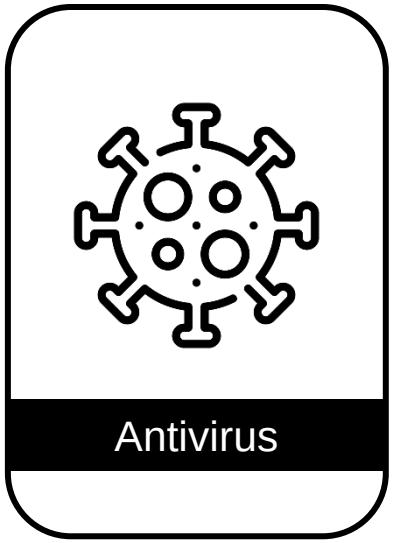
Complications of COVID-19 pharmacotherapy

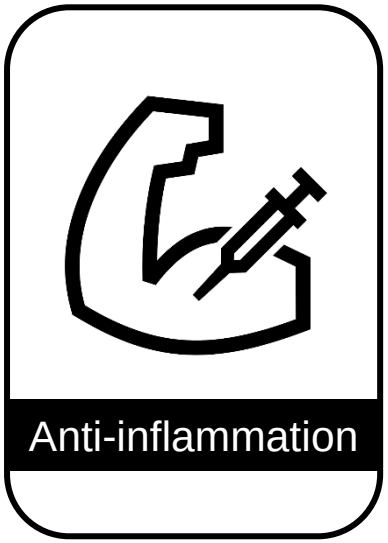
臺大醫院藥劑部
吳建志組長

20210904

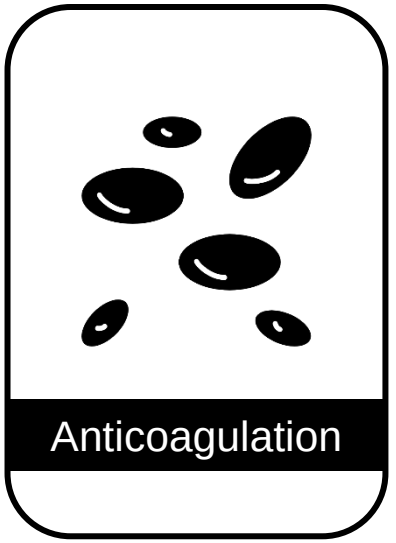
COVID-19 pharmacotherapy



Remdesivir



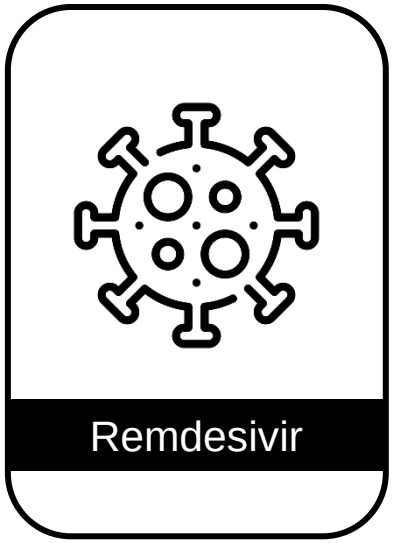
Steroid
IL-6 antagonist
JAK inhibitor



LMWH/Heparin

JAK: janus kinase inhibitor

Complications

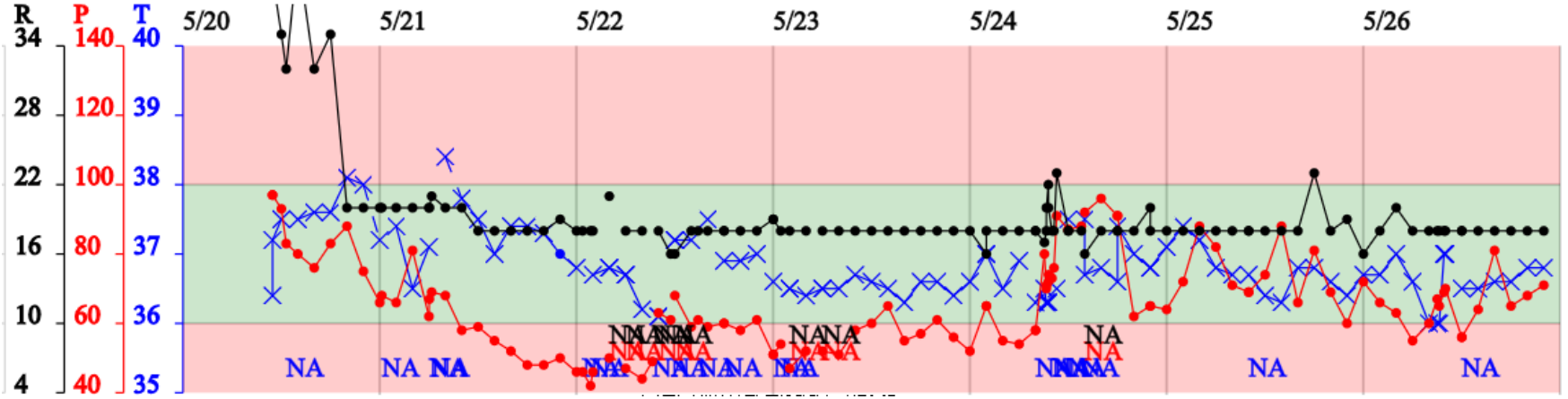


Bradycardia

Case 1

- 56 y/o female, 155 cm/64.3 kg
- PMH: DM
- Chief complain: progressive dyspnea

PMH: past medical history



▲ Intubation

Remdesivir	200mg stat, then 100mg qd
Betamethasone	6mg IV QD
Tocilizumab	▲ 480mg IF stat
Enoxaparin	40mg SC QD
Fentanyl	40mcg/hr cIF
Propofol	40mg/hr cIF
Dopamine	
Procaterol	25mcg PO BID

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Research note

Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns

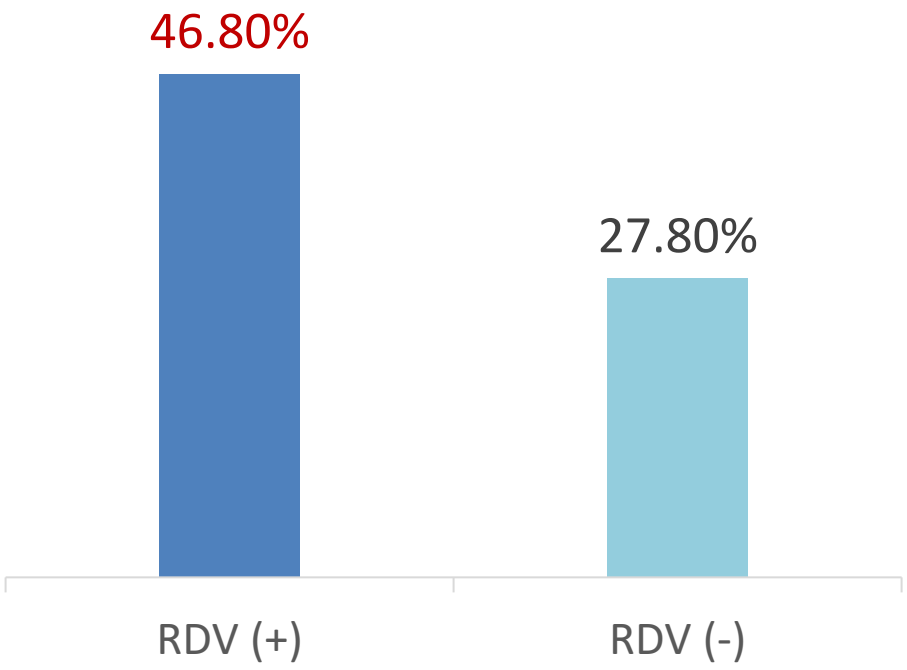
	Reporting OR (95% CI)
Primary analysis[a]	1.65 (1.23-2.22)
Restricting to severe COVID19[b]	3.52 (1.70-7.28)
Compared to hydroxychloroquine	1.73 (1.25-2.39)

a: compared to Hydroxychloroquine, tocilizumab, lopinavir/ritonavir, steroid
b: compared to tocilizumab and steroid

Median onset: 2.4 days (1-6 days)

Remdesivir treatment and transient bradycardia in patients with coronavirus diseases 2019 (COVID-19)

- 62 user vs. 79 non-user

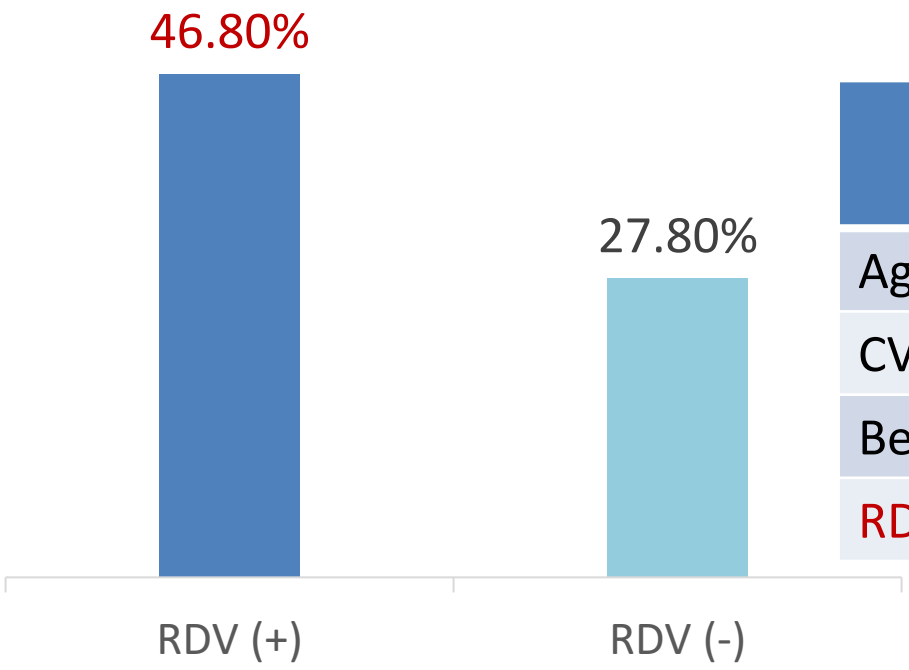


RDV: remdesivir

Journal of infection 2021;83:237-238

Remdesivir treatment and transient bradycardia in patients with coronavirus diseases 2019 (COVID-19)

- 62 user vs. 79 non-user



	Multivariate analysis OR	P
Age	1.02 (0.99 – 1.05)	0.29
CVD	1.63 (0.64 – 4.13)	0.30
Beta-blockers	0.94 (0.39 – 2.24)	0.88
RDV use	2.15 (1.05 – 4.41)	0.04*

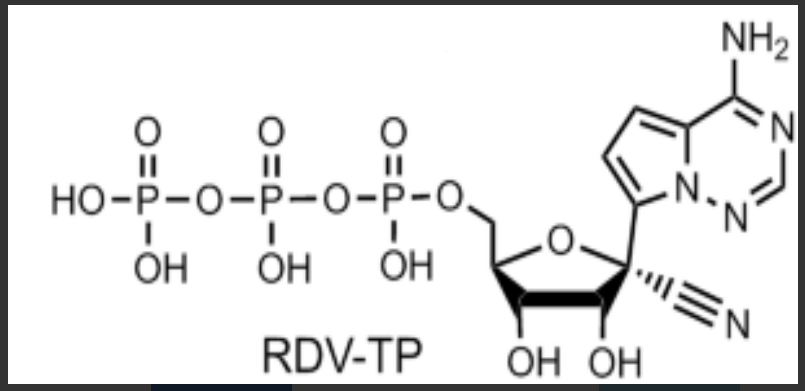
Possible mechanism: structure of RDV metabolite is similar to ATP

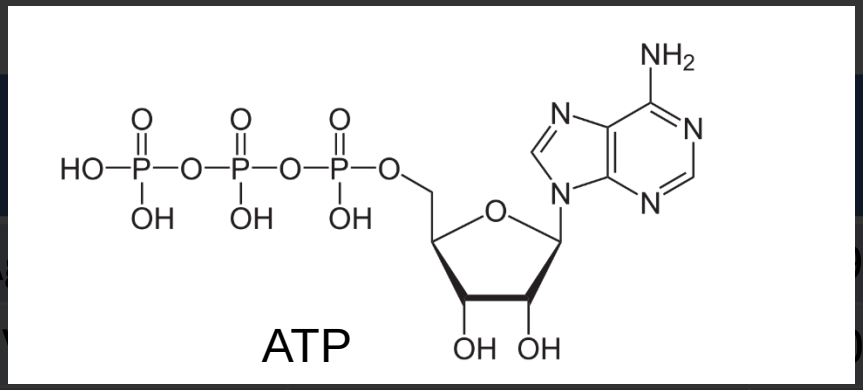
RDV: remdesivir, CVD: cardiovascular disease

Journal of infection 2021;83:237-238

Remdesivir treatment and transient bradycardia in patients with coronavirus diseases 2019 (COVID-19)

- 62 user vs. 79 non-user





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RDV use	2.15 (1.05 – 4.41)	0.04*

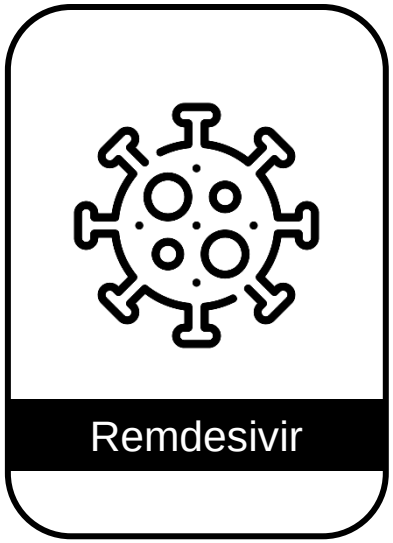
RDV (+) RDV (-)

Possible mechanism: structure of RDV metabolite is similar to ATP

RDV: remdesivir, CVD: cardiovascular disease

Journal of infection 2021;83:237-238

Special issues

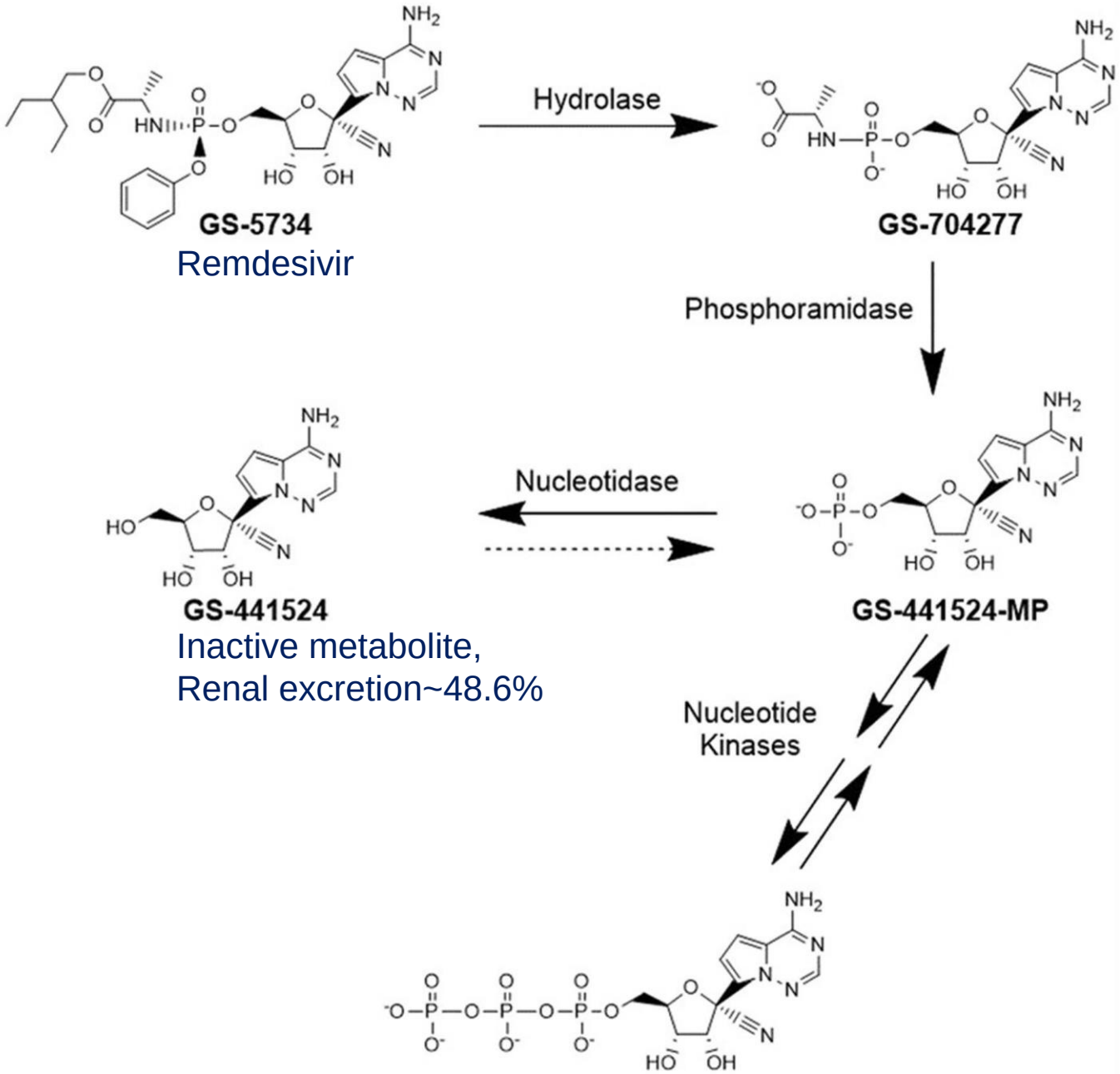


Use in ESRD

ESRD: End stage renal disease

Remdesivir in renal impairment

- eGFR <30 mL/min
  - No formal safety or pharmacokinetic data are available for patients with kidney impairment or who are receiving renal replacement therapies.
  - Manufacturer’s labeling does not recommend use
  - Significant toxicity with a short duration of therapy is unlikely. Benefits may outweigh the risks in select patients



GS-5734
Remdesivir

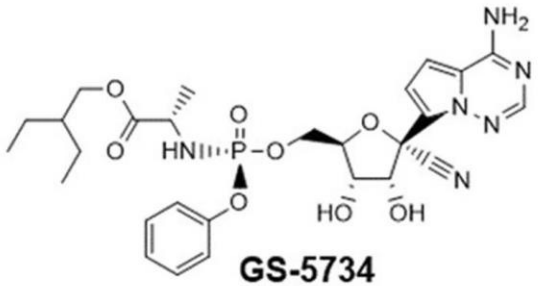
GS-704277

GS-441524
Inactive metabolite,
Renal excretion~48.6%

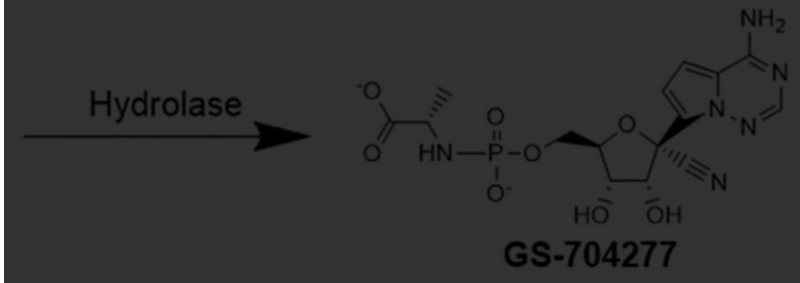
GS-441524-MP

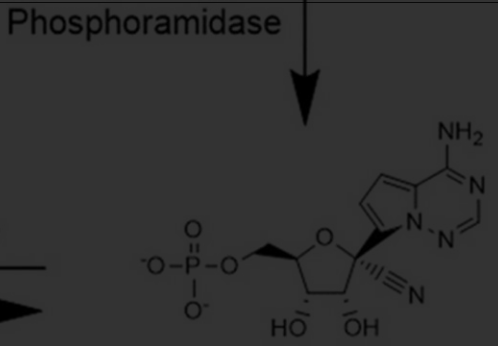
GS-443902 Active form

Clin Pharmacokinet 2021;60(5):569-83



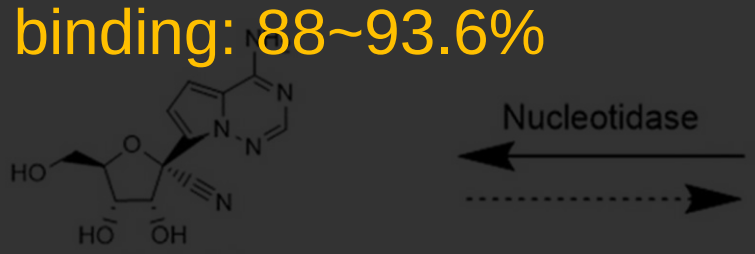
Remdesivir





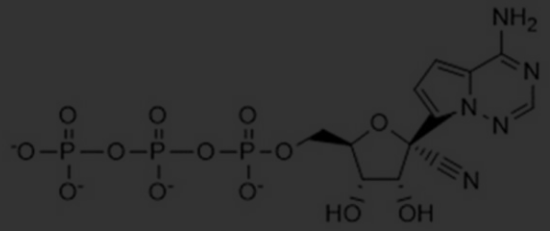
Protein binding: 88~93.6%

V_d: 93L



Metabolism: in the liver through carboxylesterase 1 (80%), cathepsin A(10%) and CYP3A(10%)

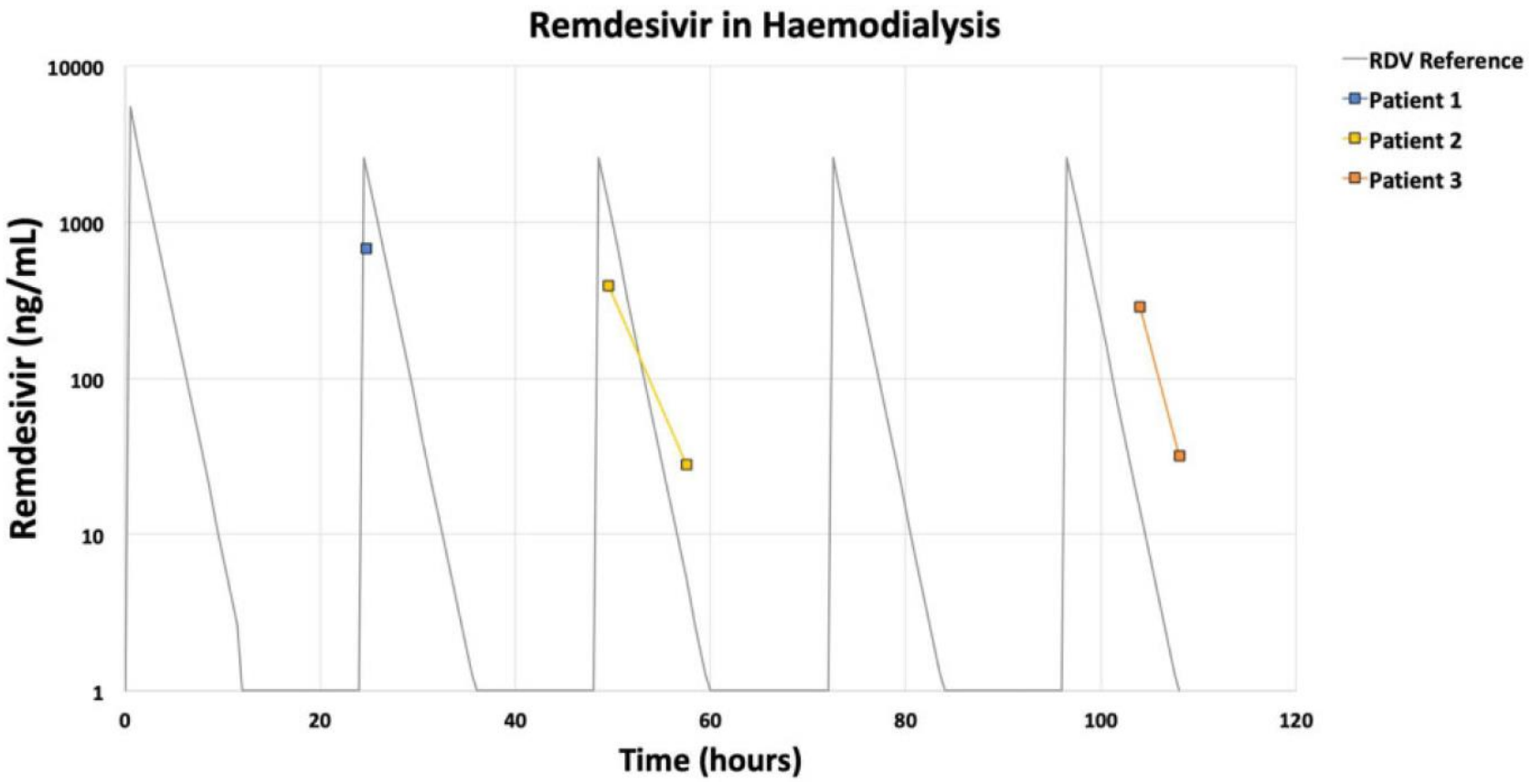
Renal excretion: 10%



Active form

Clin Pharmacokinet 2021;60(5):569-83

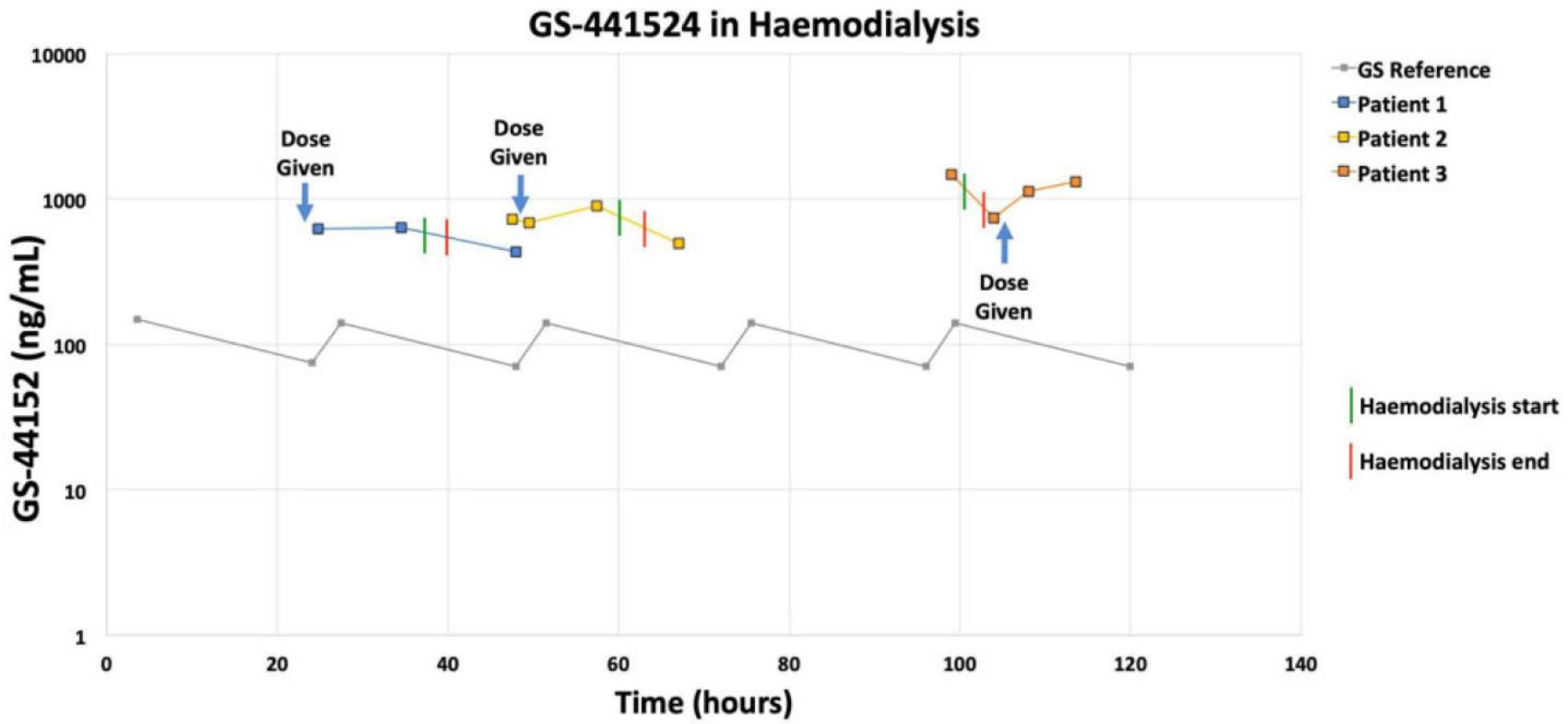
Remdesivir plasma concentrations in patients with ESRD on hemodialysis



$T_{1/2}$ = 2hr in ESRD vs. $T_{1/2}$ = 1hr in healthy volunteer

J Antimicrob Chemother 2021; 76: 822–825

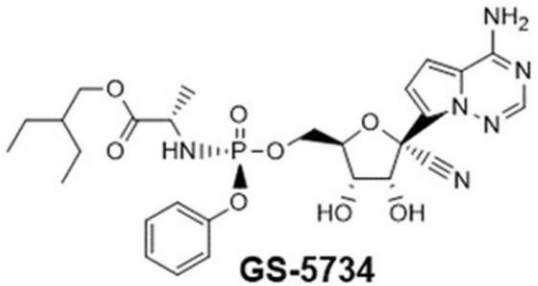
GS441524 plasma concentrations in patients with ESRD on hemodialysis



Accumulation ~ 3-10 fold higher than day 5 C_{max} of health volunteer

Hemodialysis removal ~ 50%

J Antimicrob Chemother 2021; 76: 822–825



GS-5734

Remdesivir

Sulfobutylether β cyclodextrin (SBECD):
3g/100mg Lyophilized formulation remdesivir
6g/100mg Liquid formulation remdesivir
6.4g/400mg voriconazole
Max daily dose: 250 mg/kg

International Journal of Antimicrobial Agents 46 (2015) 362–366

Contents lists available at ScienceDirect

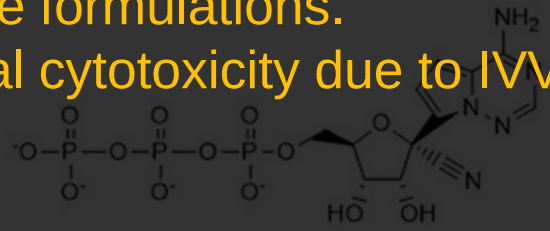
International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

Worsening renal function in patients with baseline renal impairment treated with intravenous voriconazole: A systematic review

- Similar worsening renal function for intravenous voriconazole (IVV) and oral voriconazole formulations.
- No evidence for renal cytotoxicity due to IVV at clinical doses.



GS-443902 Active form

Clin Pharmacokinet 2021;60(5):569-83

Clinical Infectious Diseases

MAJOR ARTICLE

Remdesivir Use in the Setting of Severe Renal Impairment: A Theoretical Concern or Real Risk?

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

ANTIVIRAL AGENTS

A Valid Warning or Clinical Lore: an Evaluation of Safety Outcomes of Remdesivir in Patients with Impaired Renal Function from a Multicenter Matched Cohort

KI REPORTS
KIReports.org

CLINICAL RESEARCH

Use of Remdesivir in Patients With COVID-19 on Hemodialysis: A Study of Safety and Tolerance

Clinical Infectious Diseases
MAJOR ARTICLE

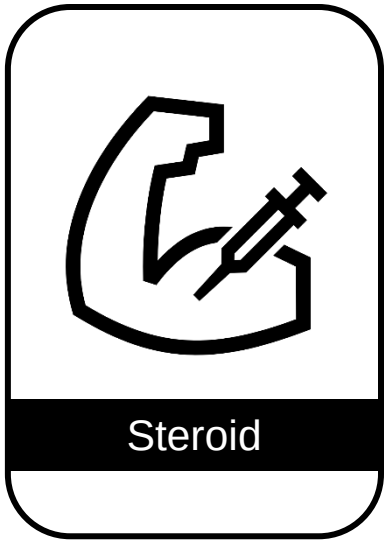
Remdesivir Use in the Setting of Severe Renal Impairment: A Theoretical Concern or Real Risk?

- Nephrotoxicity and hepatotoxicity occurred infrequently and overall were not significantly different between those with and without severe renal impairment.
- Remdesivir could be a considered therapy for severe infections due to SARS-CoV-2 in patient with severe renal failure

KI REPORTS
KIReports.org
CLINICAL RESEARCH

Use of Remdesivir in Patients With COVID-19 on Hemodialysis: A Study of Safety and Tolerance

Complications

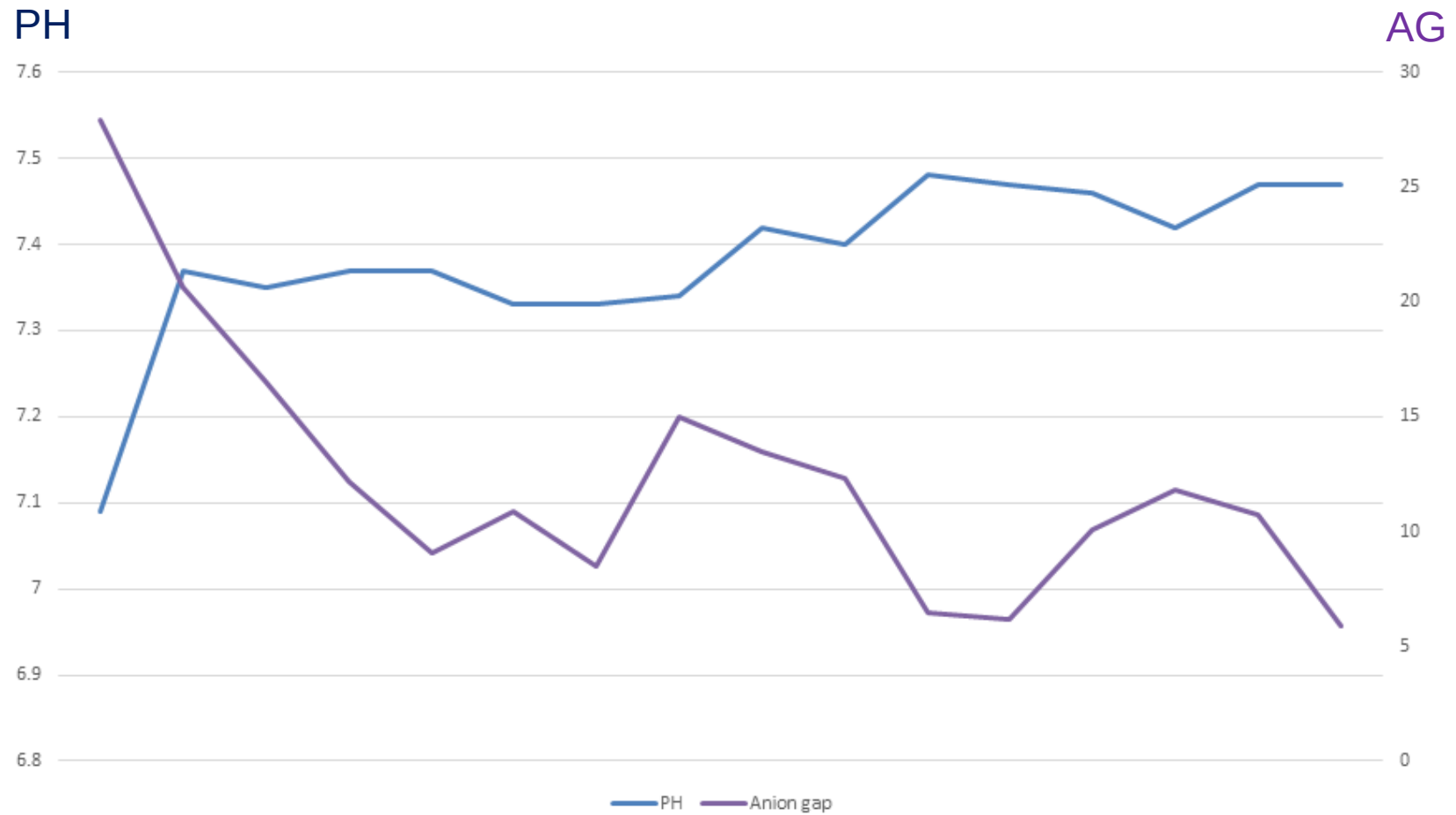


Diabetes ketoacidosis

Case 2

- 55 y/o male, 170 cm/66 kg
- PMH: denied any underlying disease
- Chief complain: consciousness drowsiness
- Lab in ER:
  - PH/PCO_2/HCO_3 = 7.09/27.2/8.1
  - Blood ketone = 6.4
  - Anion gap = 27.9
- COVID 19 medication
  - Remdesivir 6/3-7
  - Betamethasone 3mg on 6/1-2, 6mg on 6/3-10
  - Tocilizumab 560mg on 6/1
  - Enoxaparin 40mg SC QD since 6/4

PMH: past medical history



Insulin pump — 2U/hr → 8U SC TID → 2U/hr

RI

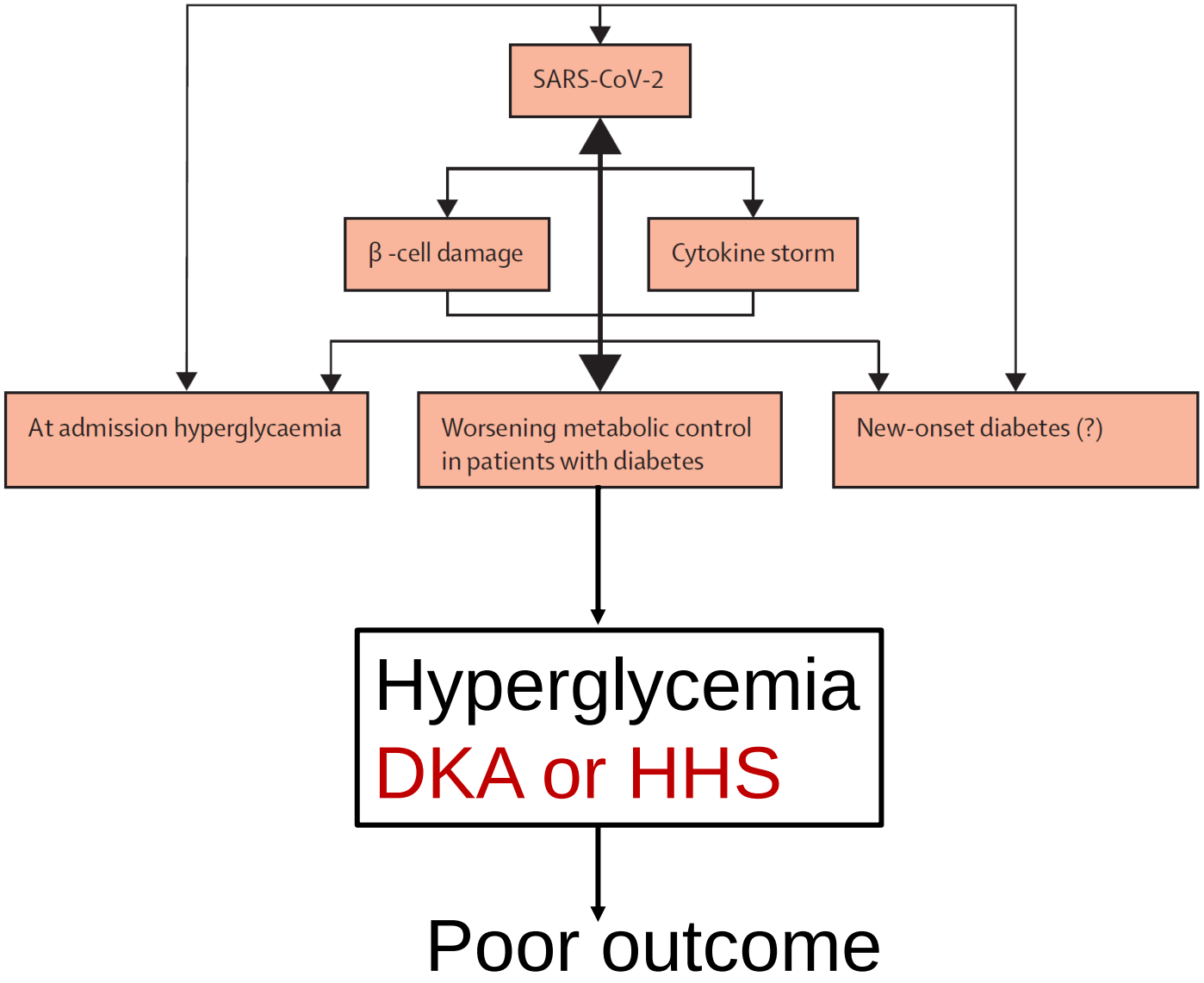
Insulin glargine — 12U SC HS → 20U QD SC

Insulin aspart — 7U TID SC

Lactated Ringer

D_5W — BS = 200-250

K_3PO_4 — K:3.7/P:1.8 → K:3.0/P:2.4

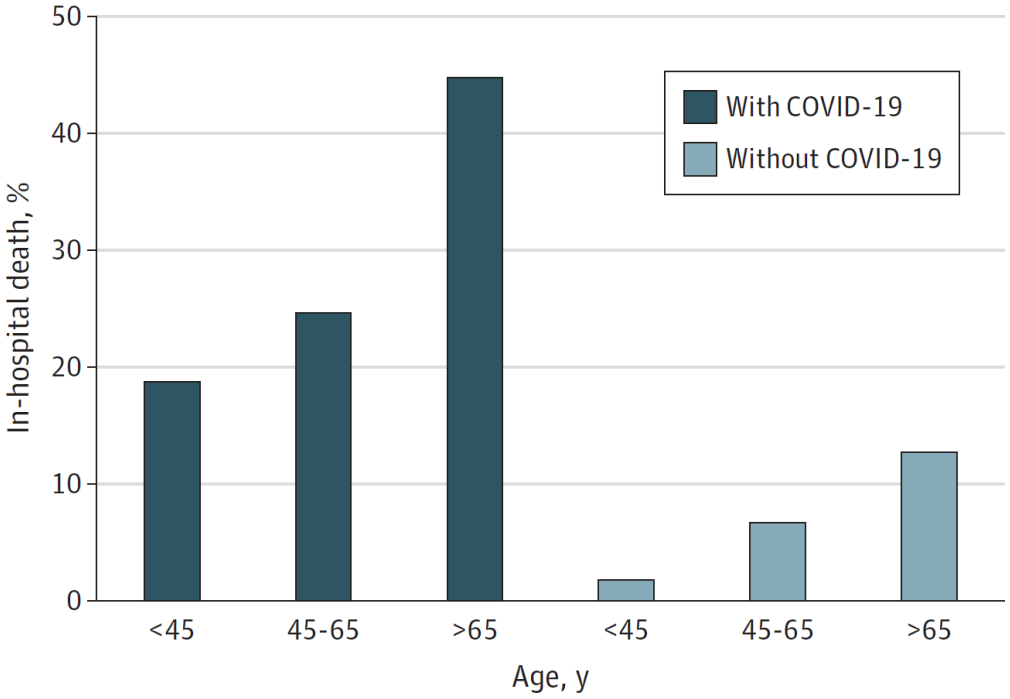


HHS: Hyperglycemic Hyperosmolar State

Lancet Diabetes Endocrinol 2020: 8; 782–92

Research Letter | Diabetes and Endocrinology

Characteristics of and Mortality Associated With Diabetic Ketoacidosis Among US Patients Hospitalized With or Without COVID-19



COVID19 patients:

- More heart comorbidities, DM complications and AKI
- Higher BW, insulin requirement

Extremely higher mortality rate of DKA in COVID19 patients

JAMA Network Open. 2021;4(3):e211091.

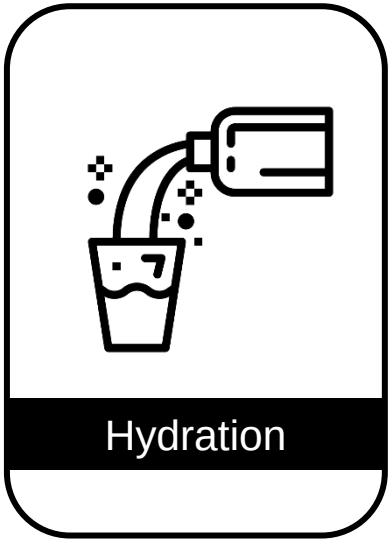
DKA severity

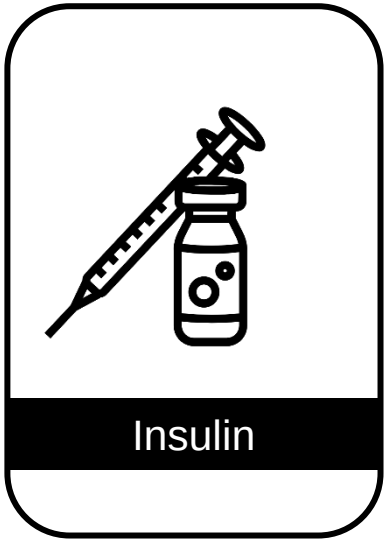
	Mild	Moderate	Severe
PH	7.25-7.30	7.00-7.24	<7.00
HCO_3^- (mmole/L)	15-18	10-14	<10
Anion gap	>10	>12	>12
Mental status	Alert	Alert/drowsy	Stupor/coma
Insulin	SC/IV	SC/IV	IV
Frequency of BG monitoring	Q1-2h	Q1-2h	Q1h

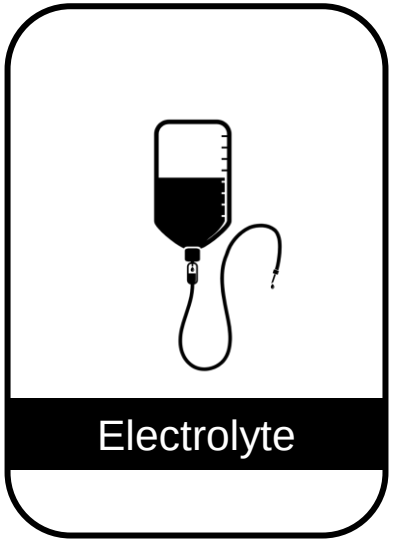
BG: blood glucose

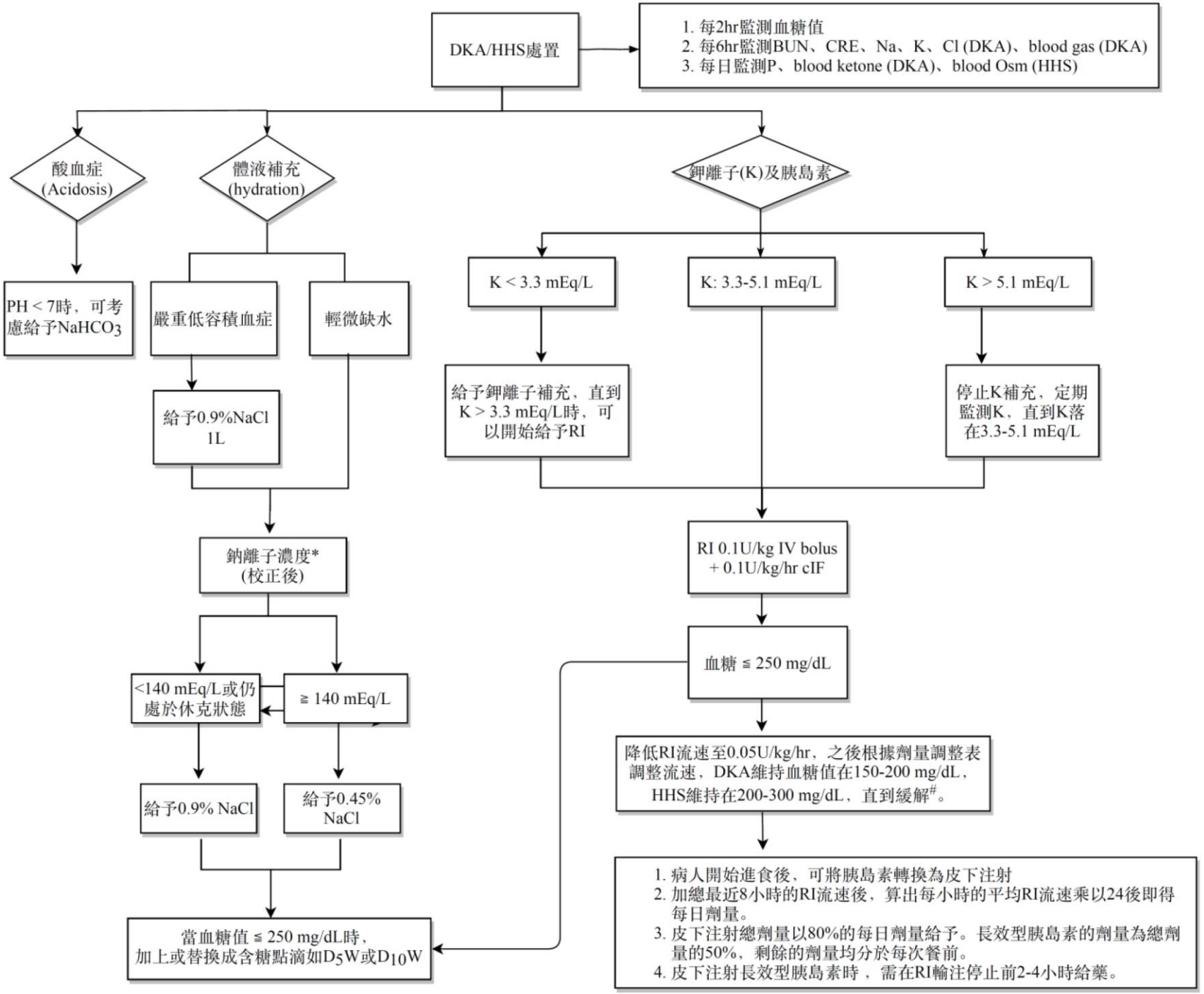
J Clin Endocrinol Metab 2020;105:2819–2829

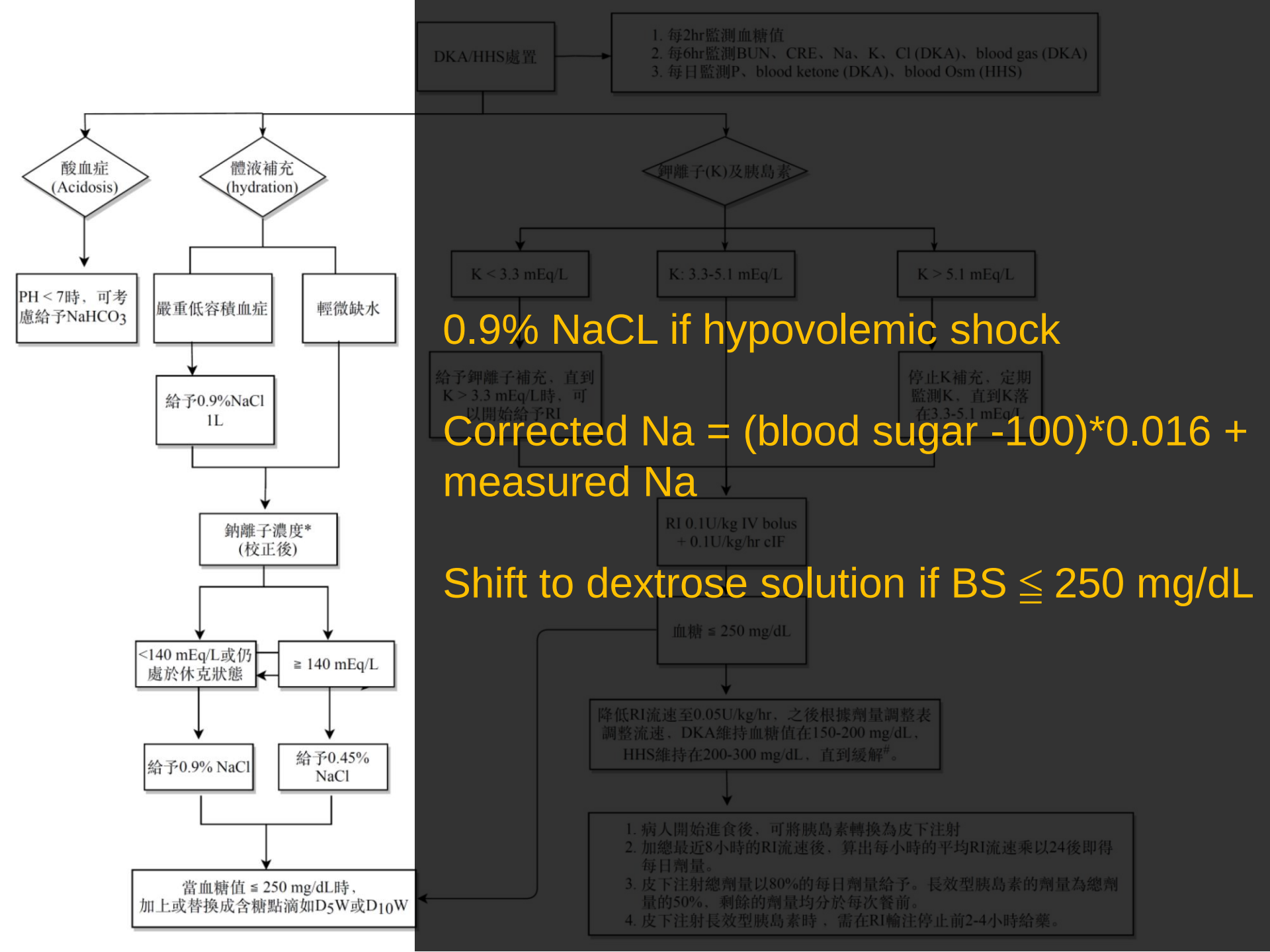
DKA management







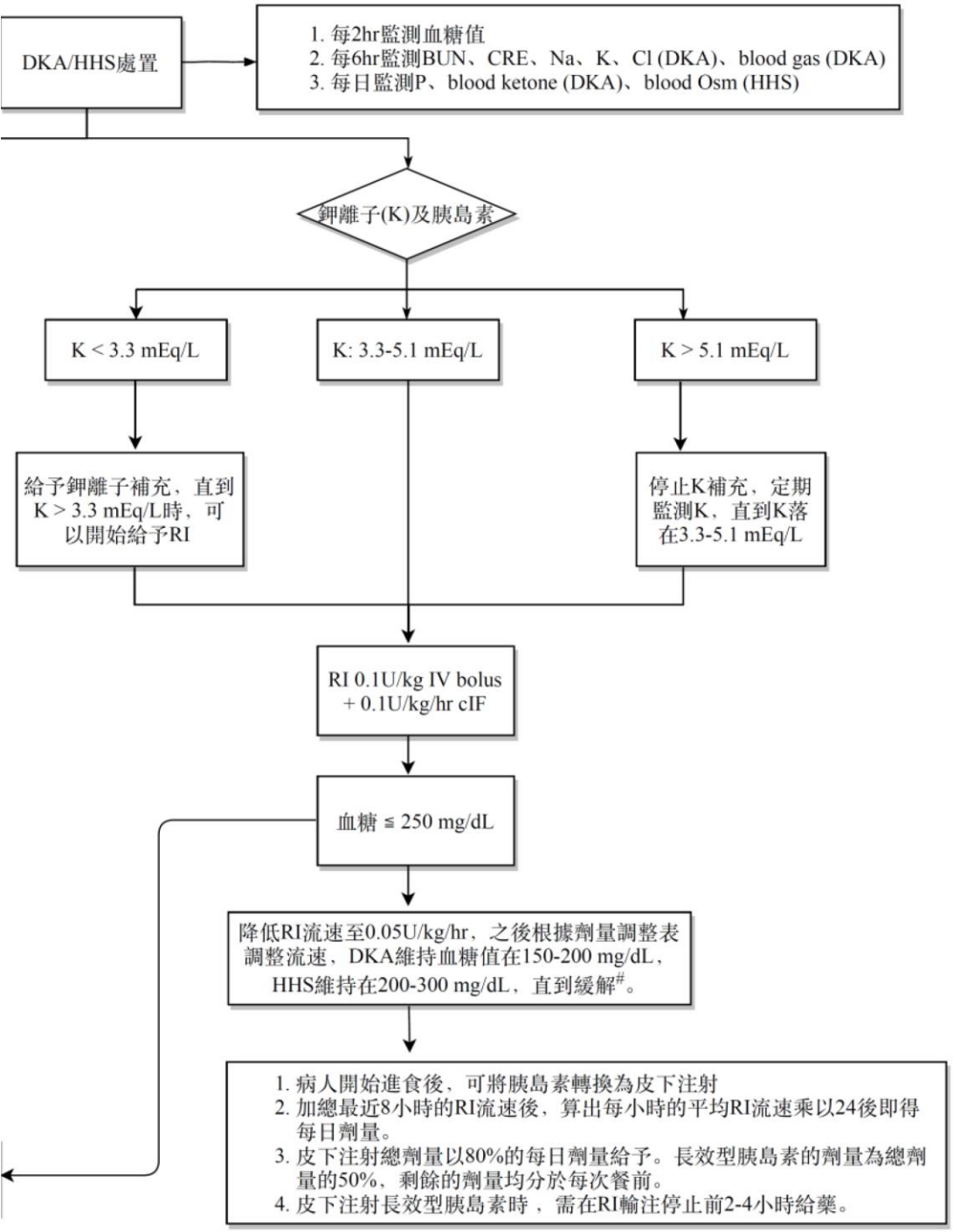

DKA/HHS處置
1. 每2hr監測血糖值
2. 每6hr監測BUN、CRE、Na、K、Cl (DKA)、blood gas (DKA)
3. 每日監測P、blood ketone (DKA)、blood Osm (HHS)
酸血症 (Acidosis)
體液補充 (hydration)
鉀離子(K)及胰島素
PH < 7時，可考慮給予NaHCO3
嚴重低容積血症
輕微缺水
給予0.9%NaCl 1L
K < 3.3 mEq/L
K: 3.3-5.1 mEq/L
K > 5.1 mEq/L
給予鉀離子補充，直到K > 3.3 mEq/L時，可以開始給予RI
停止K補充，定期監測K，直到K落在3.3-5.1 mEq/L
鈉離子濃度* (校正後)
RI 0.1U/kg IV bolus + 0.1U/kg/hr cIF
<140 mEq/L或仍處於休克狀態
≧ 140 mEq/L
血糖 ≦ 250 mg/dL
給予0.9% NaCl
給予0.45% NaCl
降低RI流速至0.05U/kg/hr，之後根據劑量調整表調整流速，DKA維持血糖值在150-200 mg/dL，HHS維持在200-300 mg/dL，直到緩解#。
當血糖值 ≦ 250 mg/dL時，加上或替換成含糖點滴如D5W或D10W
1. 病人開始進食後，可將胰島素轉換為皮下注射
2. 加總最近8小時的RI流速後，算出每小時的平均RI流速乘以24後即得每日劑量。
3. 皮下注射總劑量以80%的每日劑量給予。長效型胰島素的劑量為總劑量的50%，剩餘的劑量均分於每次餐前。
4. 皮下注射長效型胰島素時，需在RI輸注停止前2-4小時給藥。



0.9% NaCL if hypovolemic shock

Corrected Na = (blood sugar -100)*0.016 + measured Na

Shift to dextrose solution if BS ≦ 250 mg/dL


DKA/HHS處置
1. 每2hr監測血糖值
2. 每6hr監測BUN、CRE、Na、K、Cl (DKA)、blood gas (DKA)
3. 每日監測P、blood ketone (DKA)、blood Osm (HHS)
鉀離子(K)及胰島素
K < 3.3 mEq/L
K: 3.3-5.1 mEq/L
K > 5.1 mEq/L
給予鉀離子補充，直到K > 3.3 mEq/L時，可以開始給予RI
停止K補充，定期監測K，直到K落在3.3-5.1 mEq/L
RI 0.1U/kg IV bolus + 0.1U/kg/hr cIF
血糖 ≦ 250 mg/dL
降低RI流速至0.05U/kg/hr，之後根據劑量調整表調整流速，DKA維持血糖值在150-200 mg/dL，HHS維持在200-300 mg/dL，直到緩解#。
1. 病人開始進食後，可將胰島素轉換為皮下注射
2. 加總最近8小時的RI流速後，算出每小時的平均RI流速乘以24後即得每日劑量。
3. 皮下注射總劑量以80%的每日劑量給予。長效型胰島素的劑量為總劑量的50%，剩餘的劑量均分於每次餐前。
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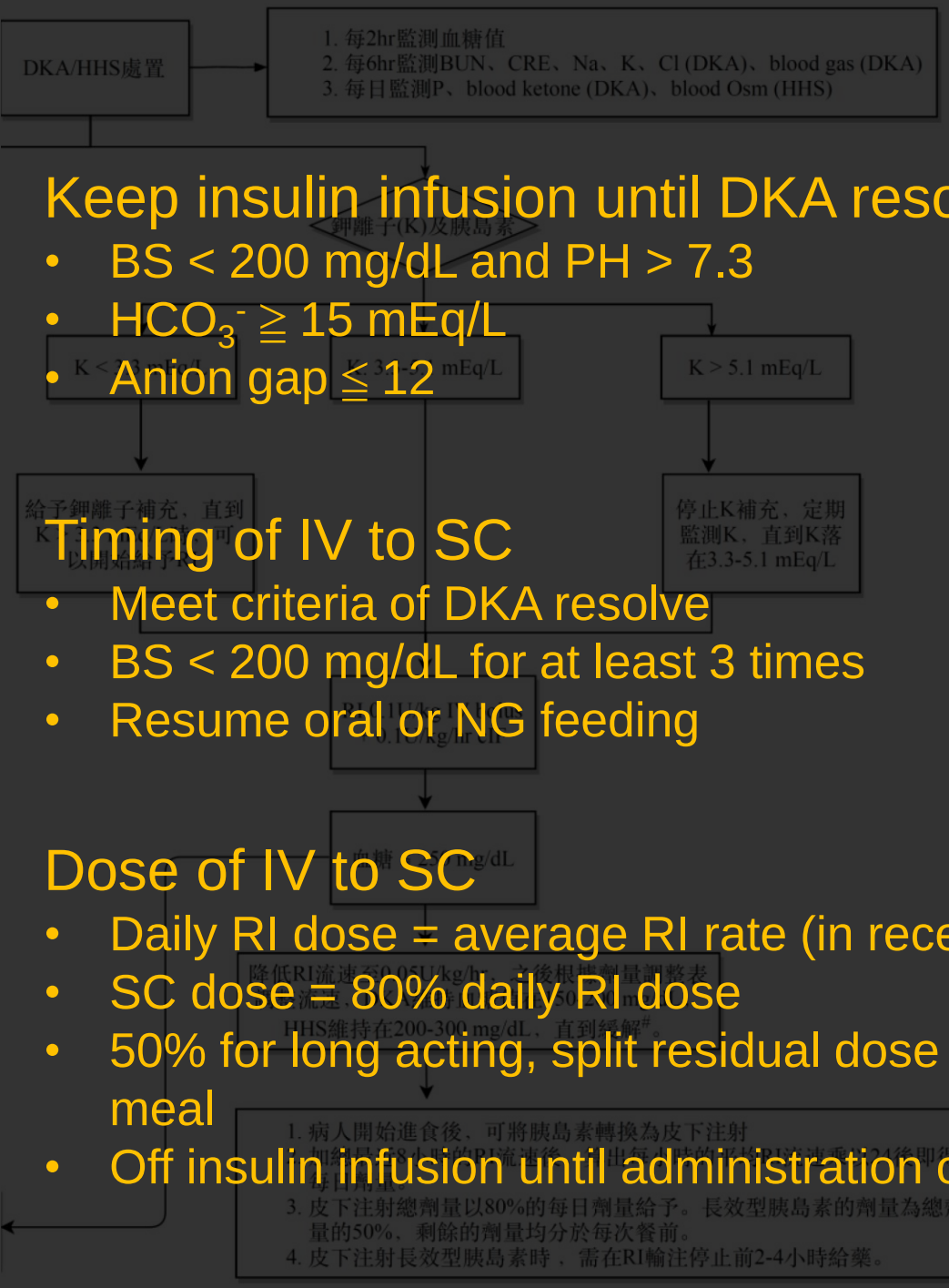


Keep insulin infusion until DKA resolved (meet 2 of 3 below)

- BS < 200 mg/dL and PH > 7.3
- HCO_3^- ≧ 15 mEq/L
- Anion gap ≦ 12

Timing of IV to SC

- Meet criteria of DKA resolve
- BS < 200 mg/dL for at least 3 times
- Resume oral or NG feeding

Dose of IV to SC

- Daily RI dose = average RI rate (in recent 8 hr)*24
- SC dose = 80% daily RI dose
- 50% for long acting, split residual dose to short acting insulin before each meal
- Off insulin infusion until administration of long acting insulin for 2-4 hrs

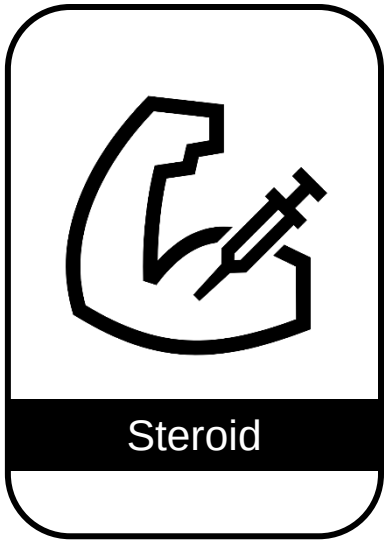
國立臺灣大學醫學院附設醫院

文件名稱	連續輸注胰島素於糖尿病酮酸中毒及高血糖高滲透壓狀態之使用建議	權責單位		藥劑部	頁碼/總頁數	1/9
文件編號	15660-3-000004	版次	1	修制訂日期	2020/11/13	
				檢視日期	2020/11/13	

國立臺灣大學醫學院附設醫院

文件名稱	加護病房成人使用連續輸注胰島素之劑量調整建議	權責單位		藥劑部	頁碼/總頁數	1/5
文件編號	15660-3-000003	版次	1	修制訂日期	2020/11/13	
				檢視日期	2020/11/13	

Complications

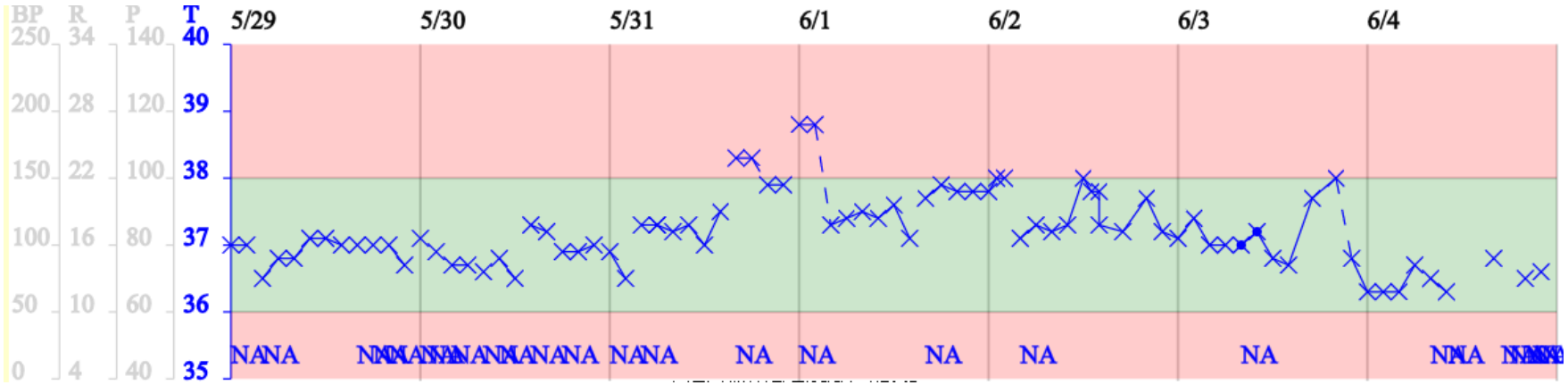


Critical illness related corticosteroid insufficiency (CIRCI)

Case 3

- 56 y/o female, 155 cm/56 kg
- PMH: Asthma without medication use, HTN, HBV carrier
- Home medication:
  - Baraclude (0.5mg/tab) 1tab po qd
  - Amvlo (5&160mg/tab) 1tab po qd
  - Syntrend (25mg/tab) 1tab po qd
- 5/16 symptom onset (fever, dyspnea), 5/20 admission, 5/23 intubation

PMH: past medical history

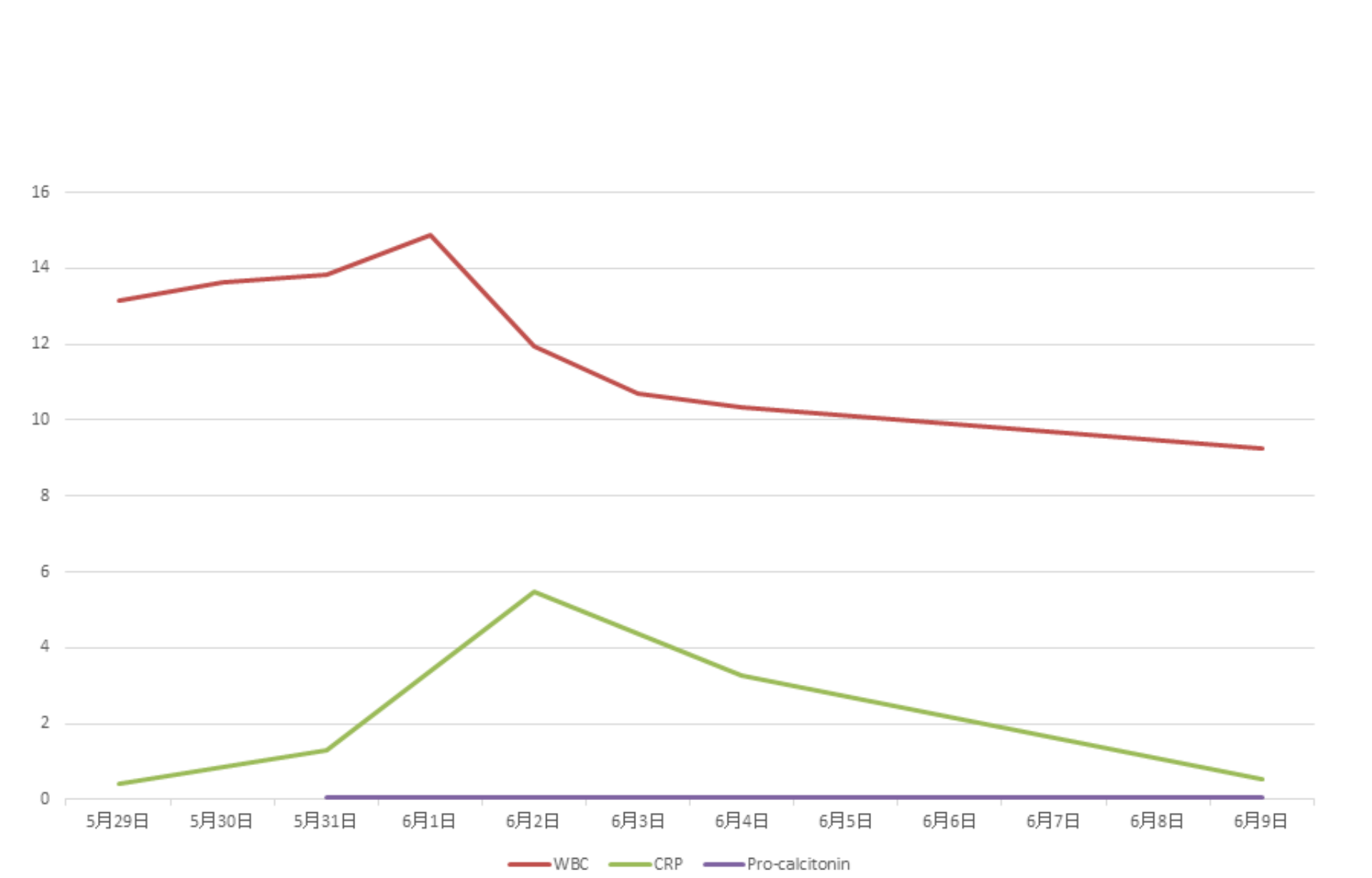


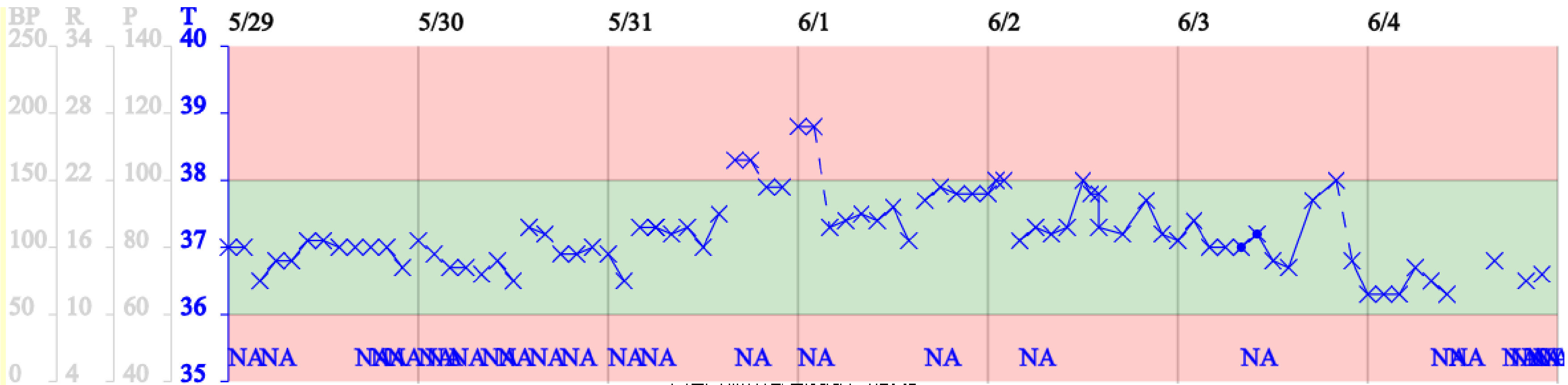
Remdesivir 5/22-26
Betamethasone 5/20-29
Enoxaparin since 5/24

Cefepime

Ertapenem

U/C: ESBL E.coli


16
14
12
10
8
6
4
2
0
5月29日
5月30日
5月31日
6月1日
6月2日
6月3日
6月4日
6月5日
6月6日
6月7日
6月8日
6月9日
WBC
CRP
Pro-calcitonin



Remdesivir 5/22-26
Betamethasone 5/20-29
Enoxaparin since 5/24

Cefepime

Ertapenem

U/C: ESBL E.coli

Cortisol

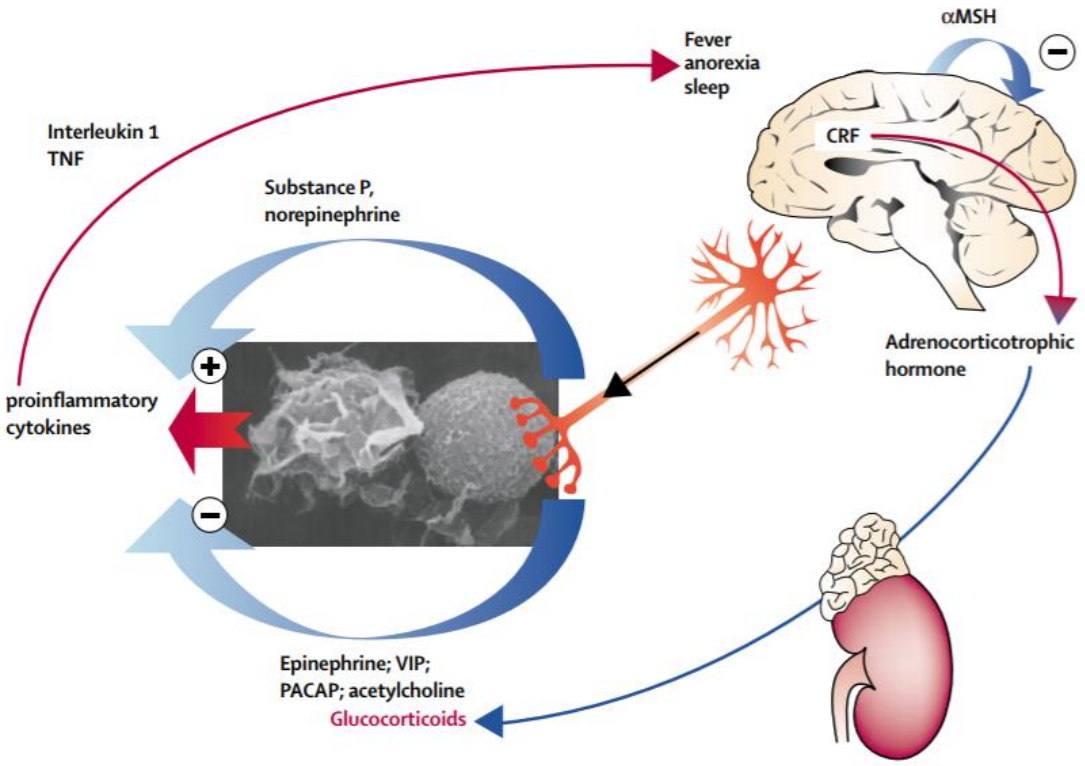
ACTH: < 5
Cortisol: 1.5

Urine	5/27	5/31	6/4	6/7	6/9	6/16
WBC	0-2	30-49	>= 100	20-29	>= 100	0-2
Epi	0-2	0-2	0-2	0-2	0-2	0-2
Others	Yeast (+)		Yeast (3+)	Yeast (2+)		

Pathophysiology of CIRCI

1. Dysregulation of the HPA axis
2. Altered adrenal synthesis of cortisol
3. Altered cortisol metabolism
4. Tissue resistance to corticosteroids

Multidirectional crosstalk between the **CRH/ACTH pathways**, **autonomic nervous system**, **vasopressinergic system**, and **immune system**



HPA: Hypothalamic-pituitary-adrenal

Signs and symptoms of CIRCI

General

- Fever
- Asthenia

Neuro

- Confusion
- Delirium
- Coma

Respiratory

- Persistent hypoxia

GI

- Nausea
- Vomit
- Intolerant to EN

CV

- Hypotension
- ⬇sensitivity to catecholamine
- High cardiac index

Lab

- Hypoglycemia
- HypoNa
- HypoK
- Metabolic acidosis
- Hypereosinophilia

Imaging

- Hemorrhage or necrosis in hypothalamus, pituitary gland or adrenal gland

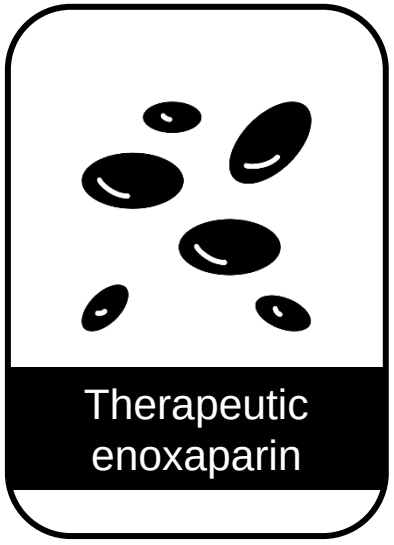
CIRCI based on cortisol level

- < 10 µg/dl – definitely
- > 34 µg/dl – less likely
- 10 – 34 µg/dl – probably
  - ACTH test (250 mcg): < Δ9 µg/dl at 60 mins

CIRCI rate in ICU COVID19 patients: ~50%

Intensive Care Medicine 2017;43:1751–63
Critical Illness-related Corticosteroid Insufficiency is Common in Covid-19 and Treatment Provide Survival Benefit: https://doi.org/10.21203/rs.3.rs-391924/v1

Complications



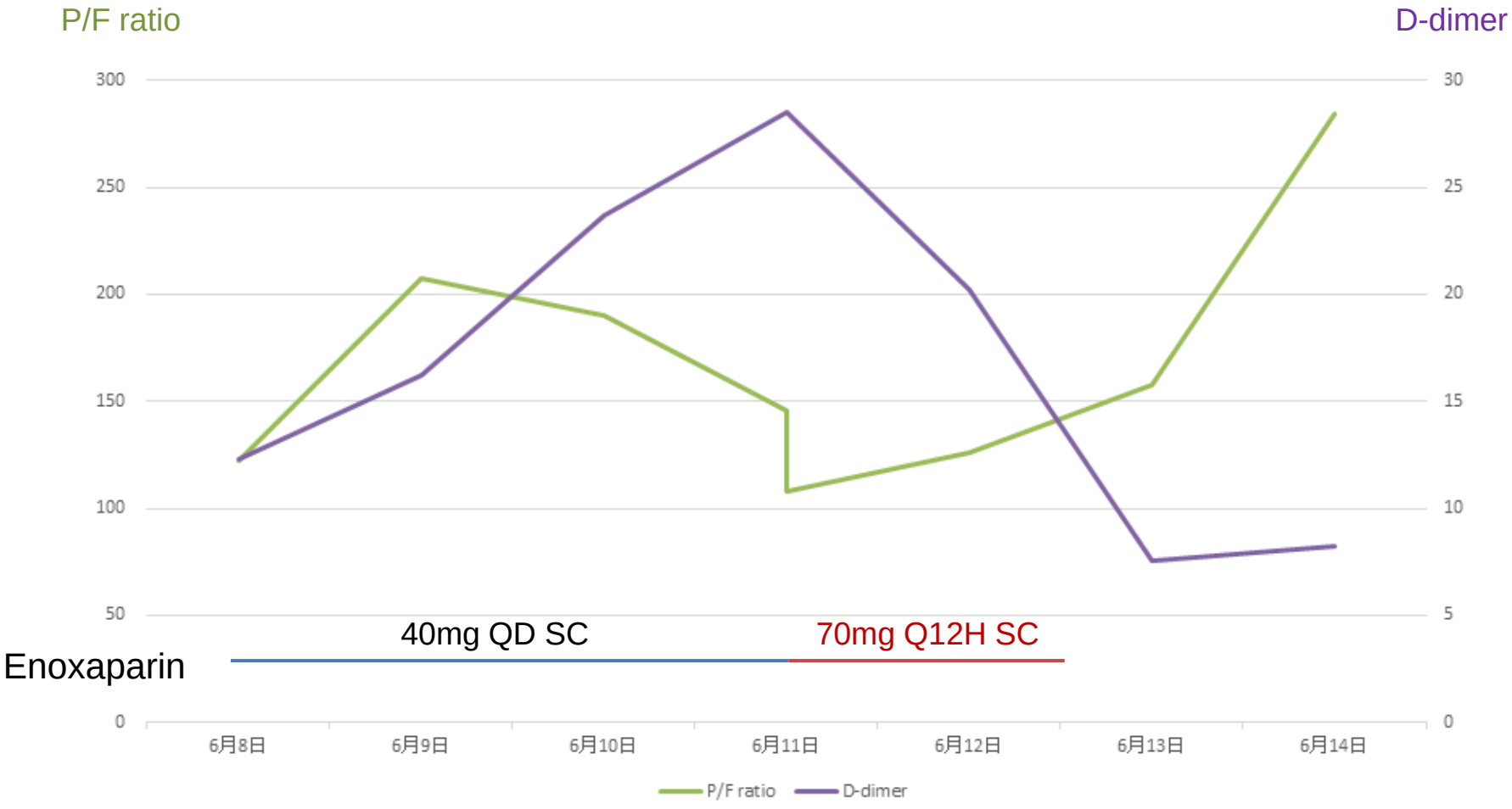
Bleeding

Case 4

- 76 y/o male, 162 cm/68 kg
- PMH: HTN, Dyslipidemia, Meniere's disease
- Home medication:
  - Aspirin 100mg po qd, amiodarone 100mg po qd, bisoprolol 1.25mg po qd, valsartan 160mg po qd, rosuvastatin 10mg po qd, benzbromarone 50mg po qd
- 6/1 symptom onset (fever), 6/6 admission (dyspnea), 6/7 intubation

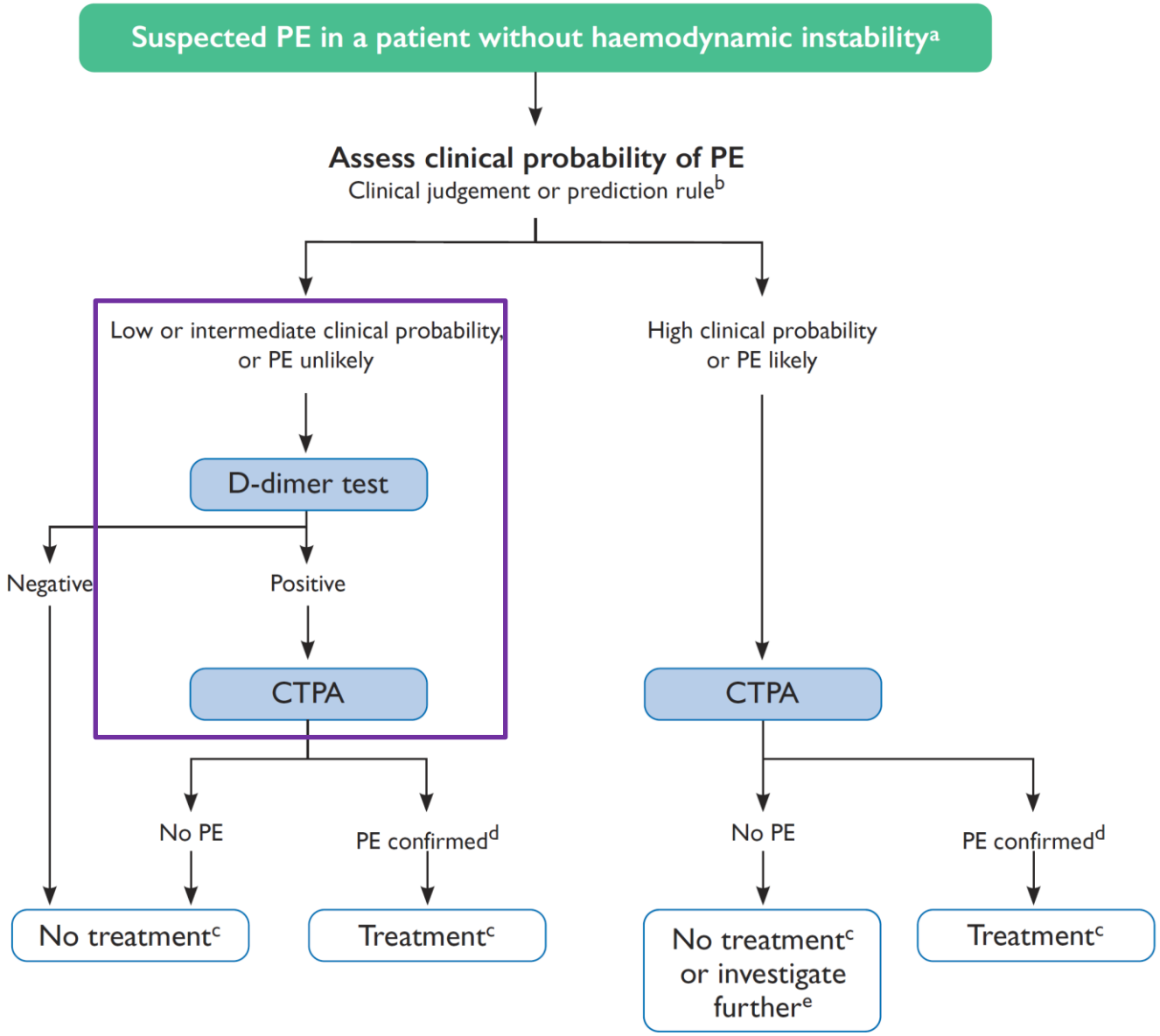
Remdesivir 6/8-12
Betamethasone 6/7-16

Shock, vasopressor use,
lactic acid: 5.56
HB (10.7 → 7.6)



CT report on 6/12:

1. No imaging evidence of pulmonary embolism.
2. Acute venous thrombosis at left jugular vein.
3. Infection/inflammation process at bilateral lungs, compatible with the history of viral pneumonia.
4. Right retroperitoneal hematoma with active bleeding.



D-dimer has excellent negative predictive value but poor positive predictive value

European Heart Journal 2020;41:543603

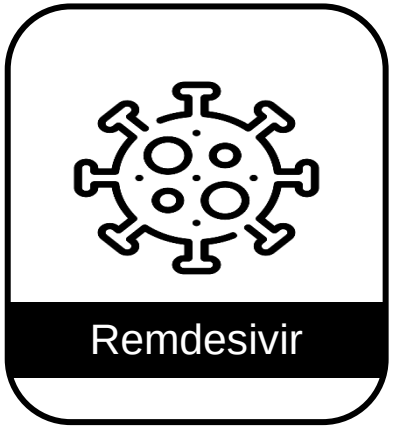
Thromboprophylaxis in critical care

	REMAP-CAP, ATTACC and ACTIV4	INSPIRATION
Intervention	Therapeutic dose (534)	Enoxaparin 1mg/kg qd SC (Intermediate dose) (276)
Control	Usual care (intermediate or prophylactic dose) (564)	Enoxaparin 40mg qd SC (286)
Primary outcome	Organ support free days up to D21: 1 vs 4 days, OR=0.83 (0.67-1.03)	Venous/arterial thrombosis events + all-cause mortality within D30: 45.7% vs 44.1%, OR=1.06 (0.76-1.48)
Major bleeding	3.8% vs 2.3%	2.5% vs 1.4%

OR: odds ratio

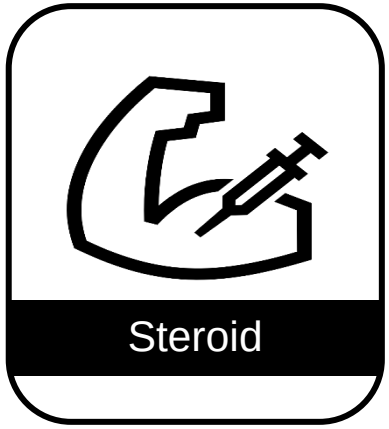
Applied prophylactic dose in critical care routinely
Therapeutic dose only for confirmed or highly suspected PE/VTE

N Engl J Med 2021;385:777-789
JAMA. 2021;325(16):1620-1630



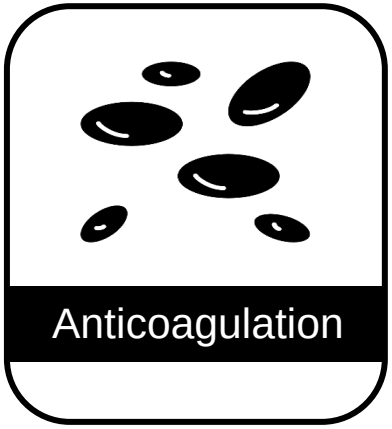
Remdesivir may lead to clinically significant bradycardia because of its active metabolite similar to ATP

Applied remdesivir in patients with severe renal failure should be benefit over risk



DKA is common in COVID19 and steroid use may complicate its management. Treatment protocol is beneficial for DKA management.

Beware of CIRCI after complete steroid course for COVID19 in critical care patients.



High D-dimer is not a good predictor for PE. Applied therapeutic dose of anticoagulation in ICU should be meticulous

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