

Nebulized Hydroxychloroquine for COVID-19 Treatment: 80x Improvement in Breathing ^[1]

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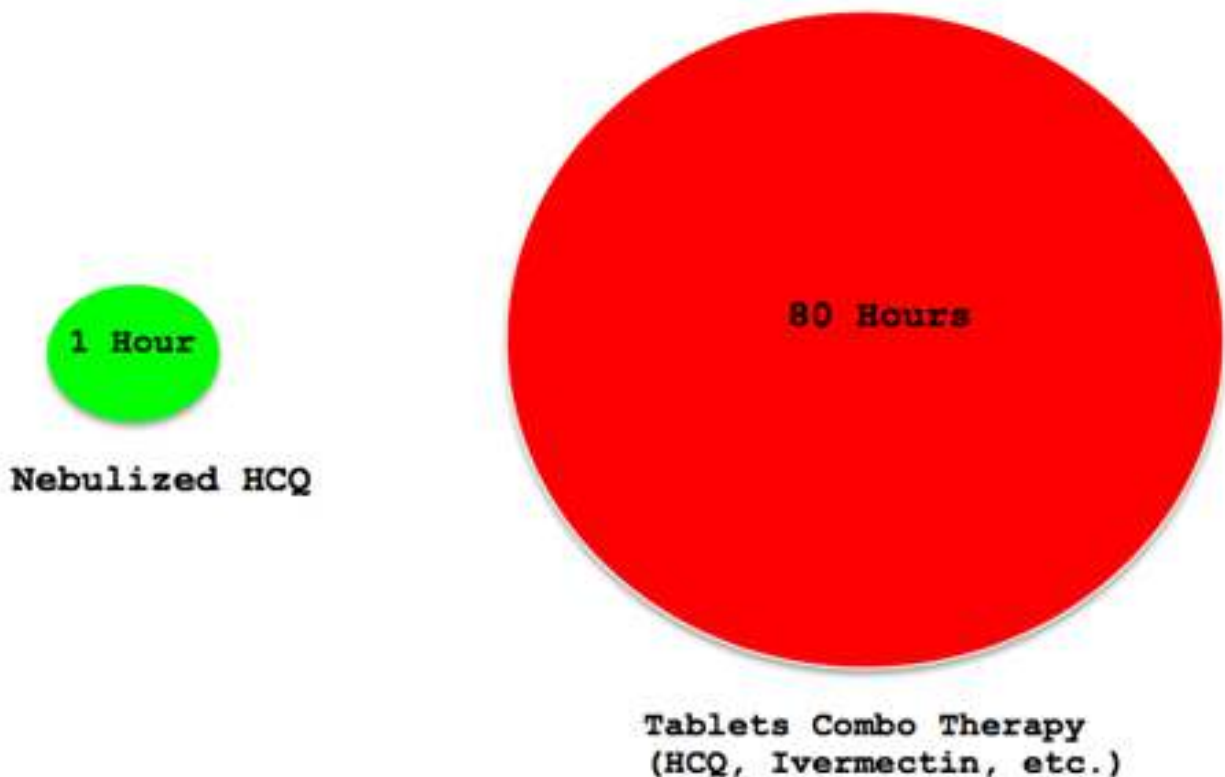
Key Priority: Radically improve breathing

Nebulized hydroxychloroquine as 150 mg HCQ in 6 ml (25 mg/ml) of isotonic sterile solution within the first five (5) days of COVID-19 symptoms (“*Nebu HCQ*”) has resulted in immediate improvement (<1 hour after use) in breathing in COVID-19 infected patients. Nebu HCQ served as **a rescue medication with an 80x improvement in time and efficiency** when compared to HCQ tablet (400-600 mg per day) combination therapy or Ivermectin combination therapy. No adverse events were reported outside of a bitter taste that quickly subsided.

The protocol used is as follows: 6 ml (25 mg HCQ per ml) per nebulizer session (15 minutes). Two sessions (12 ml total) in the first hour for patients with mild to moderate pulmonary symptoms from COVID-19.

Since March 2020, my team has successfully treated over 3,000 patients with Covid-19 with the Zelenko Protocol. Our high-risk patient survival rate was >99.3% (0.7% mortality) which represents a radical improvement when compared to national data of high-risk patients with a survival rate of 92.5% (7.5% mortality). I have provided counsel to governments, physicians and hospital networks regarding prophylaxis and prehospital care of Covid-19 and I am fully familiar with their results. Based on this real world experience and data, nebulized hydroxychloroquine significantly improves patient outcomes and should be considered as part of the armamentaria against Covid-19.

Average time of clinical improvement of pulmonary compromise precipitated by Covid 19



Covid-19 is primarily spread through the respiratory system and may result in significant pulmonary complications. Left untreated, a subset of patients will progress to acute respiratory distress syndrome (ARDS) and/or pulmonary infarcts. Oral HCQ and Ivermectin combination therapies have proven to be effective prehospital treatments of Covid-19 and its associated complications. However, treatment with oral HCQ/Ivermectin may take an average of 80 hours to achieve significant clinical improvement as well as 3-7 days to achieve optimal alveolar concentration of medication.^[3]

Nebu HCQ administered as microdroplets directly to the lungs achieves optimal alveolar concentration in approximately one (1) hour and is associated with faster clinical improvement, reduction in pulmonary complications and a reduction in medical costs. The clinical data presented in this paper was generated through the routine practice of medicine and is considered “Real World Evidence” according to the 21st Century Cures Act.^[4]

Key Clinical Data Points for Nebu HCQ

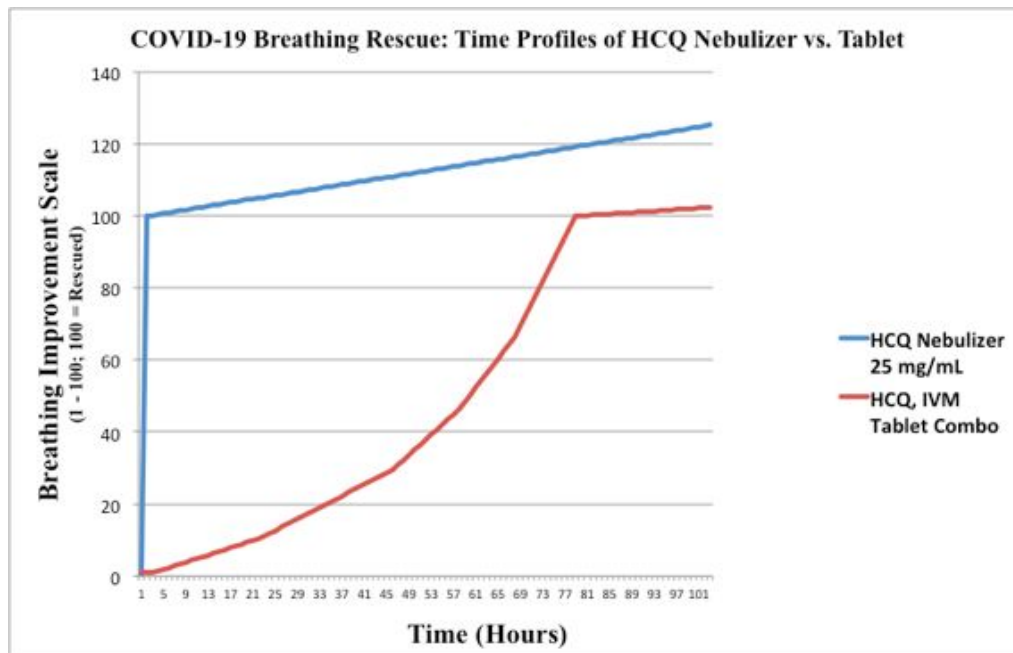
- 150mg HCQ (2 ampules - each ampule contains 3ml of HCQ (25mg/ml) (6ml in total)) was administered over 15 minutes via nebulizer. Patients were then clinically reevaluated after 30 minutes. If deemed clinically necessary, an additional 150mg of HCQ (2 ampules (25mg/ml) (6ml in total)) was administered. Treatment was well tolerated. Patients were then again clinically reevaluated after 30 minutes and again after two days either virtually or in an outpatient setting.
- 95% of COVID-19 and suspected COVID-19 patients (20/21) suffering from pulmonary symptoms responded positively to treatment with Nebu HCQ.
 - Positive patient response is defined as having significant improvement in breathing within a short period of time after the first Nebu HCQ session - measured by spirometer and/or medical practitioner assessment before and after use.
 - 95% of patients breathing improved within one (1) hour of the first Nebu HCQ session, a significant improvement over steroids (Budesonide inhalation and Dexamethasone tablets), which take approximately 24 hours for breathing to improve.
- Spirometry data showed a 29% median improvement in breathing after one (1) hour of nebulizer treatment.
- Fifteen (15) patients used the Nebu HCQ for post-exposure prophylaxis (PEP) after known exposure to COVID-19. To date, none developed COVID-19 symptoms.
- For safety reasons, patients were monitored for heart rate, blood pressure, pulse, EKG and clinical changes. The dosage noted above was well tolerated in all patients with no adverse events except for a bitter taste in the mouth which resolved quickly.
- No hospitalizations or deaths occurred in any of the patients treated with Nebu HCQ. The median age for patients treated with Nebu HCQ was 63.5 years old.
- Clinical dose response was generally equal among patients regardless of demographic (age, comorbidities, etc.)

Nebu HCQ Patient Demographics

- Patients were risk stratified and only high risk patients were treated with Nebu HCQ.
- Risk stratification included: Age, Health Worker, Factor XI deficiency, Myocarditis, Obesity, Hypertension, Diabetes, Gout, History of Cancer, Crohn's disease, Hypotension, Hypertension, CVD, COPD, Lung Disease, Kidney Disease, Sleep Apnoea, Thyroid Disease, Osteoporosis, MS, Cardiac History.
- Nebu HCQ patients were additionally treated with various oral medications: Azithromycin, Doxycycline, Prednisone, Dexamethasone, Motrin/Tylenol, Zinc , Vitamins C and D, and Quercetin.
- Symptoms from high risk patients included: Fever, hypoxia, shortness of breath, loss of taste and/or smell, weakness, cough, headache, rhinorrhea, myalgia, diarrhea, and/or chest tightness.

Additional data is being collected in more patients as Nebu HCQ is being used by other physicians/patients in the USA and internationally. Initial analysis indicates results consistent with the foregoing data.

Mechanism - Time and Dose



Clinical outcomes of breathing rescue based on Real World Evidence of high risk COVID-19 symptomatic patients. 6 mL per nebulizer session.

Clinical outcomes of breathing rescue based on Real World Evidence of high risk COVID-19 symptomatic patients. 6 ml per nebulizer session.

HCQ utility against COVID-19 is time and dose dependent. The main issue is the time it takes for the proper HCQ dose to reach the lungs. The protocol used prior to the development of Nebu HCQ was HCQ tablets (200 mg twice daily) with zinc sulfate capsules (220 mg once daily) and azithromycin capsules (500 mg once daily).

The unusual pharmacology of HCQ presents a key limitation of tablets as only approximately 1 - 2% of HCQ will reach the lung as the tablets must be ingested and traverse the digestive system until a small portion goes into the bloodstream and eventually a smaller portion reaches the respiratory system.^[5] Once a patient is infected, to reduce COVID-19 pulmonary complications 3-7 days of tablet ingestion is needed. To prevent patient infections as a prophylaxis, 5-10 days of tablet ingestion is needed to obtain antiviral tissue concentrations.^[6] These time periods are difficult to accelerate with HCQ oral tablet ingestion because of safety concerns and limitations on the maximum daily dosage.

Nebu HCQ, that is, isotonic HCQ solution delivered via nebulizer as aerosolized microdroplets, rapidly boosts HCQ potency in lung and respiratory tissue and achieves in approximately one (1) hour the lung tissue concentration equivalent to that accrued over 3-7 days of HCQ oral tablet ingestion.^[7] Nebu HCQ rapidly brings high tissue concentrations of HCQ into the lungs and airways, with significantly less overall HCQ exposure to the body when compared to oral HCQ.

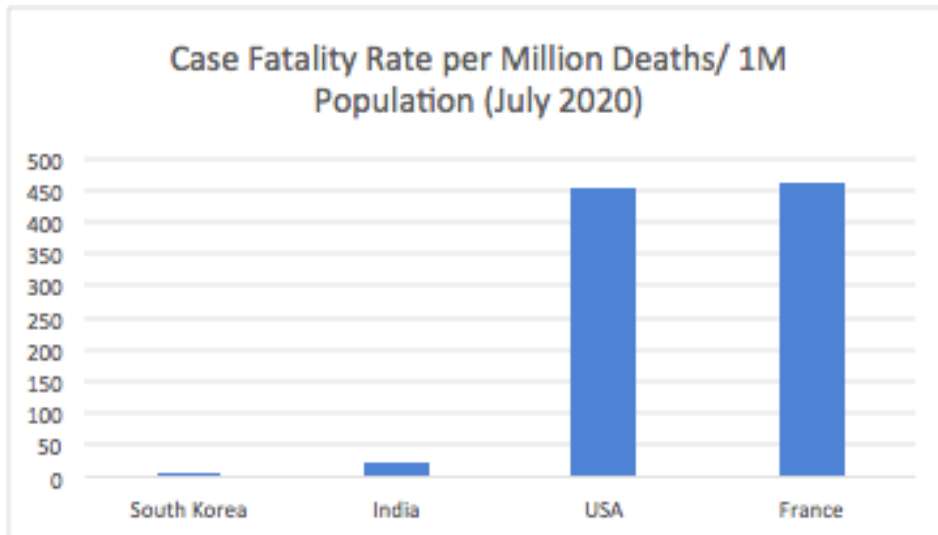
HCQ in its natural alkaline molecular form diffuses freely across cell membranes and is sequestered as protonated conjugates in acidic cellular organelles (e.g. endosomes). Such organelles are abundant in lung tissue and in alveolar cells in particular.^[8] Consequently, even when administered orally or intravenously, these agents will accumulate in lung tissue in higher concentrations, 100-fold or greater, than in plasma.^[9]

Nebu HCQ provides highly efficient sequestration of HCQ as protonated molecular conjugates in alveolar organelles. Approximately 90% of HCQ in microdroplets reaching the lungs will be sequestered in the alveoli resulting in an approximate 80x concentration boost as compared to tablets.^[10] This was clinically confirmed as patients had pulmonary function improvement within one (1) hour of use as compared to approximately 80 hours of oral HCQ.

Mechanism - Inflammation

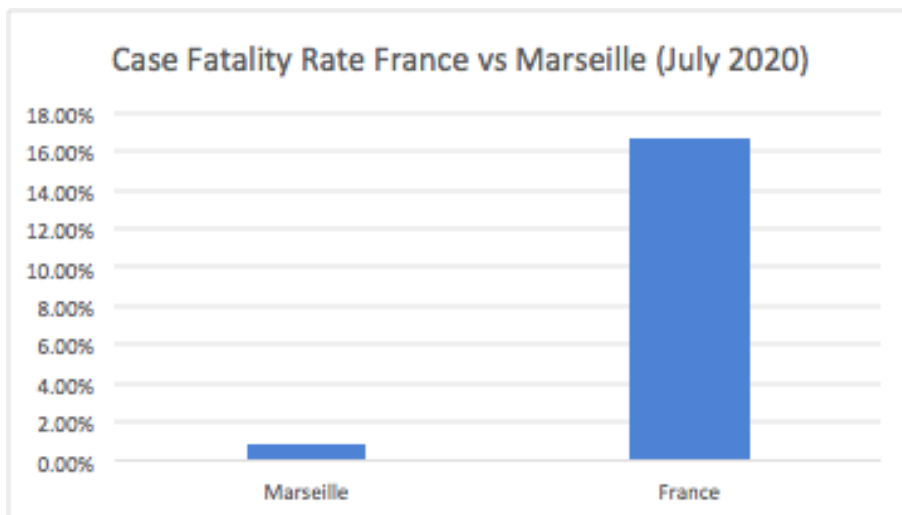
HCQ suppresses pro-inflammatory cytokines including TNF- α , IL-1 β and IL-6, as widely applied in their treatment of autoimmune conditions.^[11] As the release of these same inflammatory cytokines are behind ARDS, HCQ offers further clinical benefits by mitigating this key cause of COVID-19 morbidity. This can be seen in geographies in which HCQ tablets are

used against COVID-19 (e.g. South Korea, India) vs. geographies in which HCQ use against COVID-19 is restricted (e.g. USA, France).^[12]



Source: <https://www.worldometers.info/coronavirus/>

Didier Raoult MD PhD from IHU hospital in Marseille, France is considered one of the world's leading infectious disease specialists and the most cited microbiologist in Europe, uses HCQ aggressively against COVID-19. The French government banned the use of HCQ to treat COVID-19. Dr. Raoult ignored the ban and continued to treat his patients with the HCQ combination therapy, while the rest of France abided by the ban. As of July 2020, the fatality rate of Dr. Raoult's patients (>3000) was less than 1% whereas the rest of France had a case fatality rate of more than 15%.^[13]



Source: <https://www.worldometers.info/coronavirus/> and <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7315163/>

Indications beyond COVID-19

The immunomodulatory effects of HCQ oral tablets are useful in the treatment of several lung conditions, including interstitial lung disease, sarcoidosis and fibrosis.^[14] There are also indications that oral HCQ has positive effects on patients with influenza, asthma and smoker's cough. Since Nebu HCQ resulted in immediate improvement in breathing for COVID-19 patients, using Nebu HCQ to treat these other respiratory conditions should be promptly investigated.

Supply

There are HCQ supply concerns due to its wide utility against various conditions (e.g. auto-immune, cancer, etc.). Because of the widespread nature of COVID-19, it has proven difficult to scale HCQ production to meet the world's supply needs in a cost efficient fashion. This has led to significant governmental restrictions on HCQ as well as price gouging.

Nebu HCQ achieves a ~ 10x reduction in need, based on each patient needing an exponentially smaller dosage due to direct application to the lung and respiratory system. Therefore, the exponential reduction in required per patient HCQ dosage has significant positive implications for supply concerns.

It is likely that the adoption and widespread use of Nebu HCQ in the outpatient setting will significantly reduce mortality and transmission of COVID-19 at a reduced cost.

Compounding

Many US-based physicians provide nebulization treatments as an off-label usage of FDA-approved drugs.^[15] US FDA policy states that healthcare providers may prescribe an FDA-approved drug "for an unapproved use when they judge that it is medically appropriate for their patient."^[16] Such an unapproved use could include being "given in a different way, such as when a drug is approved as a capsule, but it is given instead in an oral solution." In practice, as determined from an analysis of representative data from 2001, out of 150 million prescriptions in the US, accounting for about 56% of all estimated drug use, 21% were off-label.^[17]

Innovation

Dr. Zelenko notes that ACE2 Technology LLC ("ACE2") developed Nebu HCQ and that Dr. Zelenko is a consultant to ACE2. Nebu HCQ and its method of use are the subject of US patent

filing number 63034025 and other international filings. For further information, please contact: ACE2 Technology LLC c/o Gary S. Greenstein ESQ PC., gary@ggtechlaw.com.

Disclaimer

This white paper is for informational purposes only for medical professionals.

^[1] R. Derwand, M. Scholz, V. Zelenko. COVID-19 outpatients: early risk-stratified treatment with zinc plus low-dose hydroxychloroquine and azithromycin: a retrospective case series study *Int J Antimicrob Agents* (October) (2020), p. 106214, 10.1016/j.ijantimicag.2020.106214

^[2] Email: zev@VladimirZelenkoMD.com. Vladimir Zelenko MD is a board certified physician in the state of New York, inventor of the Zelenko Protocol. He has provided counsel to the White House, governments on four (4) different continents, thousands of physicians, celebrities and nursing homes amongst others regarding his 99.3% success rate in prevention and treatment of COVID-19 in high risk patients. His work has been peer reviewed and published with eminent physicians.

^[3] Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020. Yeo LY, Friend JR, McIntosh MP, Meeusen EN, Morton DA. Ultrasonic nebulization platforms for pulmonary drug delivery. *Expert Opin Drug Deliv*. 2010;7(6).663-679. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of beta2-agonist particle size. *Am J Respir Crit Care Med*. 2005;172(12).1497-1504. O'Callaghan C, Barry PW. The science of nebulised drug delivery. *Thorax*. 1997;52 Suppl 2.S31-44. Figure Schuepp KG, Devadason SG, Roller C, et al. Aerosol delivery of nebulised budesonide in young children with asthma. *Respir Med*. 2009;103(11).1738-1745. (about 50% deposited in lungs for children who were not crying during the nebulizer session). McChesney EW, Conway WD, Banks WF, Jr., Rogers JE, Shekosky JM. Studies of the metabolism of some compounds of the 4-amino-7-chloroquinoline series. *J Pharmacol Exp Ther*. 1966;151(3).482-493.

^[4] 21st Century Cures Act, Section 3022. H.R. 34, 114th Congress. 2016. <https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf>. Section 3022 of the Cures Act, defines Real World Evidence as: “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials ... including ongoing safety surveillance, observational studies, registries, claims, and patient-centered

outcomes research activities...” The Cures Act goes on to state Real World Evidence may support new indications for generic drugs. There is very significant Real World Evidence that supports the approval of using generic drugs to effectively treat COVID-19 in the outpatient setting.

[5] McChesney EW, Conway WD, Banks WF, Jr., Rogers JE, Shekosky JM. Studies of the metabolism of some compounds of the 4-amino-7-chloroquinoline series. *J Pharmacol Exp Ther.* 1966;151(3).482-493.

[6] Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis.* 2020.

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[8] Kaufmann AM, Krise JP. Lysosomal sequestration of amine-containing drugs: analysis and therapeutic implications. *J Pharm Sci.* 2007;96(4).729-746. Van der Velden JL, Bertoncetto I, McQualter JL. LysoTracker is a marker of differentiated alveolar type II cells. *Respiratory Research.* 2013;14(1).123.

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^[10] Scheim, Nebulized hydroxychloroquine plus oral azithromycin for COVID-19 treatment: from days to hours for optimal lung tissue concentrations and viral immobilization (2020). David Scheim PhD is a commissioned officer in the US Public Health service, inactive reserve and earned his PhD from MIT. He developed the clinical/genetic tracking software for the eyeGENE system, NEI, NIH, and proposed the use of sodium thiosulfate for preventing hearing loss with high-dose carboplatin treatment of brain tumors, now in clinical use worldwide. He has significant experience in drug repurposing.

Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6:16. McChesney EW, Shekosky JM, Hernandez PH. Metabolism of chloroquine-3-14C in the rhesus monkey. *Biochemical Pharmacology*. 1967;16(12):2444-2447. McChesney EW, Conway WD, Banks WF, Jr., et al. Studies of the metabolism of some compounds of the 4-amino-7-chloroquinoline series. *J Pharmacol Exp Ther*. 1966;151(3):482-493.

^[11] See Footnote 11, Scheim.

^[12] <https://www.worldometers.info/coronavirus/> (last visited January 4, 2020)

^[13] Raoult, et. al., Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis, *Travel Med Infect Dis*. 2020 July-August. Compared to France, <https://www.worldometers.info/coronavirus/> as of July 2020.

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^[15] Luyt CE, Brechot N, Combes A, et al. Delivering antibiotics to the lungs of patients with ventilator-associated pneumonia: an update. *Expert Rev Anti Infect Ther.* 2013;11(5).511-521.

^[16] US Food and Drug Administration: Understanding Unapproved Use of Approved Drugs "Off Label".

<https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label>.

^[17] Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med.* 2006;166(9).1021-1026. Stafford RS. Regulating Off-Label Drug Use — Rethinking the Role of the FDA. *New England Journal of Medicine.* 2008;358(14).1427-1429.