



# Hydroxychloroquine及Chloroquine 使用於COVID-19治療建議修正

臺北市立聯合醫院教研部  
林政宜教學主治醫師  
教學主治醫師群  
邱婷芳主任  
璩大成副總院長

# H(CQ)對COVID-19治療建議修正

- 美國FDA取消自3/28/2020起對H(CQ)使用於COVID-19治療的緊急使用授權(EUA)
- 此決定源自於，
  1. 依目前建議劑量無法達到抗病毒效益
  2. 之前H(CQ)使病毒量下降的實驗結果無法被複製，且最近的隨機對照研究顯示HCQ與標準治療間無RT-PCR陰轉差異
  3. 目前US treatment guideline並不允許臨床測試外治療用，NIH guideline亦同
  4. 大型隨機對照研究顯示無論對死亡率或其他臨床指標如住院時間或呼吸器使用等無助益。

# H(CQ)研究整理

TABLE 1: Publications Relevant to Viral Shedding<sup>17</sup>

Article (design)	Comparison groups (n)	Viral shedding outcomes
Tang W, et al <i>BMJ</i> (randomized, open-label, stopped early)	HCQ 1200 mg/day x 3 d then 800 mg/day to complete 2-3 weeks plus standard of care (75) SOC alone (75)	53 HCQ and 56 SOC PCR(-) “well before” day 28 endpoint; K-M “probability of negative conversion” by 28 days reported as “similar”; median time to (-) 8 and 7 days respectively; proportion (-) “similar” at multiple time points
Huang M, et al <i>J Mol Cell Biol</i> (randomized, 2 antiviral arms)	CQ 500 mg bid x 10 d (10) Lopinavir/ritonavir (12)	All CQ patients PCR(-) by day 13, 11 of 12 L/r patients PCR(-) by day 14; authors say CQ PCR(-) % “slightly higher” on some days
Chen X, et al medRxiv preprint (retrospective, observational)	Retrospective analysis of multiple interventions (CQ in 25 of 284 on page 7, 28 on page 9; also steroids, L/r, arbidol, oseltamivir)	CQ (and other antivirals) not associated with improvement in viral clearance; median 6 days from admission in 121 on no antivirals, 7 days in 17 patients receiving CQ without other antivirals
Mallat J, et al medRxiv preprint (retrospective, observational)	HCQ 400 mg/day (21) Non-HCQ (13)	Median time to (-) PCR 17 days HCQ, 10 days non-HCQ; 14/23 HCQ, 10/11 controls (-) day 14
Huang M, et al medRxiv preprint (prospective, observational)	CQ Phosphate 500 mg (300 mg base) once or twice daily until (-) (233 but analyzed only 197 who “completed”) Historical controls (192 “collected”; 176 analyzed)	Median time to (-) PCR 3 days CQ, 9 days controls; 91% and 94-96% CQ, 57% and 80% controls (-) at days 10 and 14; 3 CQ patients “re-positive” after discharge
Article (design)	Comparison groups (n)	Viral shedding outcomes
Shabrawishi M, et al medRxiv preprint (retrospective, observational)	HCQ (any dose) ± AZI/other AV (45) Supportive care (48) (excluded those transferred to ICU or isolation facility while still PCR(+))	No significant difference in time to first (-) PCR or proportion (-) by 5 or 12 days (median 3 days from treatment start, 33 by 5 days and 38 by 12 days in each group)
Kim M, et al medRxiv preprint (retrospective, observational)	HCQ 200 mg bid + antibiotics (22) Lopinavir/ritonavir + antibiotics (35) Conservative treatment (40)	Hazard ratio for time to viral clearance 0.49 for HCQ/antibiotics (mean 15.3 days) versus L/r plus antibiotics (mean 19.1 days), 0.44 for HCQ/antibiotics versus conservative treatment (20.7 days)
Hraiech S, et al <i>Ann Intensive Care</i> (retrospective, observational)	HCQ 600 mg/day + AZI (17) Lopinavir/ritonavir (13) No antivirals (15)	At day 6 of treatment, PCR(-) in 3 HCQ/AZI, 5 L/r, 2 no-antivirals

由左列使用H(CQ)對於COVID-19治療的RCT顯示，證據等級最高由Tang W. et al進行，收入150位病患的隨機研究，實驗組及對照組在上下呼吸道檢體陰轉率在各時間點並無顯著差異。其餘小型隨機研究及觀察性研究結果並不一致顯示與其他組別間的差異。

# US National treatment guidelines

- NIH treatment guideline於6/11/2020更新，建議**AGAINST**對於HCQ/CQ除臨床試驗外對COVID-19病患治療。
- 英國進行的大型隨機臨床試驗(RECOVERY trial)目標收入12000位COVID-19病患，major outcome是28天內all cause mortality。主持人於6/5宣布關閉HCQ arm，原因是缺乏益處。
- 1542位使用HCQ與3132位常規治療組比較，mortality rate分別為25.7% vs 23.5%(HR: 1.11, CI: 0.98~1.26,  $p=0.10$ )，其他臨床指標如住院天數及是否需使用呼吸器亦無發現益處。

# Potential risks of HCQ/CQ

- 集合FARES(FDA Adverse Event Reporting System)，AAPCC(American Association of Poison Control Centers)及NPDS(National Poison Data System)資料庫的發現，5/6/2020的結果顯示，347位使用HCQ及38位使用CQ病人，QT prolongation是最常見副作用。其中109位出現嚴重心臟副作用，80位(73%)QT prolongation，4(4%)Torsades de Pointes，14(13%)VT/Vf，25(23%)fatal outcome。
- 另有113位(59%)病患出現非心臟嚴重副作用如Hepatitis, increased liver enzymes, hyperbilirubinemia。

# 結論

- 結合以上研究及CDC reviewer整理相關治療共11篇觀察性研究發現，各研究間endpoint存在相當不一致性，point estimate imprecise，confidence interval無顯示統計差異。
- 雖然3/28當時資料顯示HCQ/CQ治療可能有益，但隨研究資料及副作用報告累積結果已經無法確認HCQ/CQ治療符合當初緊急授權使用必要性。故於6/15取消HCQ/CQ使用於COVID-19治療的緊急授權使用(EUA)。