SOCIETÀ ITALIANA DI TOSSICOLOGIA
SITOX
1972

21° Congresso Nazionale

Società Italiana di Tossicologia

Pericolo, rischio e rapporto rischio-beneficio

www.sitox.org

BOLOGNA
20-22 Febbraio 2023

Modulazione ormonale ed infezione da SARS-CoV-2: aspetti farmaco - tossicologici

Veronica Cocetta

Dipartimento di Scienze del Farmaco
Università degli Studi di Padova

Gebhard *et al. Biology of Sex Differences* (2020) 11:29
https://doi.org/10.1186/s13293-020-00304-9

Biology of Sex Differences

REVIEW Open Access

Impact of sex and gender on COVID-19 outcomes in Europe

Catherine Gebhard[1,2,3*†], Vera Regitz-Zagrosek[4,5,6†], Hannelore K. Neuhauser[6,7], Rosemary Morgan[8] and Sabra L. Klein[9]

Editorial > J Womens Health (Larchmt). 2020 Apr;29(4):465-466. doi: 10.1089/jwh.2020.8472.

Sex and Gender Disparities in the COVID-19 Pandemic

Jewel Gausman [1], Ana Langer [1]

Affiliations + expand

PMID: 32320331 DOI: 10.1089/jwh.2020.8472

ARTICLE

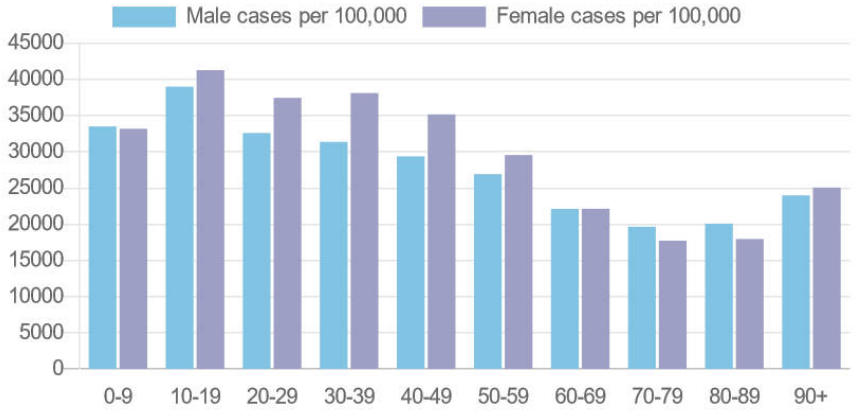
https://doi.org/10.1038/s41467-020-19741-6 OPEN

Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission

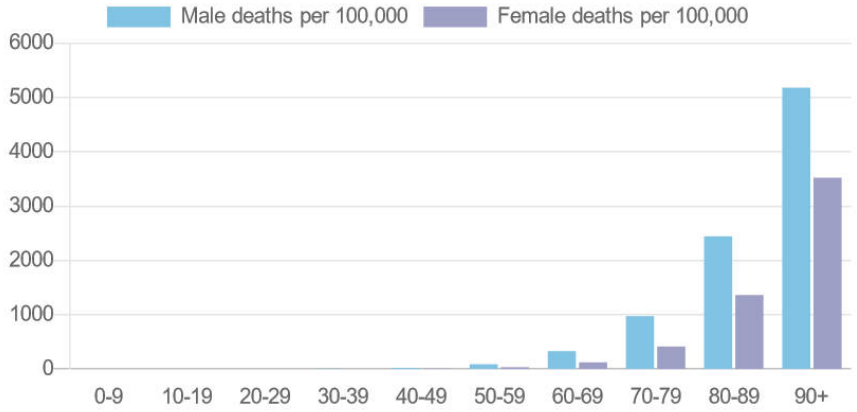
Hannah Peckham[1,2], Nina M. de Gruijter[1,2], Charles Raine[2], Anna Radziszewska[1,2], Coziana Ciurtin[1,2], Lucy R. Wedderburn[1,3,4], Elizabeth C. Rosser[1,2,7], Kate Webb[5,6,7✉] & Claire T. Deakin[1,3,4,7✉]

Casi e decessi per sesso ed età

Casi per età e sesso (tassi per 100,000)

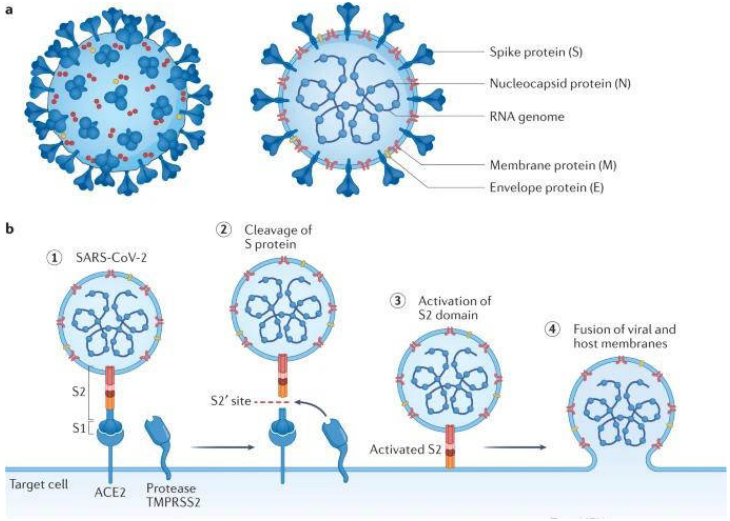


Morte per età e sesso (tassi per 100,000)

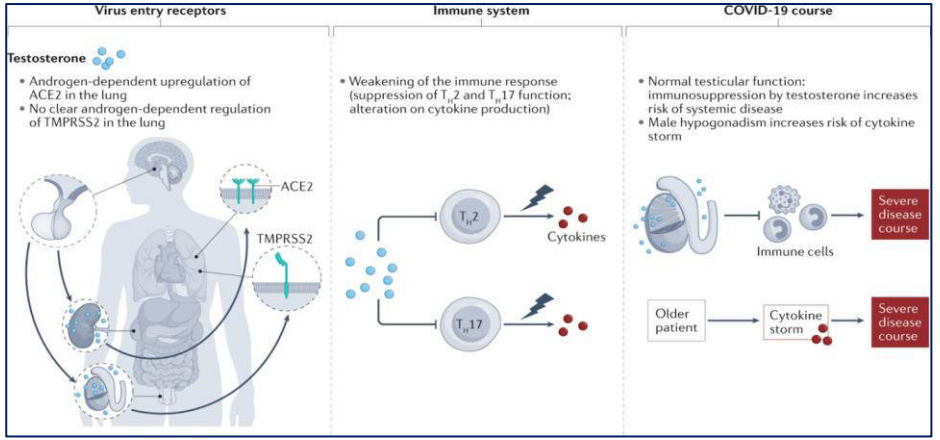


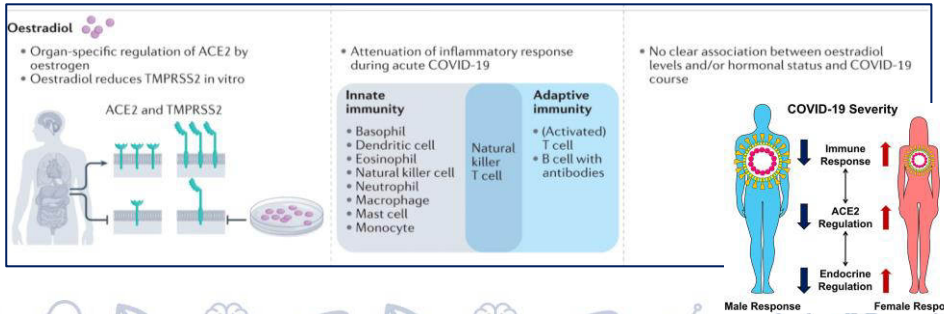
Globalhealth5050.org

Diversa Sensibilità di Genere all'Infezione da SARS-CoV-2

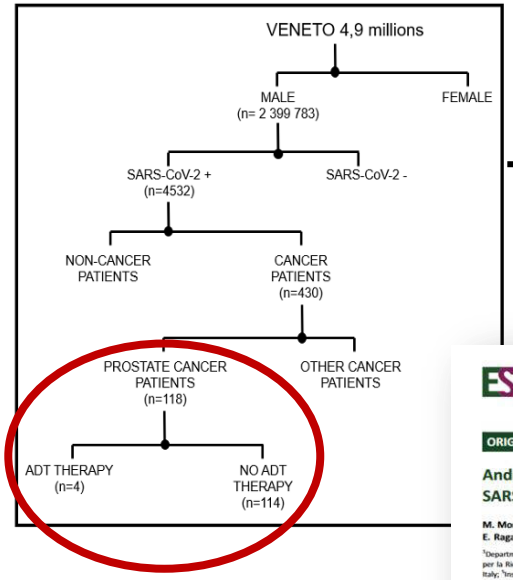


Adattato da Lamers&Haagmans,
Nat Rev Microbiol, 2022





Terapia di deprivazione androgenica (ADTS) – Infezione da SARS-COV-2



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY

ORIGINAL ARTICLE

Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532)

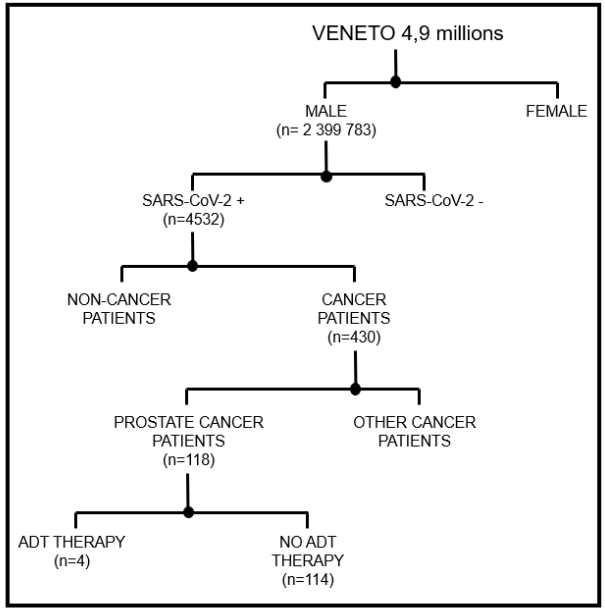
M. Montopoli[1,2], S. Zumerle[2,3], R. Vettor[4], M. Rugge[3,4], M. Zorzi[5], C. V. Catapano[6], G. M. Carbone[6], A. Cavalli[6], F. Pagano[7], E. Ragazzi[1], T. Prayer-Galetti[7] & A. Alimonti[2,3,5,8]*

[1]Department of Pharmaceutical and Pharmacological Sciences, Università degli Studi di Padova, Padova; [2]IIMM – Veneto Institute of Molecular Medicine, Fondazione per la Ricerca Biomedica Avanzata, Padova; [3]Department of Medicine, Università degli Studi di Padova, Padova; [4]Veneto Tumour Registry – Azienda Zero, Padova, Italy; [5]Institute of Oncology Research, Oncology Institute of Southern Switzerland, Università della Svizzera Italiana, Bellinzona; [6]Institute for Research in Biomedicine, Università della Svizzera Italiana, Bellinzona, Switzerland; [7]Department of Oncological and Gastroenterological Sciences – Urology Unit, Azienda Ospedaliera di Padova, Padova, Italy; [8]Department of Health Sciences and Technology, ETH Zürich, Zurich, Switzerland

Available online 6 May 2020

Montopoli et al., Ann Oncol 2020

Terapia di deprivazione androgenica (ADTS) – Infezione da SARS-COV-2



Montopoli et al., Ann Oncol 2020

Table 3. Epidemiological characteristics of prostate cancer patients with confirmed SARS-CoV-2 infection in Veneto, treated with or without androgen-deprivation therapy

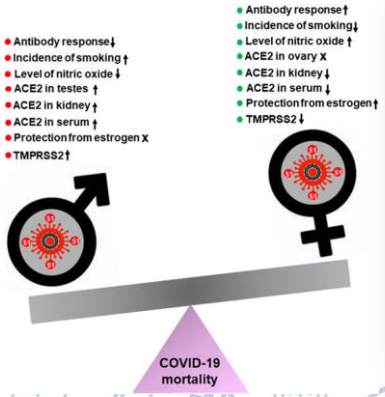
	PCa in ADT	PCa non-ADT	OR (95% CI)	Other tumors	OR (95% CI)
Cancer patients in Veneto Region population	5273	37 161[a]		84934[a]	
Total no. of SARS-CoV-2-positive	4	114	4.05 (1.55–10.59) $P = 0.0043$	312	4.86 (1.88–12.56) $P = 0.0011$
Mild disease	3	83	3.93 (1.31–11.77) $P = 0.0144$	223	4.62 (1.56–13.69) $P = 0.0057$
Non-hospitalized	1	7		9	
Hospitalized	2	76		214	
Severe disease	1	31	4.40 (0.76–25.50) $P = 0.0982$	89	5.53 (0.97–31.58) $P = 0.0544$
Intensive care (ICU)	1	13		32	
Deceased	0	18		57	
Estimated total SARS-CoV-2-positive cases/100 000	76	307		367	

PCa patients with ADT were considered as reference for OR calculation. Patients are presented referring to the degree of infection severity.
ADT, androgen-deprivation therapy; CI, confidence interval; OR, odds ratio; PCa, prostate cancer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a] Prevalent cancer patients' data are as of January 1st, 2016 (source: Veneto Tumor Registry. Available at https://gecoopendata.registrotumoriveneto.it/prevalenza.php?lang=EN).

La terapia di deprivazione androgenica è associata ad una riduzione dei casi di infezione da SARS-CoV-2 in pazienti affetti da tumore prostatico

Modulazione dei recettori degli estrogeni e COVID-19

	SARS-CoV-2 positivity		Hospitalization		Death	
Anti-estrogenic therapy	POR°	90% CI	POR°	90% CI	POR°	90% CI
None*	1.00	-	1.00	-	1.00	-
Any	0.75	0.54 - 1.04	0.90	0.49 - 1.66	0.88	0.40 - 1.92
Selective estrogen receptor modulators, degraders or down-regulators	0.42	0.21 - 0.83	0.59	0.16 - 2.21	0.55	0.08 - 3.81
Aromatase inhibitors	0.86	0.61 - 1.22	1.11	0.58 - 2.15	0.99	0.43 - 2.24
LHRH agonists	0.76	0.27 - 2.16	-§		-§	



EXSCALATE 4COV

RALOXIFENE

Effetto antivirale di Raloxifene e SERM

J Hepatol. 2012 Dec;57(6):1186-92. doi: 10.1016/j.jhep.2012.08.003. Epub 2012 Aug 10.

Raloxifene hydrochloride is an adjuvant antiviral treatment of postmenopausal women with chronic hepatitis C: a randomized trial.

Furusyo N[1], Ogawa E, Sudoh M, Murata M, Ihara T, Hayashi T, Ikezaki H, Hiramine S, Mukae H, Toyoda K, Taniai H, Okada K, Kainuma M, Kajiwara E, Hayashi J.

FEBS Open Bio 2 (2012) 279–283

ELSEVIER

FEBS openbio

journal homepage: www.elsevier.com/locate/febsopenbio

Raloxifene inhibits hepatitis C virus infection and replication

Midori Takeda[a,1], Masanori Ikeda[a,*,1], Kyoko Mori[a], Masah
Takaji Wakita[b], Nobuyuki Kato[a]

[a]Department of Tumor Virology, Okayama University Graduate School of Medicine, Dentistry, and Ph
[b]Department of Virology II, National Institute of Infectious Disease, Tokyo 162-8640, Japan

Microbes Infect. 2013 Jan;15(1):45-55. doi: 10.1016/j.micinf.2012.10.003. Epub 2012 Oct 23.

Selective estrogen receptor modulators inhibit hepatitis C virus infection at multiple steps of the virus life cycle.

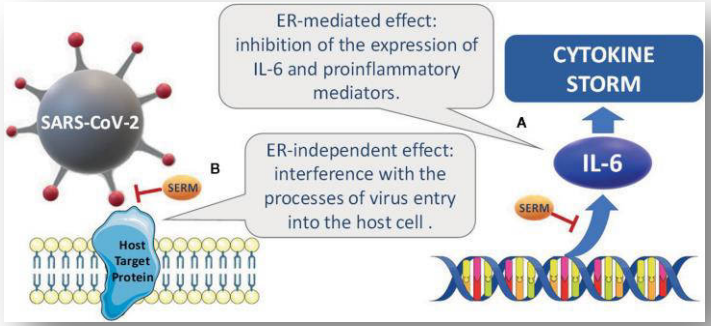
Murakami Y[1], Fukasawa M, Kaneko Y, Suzuki T, Wakita T, Fukazawa H.

BMB Reports Online
http://www.bmbreports.org

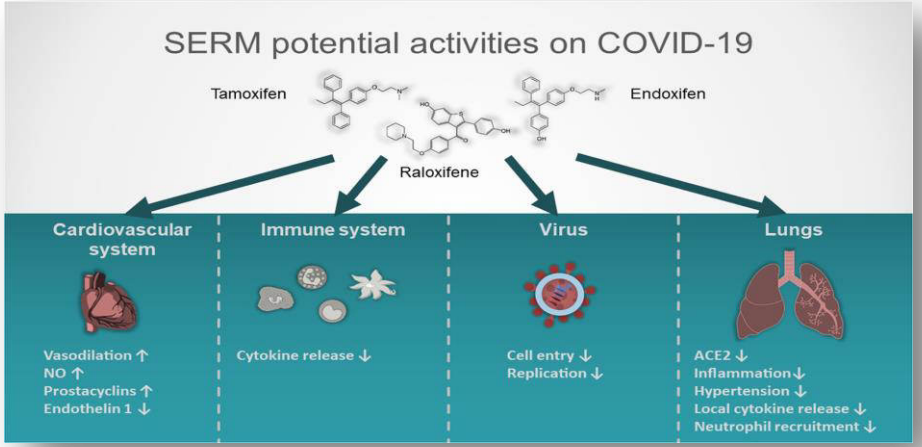
Antiviral activity of sertindole, raloxifene and ibutamoren against transcription and replication-competent Ebola virus-like particles

Yi-Seul Yoon, Yejin Jang, [...], and Meehyein Kim

Meccanismi dei SERMs

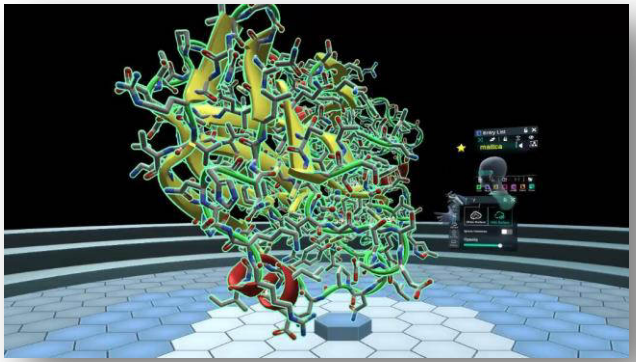


Calderone et al., Front in Pharma, 2020



Allegretti et al., Cell death and dis, 2021

Proteina SPIKE e Recettori Estrogenici



SCIENCE ADVANCES | RESEARCH ARTICLE

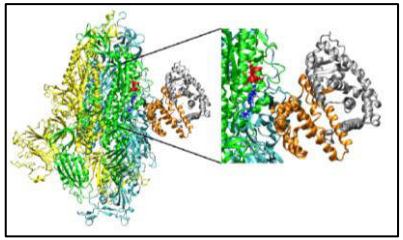
CORONAVIRUS

The SARS-CoV-2 spike protein binds and modulates estrogen receptors

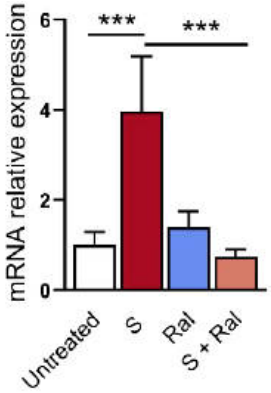
Oscar Solis[1], Andrea R. Beccari[2], Daniela Iaconis[2], Carmine Talarico[2], Camilo A. Ruiz-Bedoya[3,4,5], Jerome C. Nwachukwu[6], Annamaria Cimini[7,8], Vanessa Castelli[7], Riccardo Bertini[9], Monica Montopoli[10,11], Veronica Cocetta[10], Stefano Borocci[12], Ingrid G. Prandi[12], Kelly Flavahan[3,4,5], Melissa Bahr[3,4,5], Anna Napiorkowski[3,4,5], Giovanni Chillemi[12], Masato Ooka[13], Xiaoping Yang[14], Shiliang Zhang[15], Menghang Xia[13], Wei Zheng[13], Jordi Bonaventura[16], Martin G. Pomper[17], Jody E. Hooper[18], Marisela Morales[15], Avi Z. Rosenberg[14], Kendall W. Nettles[6], Sanjay K. Jain[3,4,5], Marcello Allegretti[19]*, Michael Michaelides[1,20]*

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein binds angiotensin-converting enzyme 2 as its primary infection mechanism. Interactions between S and endogenous proteins occur after infection but are not well understood. We profiled binding of S against >9000 human proteins and found an interaction between S and human estrogen receptor α (ERα). Using bioinformatics, supercomputing, and experimental assays, we identified a highly conserved and functional nuclear receptor coregulator (NRC) LXD-like motif on the S2 subunit. In cultured cells, S DNA transfection increased ERα cytoplasmic accumulation, and S treatment induced ER-dependent biological effects. Non-invasive imaging in SARS-CoV-2–infected hamsters localized lung pathology with increased ERα lung levels. Postmortem lung experiments from infected hamsters and humans confirmed an increase in cytoplasmic ERα and its colocalization with S in alveolar macrophages. These findings describe the discovery of a S-ERα interaction, imply a role for S as an NRC, and advance knowledge of SARS-CoV-2 biology and coronavirus disease 2019 pathology.

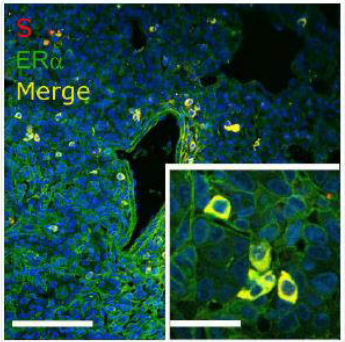
Proteina SPIKE e Recettori Estrogenici

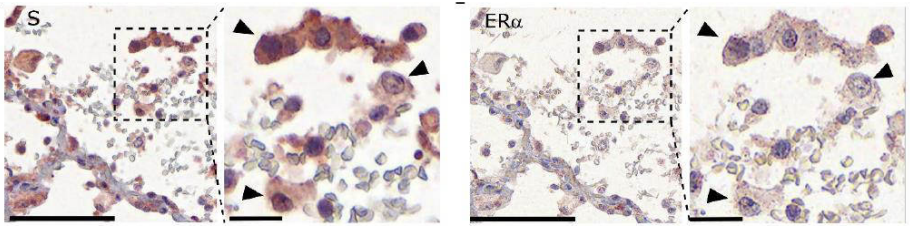


Spike protein – ERα interazione



Attivazione del signaling con espressione di targets (ACE2)





S-ERα co-localizzazione in tessuto polmonare di criceto e umano (in macrofagi)

Solis et al, Science Advances, 2022

Proteina SPIKE e Coagulopatia

Relevance of the viral Spike protein/cellular Estrogen Receptor-α interaction for endothelial-based coagulopathy induced by SARS-CoV-2

Silvia Barbieri[1, #], Franca Cattani[2, #], Leonardo Sandrini[1], Magda Maria Grillo[1], Carmine Talarico[3], Daniela Iaconis[3], Lucia Lione[4], Erika Salvatori[4], Patrizia Amadio[1], Gloria Garoffolo[1], Mariano Maffei[2], Francesca Galli[2], Andrea Rosario Beccari[3], Emanuele Marra[4], Marica Zoppi[1], Michael Michaelides[5,6], Giuseppe Roscilli[4], Luigi Aurisicchio[4], Riccardo Bertini[7], Marcello Allegretti[2, *] and Maurizio Pesce[1, *]

Proteina SPIKE e LONG-Covid

JOURNAL ARTICLE EDITOR'S CHOICE

Persistent Circulating Severe Acute Respiratory Syndrome Coronavirus 2 Spike Is Associated With Post-acute Coronavirus Disease 2019 Sequelae

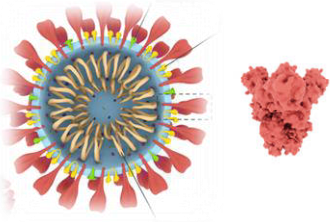
Zoe Swank, Yasmeen Senussi, Zachary Manickas-Hill, Xu G Yu, Jonathan Z Li, Galit Alter, David R Walt ✉ Author Notes

Clinical Infectious Diseases, Volume 76, Issue 3, 1 February 2023, Pages e487–e490, https://doi.org/10.1093/cid/ciac722

Conclusioni

- ✓ Ruolo degli **ormoni sessuali**

- ✓ **SERM**



- ✓ **Proteina Spike**

UNIVERSITÀ DEGLI STUDI DI PADOVA

CONFCOMMERCIO IMPRESE PER L'ITALIA ASCOM PADOVA

Fondazione Cassa di Risparmio di Padova e Rovigo

INTESA SANPAOLO

AIRC

FONDAZIONE RICERCA BIOMEDICA AVANZATA V.I.M.M.

YEARS

Dompé

AZIENDA OSPEDALIERA UNIVERSITARIA PADOVA

dsf