI	9.960,00	10.368,50	-408,5	-4%	€ 48.320	€ 52.752	-€ 4.431	-8%
FLUOROCHINOLONI	4.107,90	7.154,90	-3047	-43%	€ 4.741	€ 12.898	-€ 8.156	-63%

CONSUMO ANTIBIOTICI AOUP

FARMACI IN INCREMENTO

Principio Attivo	Grammi Gen-Mag 2020	Grammi Gen-Mag 2019	Diff. Grammi	% Diff. Grammi	Gen-Mag 2020 Valore	Gen-Mag 2019 Valore	Diff. Valore	% Diff. Valore
CEFTAZIDIMA/AVIBACTAM	6.827,50	4.195,00	2632,5	63%	€ 222.349	€ 136.802	€ 85.546	63%
AZTREONAM	3.275,00	1.249,00	2026	162%	€ 59.980	€ 13.327	€ 46.653	350%
CEFTOBIPROLE MEDOCARIL	613,50	201,50	412	204%	€ 65.291	€ 21.453	€ 43.838	204%
AZITROMICINA	1.584,70	1.298,00	286,7	22%	€ 4.353	€ 3.866	€ 487	13%
DOXICICLINA	767,00	124,00	643	519%	€ 898	€ 136	€ 761	558%

Conclusione

- **COVID-19, infezioni batteriche ed AMR: problema reale**
- **Necessità di attenta sorveglianza epidemiologica**
- **Necessita di migliore comprensione dei meccanismi biologici di interazione**
- **Replicare migliorando Infection Control e Stewardship Antimicrobica**
- **Adottare prudenza nella immunoterapia, potenzialmente favorente superinfezioni batteriche**