SHC Vancomycin Dosing Guide

A: Initial dosing considerations
B. Pharmacodynamic Targets: goal AUC and troughs
C. Loading dose
D: Initial Vancomycin Maintenance Dosing and Serum Concentration Monitoring
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A. Initial Dosing Considerations

1. Review the following prior to initiation of therapy:
   a. Indication, relevant and pending microbial culture(s)
   b. Age, gender, height, weight, BMI
   c. Renal replacement therapy
   d. Special populations (obese, elderly, severely malnourished [BMI<16], amputees, pregnancy)
   e. Prior vancomycin dosing history (if applicable)
   f. Potential drug interactions
   g. Serum creatinine (SCr), urine output (if available), creatinine clearance (CrCI)
      i. Calculate CrCI using the Cockcroft-Gault equation (Figure 1)
         a) Elderly or severely malnourished: rounding SCr up is associated with underestimation of CrCI- clinical discretion advised [Smythe 1994, Young 2017, Barber 2016, Winter 2012]
         b) Use ideal body weight (IBW) for non-obese patients
         c) Use adjusted body weight (ABW) for obese patients [BMI >30 kg/m²]
         d) Use total body weight (TBW) if TBW < IBW

   Figure 1. Cockcroft-Gault Equation
   \[
   CrCl \left( \frac{ml}{min} \right) = \frac{(140 - age) \times IBW \times (0.85 \ for \ females)}{SCr \times 72} \quad \text{IBW (male) = 50 kg + (2.3 \times \text{height} \text{ in inches} \ > 60 \ inches) } \]
   \[
   \text{IBW (female) = 45 kg + (2.3 \times \text{height} \text{ in inches} \ > 60 \ inches) } \]
   \[
   \text{ABW (kg) = IBW + 0.4 (TBW - IBW) } \]

   h. Adverse Effects
      i. Red Man Syndrome is characterized by hypotension and/or a maculopapular rash appearing on the face, neck, trunk, and/or upper extremities.
      ii. If this occurs, pharmacist may slow the infusion rate (e.g. to 90-120 mins per 1 gm.) ± increase the dilution volume upon provider request ± recommend diphenhydramine 25-50mg premedication to the provider
B. Pharmacodynamic Targets: goal AUC and troughs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Target PD Index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most indications</strong></td>
<td></td>
</tr>
<tr>
<td>AUC-based protocol†</td>
<td>AUC 400 – 600 mg*h/L</td>
</tr>
<tr>
<td>Trough-based protocol (IHD, PD, nocturnal CRRT, dose-by-level)</td>
<td>Trough ~15 (10-20) mg/L</td>
</tr>
<tr>
<td>Continuous IV infusion</td>
<td>Random 17-25 mg/L</td>
</tr>
</tbody>
</table>

| Meningitis/ventriculitis (empiric or definitive) | |
| Trough-based protocol | Trough 15-20 mg/L |

- In general, goal AUC/MIC ≥ 400 for S. aureus
- Monitor closely with trough > 15 or AUC > 650: increased risk of nephrotoxicity
- Vancomycin may be continued in clinically responding patients with MRSA w/vancomycin MIC = 2; consider ASP or ID consult

†Exclusions from AUC-based dosing: rapidly fluctuating SCR, AKI (see section D footnote), intermittent hemodialysis (IHD), peritoneal dialysis (PD), nocturnal CRRT

C: Loading dose

I. **Purpose:**
Achieves rapid attainment of targeted concentrations and AUC/MIC of >400 mg-h/L on day 1 of therapy for bacterial killing in in vitro and clinical outcomes in vivo studies

II. **Targeted populations:**
- Preferred in seriously and/or critically-ill patients with suspected or documented serious MRSA infections (e.g. severe sepsis or septic shock requiring coverage for S. aureus)

III. **Standard load for patients with normal renal function: 20-35mg/kg TBW (maximum 3g)**
The decision of whether to employ a loading dose, as well as the magnitude of this dose, should be driven by the severity of infection and the urgency to achieve a therapeutic concentration rather than body size alone.

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>Standard Loading Dose 20-25 mg/kg TBW</th>
<th>Modified Loading Dose 20-25 mg/kg TBW</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 – 45 kg</td>
<td>1,000 mg x 1</td>
<td>750 mg x 1</td>
</tr>
<tr>
<td>46 – 55 kg</td>
<td>1,250 mg x 1</td>
<td>1,000 mg x 1</td>
</tr>
<tr>
<td>56 – 65 kg</td>
<td>1,500 mg x 1</td>
<td>1,250 mg x 1</td>
</tr>
<tr>
<td>66 – 75 kg</td>
<td>1,750 mg x 1</td>
<td>1,500 mg x 1</td>
</tr>
<tr>
<td>76 – 120 kg</td>
<td>2,000 mg x 1</td>
<td>1,750 mg x 1</td>
</tr>
<tr>
<td>&gt; 120 kg</td>
<td>2,000-3,000 mg x 1</td>
<td>2,000 mg x 1</td>
</tr>
</tbody>
</table>

*Time maintenance dose start based on renal function: e.g. wait 24h to start maintenance regimen if CrCl = 30
Use total body weight (TBW); Round doses to nearest 250mg. Infuse each 1000mg over 60 minutes.
D: Initial Vancomycin Maintenance Dosing and Initial/Repeat Monitoring

I. Round doses to nearest 250mg

II. Maximum dose: 2gm per dose and 4.5g per 24 hr initially (including load)

III. Repeat Vancomycin Levels
   A. After the target AUC or trough level is achieved at steady state, trough levels should be checked every 2 to 5 days until completion of therapy or discharge. Check peak/trough after any dose initiation/change.
   i. Levels should be checked sooner when clinically warranted (i.e.: change in clinical status or renal function, concern of accumulation/supratherapeutic levels, ≥25% change in trough/SCr)
   B. If follow-up trough is within expected range, the AUC is likely within range as well
   C. If follow-up trough is outside expected range, obtain another level to recalculate AUC
   D. Troubleshooting: if a level is missed, draw level with the next dose if at steady state. Otherwise, re-send new paired peak/trough

IV. Repeat SCr: q1-3 days if hemodynamically stable. Check daily if at high risk of nephrotoxicity.

V. Preferred: estimate total daily dose using PK equations (see Part H)- see Excel calculator

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dose &amp; Frequency Total body weight (TBW)</th>
<th>TDD Range</th>
<th>Timing of Peak/Trough Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;130</td>
<td>ICU only: 15mg/kg x1 (max 3g), then use PK calculator for daily dose given as continuous infusion</td>
<td>40-45 mg/kg</td>
<td>Random level 24 hours after start of infusion</td>
</tr>
<tr>
<td>&gt; 90</td>
<td>15 mg/kg Q8-12H† Obese: use PK calculator</td>
<td>30 – 45 mg/kg/day</td>
<td>Peak 1hr after 4th / trough 30 min before 5th dose, or Peak 1hr after 3rd/ trough 30 min before 4th dose</td>
</tr>
<tr>
<td>51-89</td>
<td>10–20 mg/kg Q12H Obese: use PK calculator</td>
<td>20–40 mg/kg/day</td>
<td>Q12H: Peak 1hr after 4th / trough 30 min before 5th dose, or Peak 1hr after 3rd/ trough 30 min before 4th dose</td>
</tr>
<tr>
<td>30-50</td>
<td>10-15 mg/kg Q12H to 20 mg/kg Q24H Obese: use PK calculator</td>
<td>20 – 30 mg/kg/day</td>
<td>Q12H: as above Q24H: Peak 1hr after 3rd/ trough 30 min before 4th dose</td>
</tr>
<tr>
<td>10-29</td>
<td>10 – 15 mg/kg Q24H to 15 mg/kg Q48H Obese: use PK calculator</td>
<td>7.5 – 15 mg/kg/day</td>
<td>Q24H – Peak 1hr after 3rd/ trough 30 min before 4th dose Q48H – Peak 1hr after 2nd dose; trough 30 min before 3rd dose</td>
</tr>
<tr>
<td>&lt;10 or AKI*, dose by level</td>
<td>15 mg/kg x1, then dose by level</td>
<td>N/A</td>
<td>Trough within 24 hours of last dose, or with AM labs or every other day</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Initial: ~ 20-25 mg/kg x 1 (max 2gm) Maintenance: see appendix F</td>
<td>N/A</td>
<td>Single pre-dialysis level (preferred) Alternative: single level 4 hours after completion of dialysis session</td>
</tr>
<tr>
<td>CRRT† or nocturnal CRRT</td>
<td>Initial: 20-25 mg/kg x 1 (max 2gm) Maintenance: 10 – 15 mg/kg Q24H</td>
<td>N/A</td>
<td>Q24H: Peak 1hr after 2nd or 3rd dose; Trough 30 min before 3rd or 4th dose, respectively</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>10 – 15 mg/kg IV x1, then dose by level</td>
<td>N/A</td>
<td>Check level 24h after initial dose. Consult ASP</td>
</tr>
<tr>
<td></td>
<td><strong>Dosing for intraperitoneal (IP) instillation (NOT part of protocol) [Li, 2016] Intermittent (1 exchange/day): 15-30mg/kg IP initially, then dose by level</strong> supplement doses may be needed for APD patients</td>
<td>N/A</td>
<td>Intraperitoneal dosing (off-protocol): Level with AM labs on day 3 after any dose administered (allow fluid redistribution before drawing random level)</td>
</tr>
</tbody>
</table>

1 Note: For those with CrCLadjBW > 120mL/min, Q8H may be considered if t½ < 8hr (use Excel for t½ calculation, or appendix G)
2 Loading and maintenance doses are based on 1-2L/hr dialysate flow and ultrafiltration rates, which is estimated to mimic a creatinine clearance of 30-50 mL/min
3 AKI (based on KDIGO, RIFLE, AKIN classifications):
   i. SCr change by ≥ 0.3 mg/dL within 48h or 50% from baseline or within last 7 days
   ii. CrCl change by >25 - 50%
   iii. Urine output < 0.5 mL/kg/hr over 6 hours (oliguria)
   iv. SCr ≥0.5 mg/dL, or a 50% increase from baseline in consecutive daily readings, or a decrease in CrCl of 50% from baseline on 2 consecutive days in the absence of an alternative explanation
**E: Dose Revisions**

**AUC calculator:** This calculator is based on the Sawchuk-Zaske method and the equations used are summarized here.\(^{11}\) Click [here](#) for link to AUC calculator on Microsoft Excel.

\[
AUC = \frac{t \cdot (C_{\text{max}} + C_{\text{min}})}{2} + \frac{C_{\text{max}} - C_{\text{min}}}{k}
\]

- \(t\) = infusion duration, \(k = \frac{\ln C_1}{C_2}\)
- This AUC value applies to that calculated in a single dosing interval \(\Delta t\) must be multiplied by the dosing frequency when applicable to obtain the total AUC\(0\text{-24}\)
- \(C_{\text{max}}\) (true peak) and \(C_{\text{min}}\) (true trough) are back-calculated from measured values using this equation: \(C_2 = C_1 \times e^{-kt}\). (Details are in Part H)

**Linear proportion method:** Once a calculated AUC or trough is obtained, changes to the total daily dose (TDD) have a corresponding proportional change in troughs and AUCs when maintaining the same dosing interval, assuming stable renal function and steady state conditions.

\[
\begin{align*}
\frac{AUC \text{ (calculated)}}{AUC \text{ (desired)}} &= \frac{\text{Current TDD}}{\text{New TDD}} \\
\frac{C_{\text{min}} \text{ (observed)}}{C_{\text{min}} \text{ (desired)}} &= \frac{\text{Current TDD}}{\text{New TDD}}
\end{align*}
\]

E.g.: 1250mg IV Q12H results in an AUC of 800. To target a AUC 600, reduce to 1g q12h (rounded up from 1875mg/day). Alternatively, converting the same TDD to a q8h regimen would result in a higher trough but would not impact the AUC.

\[
\text{New TDD} = \frac{600 \times 2500mg}{800} = 1875mg
\]

**Supratherapeutic levels and/or AKI:** general approach

- A. Do not restart vancomycin until the random/trough level is estimated or confirmed to be at/near 10-20 mg/dl. Allow sufficient time for drug clearance before restarting next dose.
- B. Actions may include: pre-emptive dose adjustment, holding dose, checking level, discussion with provider, reassessing the need for vancomycin therapy.
- C. Consider SCr/renal trajectory when determining next dose and/or level
  1. Ex) rapidly declining Scr may indicate improving renal function warranting earlier redosing vs. rapidly rising Scr indicating ongoing AKI- dose by level may be indicated
F: Intermittent Hemodialysis Dosing Algorithm

**Goal pre-HD trough 15-20**
Vancomycin Loading Dose ~20-25 mg/kg (max 2000mg)

Draw pre-HD level (either before session or with AM labs on day of scheduled session)

- **Pre-HD level < 10mcg/mL:** give 10-15mg/kg post HD
- **Pre-HD level 10-15 mcg/mL:** give 500-750 mg or 7.5-10mg/kg post HD
- **Pre-HD level 15-20 mcg/mL:** give 250-500mg or 5 mg/kg post HD
- **Pre-HD level 20-25 mcg/mL:** hold x1 or give 250 mg or 2.5 mg/kg post HD
- **Pre-HD level > 25 mcg/mL:** hold vancomycin until level back in range

Repeat algorithm based on level prior to next HD session

Check level 4 to 6 hours after next HD session. Re-dose if level < 20-25

*consider dosing 20% higher pre-HD depending on acuity/severity of infection and potential harm/risk from underdosing while awaiting dialysis completion before giving post-HD dose*
G: Continuous Infusion Vancomycin

Indicated Populations:
• Critically ill patients with augmented renal function defined as CrCl > 130 ml/min

Exclusions:
• Anticipated therapy <48 hours (ex: treatment of empiric pulmonary infection where nasal PCR and provide quick de-escalation, post-op prophylaxis)
• History of neuro-muscular disease, quadriplegia/paraplegia (disease states resulting in low SCr and falsely elevated CrCl)
• Age > 50 years
• Weight < 50 kg
• Meningitis

Administration
• Infusion Time (Loading Dose): Total dose to be given as 1000 mg/hour
• Infusion Time (Maintenance Dose): Total dose to be given over 24 hours starting immediately after initial dose.

Initial Dosing: use total body weight (TBW) for dosing

<table>
<thead>
<tr>
<th>Augmented Renal Function</th>
<th>Loading Dose</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 mg/kg TBW [max 3000 mg]</td>
<td>Calculate 24 hour requirement using AUC dosing calculator (tab 1 on excel file) and start infusion based on this calculation (round to nearest 250 mg)</td>
</tr>
</tbody>
</table>

SHC Vancomycin Dosing Calculator

Monitoring
• Draw a random level at 24 hours after the start of the continuous infusion
• Goal level: 17-25 mg/L
  o If therapeutic: recheck another level at 72 hours; earlier if changes in renal function suspected to lead to out of range level, e.g. SCr change > 25%
  o If subtherapeutic: increase the dose (see adjusting doses below) and recheck level in 24 hours
  o If supratherapeutic: hold dose and reduce the dose (see adjusting doses below) and recheck level in 24 hours

Adjusting Doses:
• Subtherapeutic or Supratherapeutic: Proportional calculation (assuming SCr stable)

\[
\frac{\text{Current 24-hour dose}}{\text{Current vancomycin level}} = \frac{X \text{ (revised dose)}}{\text{Desired vancomycin level}}
\]

* If supratherapeutic, may consider re-checking level and resume continuous infusion when level is < 25 mg/mL

Converting from Intermittent Dosing to Continuous Dosing:
• Patients who are therapeutic on intermittent dosing do not require a loading dose
• Patients on continuous infusion vancomycin therapy may accumulate vancomycin and therefore may require lower total daily doses compared to intermittent therapy
If patients are therapeutic on intermittent dosing
  ▪ Add up total daily vancomycin dose
  ▪ Reduce by 10-15%
  ▪ Round to the nearest 250 mg (this will be the starting dose of continuous infusion)
If patients are sub-therapeutic or supra-therapeutic on intermittent dosing
  ▪ Dosing for continuous infusion should be calculated on a case to case basis using existing data.
  ▪ Can use SHC Vancomycin Dosing Calculator to guide dosing

Converting from Continuous Dosing to Intermittent Dosing:
If therapeutic on continuous infusion vancomycin dosing, add up 24-hour dose and divide by appropriate dosing interval
H: PK Equations (same as those used in SHC Vancomycin Excel AUC Calculator)

**AUC-based dosing: initial dosing**

1. Step 1: estimate Cl\text{vanco} (L/hr) = k_e \times V_d
   
a. In general populations: Matzke Equation: k_e = 0.00083 x CrCl + 0.0044
   
b. In obese patients: Crass et al 2018: Cl\text{vanco} = 9.656-0.078 x age – 2.009 x SCr + 1.09 x sex + 0.04 x TBW\text{0.75}, where female = 0 and male = 1.
   

2. Step 2: estimate total daily dose = Cl\text{vanco} x goal AUC\text{0-24}

**AUC-based dosing: revision from 2 levels**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Verify that doses were given on time and drawn appropriately</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Calculate the patient’s observed k_e from 2 levels</td>
<td>[ k_e = \frac{\ln(C_2/C_1)}{t_2 - t_1} ] (where C_1 usually is the peak, C_2 is usually the trough)</td>
</tr>
<tr>
<td>3</td>
<td>Calculate half-life, t_{1/2}</td>
<td>[ t_{1/2} = \frac{0.693}{k} ]</td>
</tr>
<tr>
<td>4</td>
<td>Calculate true peak, C_{\text{max}}</td>
<td>[ C_{\text{max}} = \frac{C_1}{e^{-k t}} ] (t = infusion time)</td>
</tr>
<tr>
<td>5</td>
<td>Calculate true trough, C_{\text{min}}</td>
<td>[ C_{\text{min}} = C_{\text{max}} \times e^{-k t} ] (where t = infusion time)</td>
</tr>
<tr>
<td>6</td>
<td>Calculate V_d (steady state conditions)</td>
<td>[ V_d = \frac{\text{dose} \times (1-e^{-k t})}{t \times k_e (C_{\text{max}} - [C_{\text{min}} k_e e^{-k t}])} ] (where t = infusion time)</td>
</tr>
<tr>
<td>7</td>
<td>Calculate vancomycin clearance</td>
<td>[ \text{CL}_{\text{van}} = V_d \times k_e ]</td>
</tr>
<tr>
<td>8</td>
<td>If C_{\text{min}} is high, calculate the time needed to reach desired range</td>
<td>[ \text{Time for C_{\text{min}} to reach C_{desired}} = \frac{\ln(C_{\text{desired}}/C_{\text{min}})}{k} ]</td>
</tr>
<tr>
<td>9</td>
<td>Calculate AUC during infusion using linear trapezoidal rule</td>
<td>[ AUC_{\text{inf}} = t \times \left( \frac{C_{\text{max}} + C_{\text{min}}}{2} \right) ]</td>
</tr>
<tr>
<td>10</td>
<td>Calculate AUC during elimination using logarithmic trapezoidal rule</td>
<td>[ AUC_{\text{elim}} = \left( \frac{C_{\text{max}} - C_{\text{min}}}{k} \right) ]</td>
</tr>
<tr>
<td>11</td>
<td>Calculate AUC\text{24}</td>
<td>[ AUC_{0-24} = (AUC_{\text{inf}} + AUC_{\text{elim}}) \times \frac{24}{\text{tau}} ]</td>
</tr>
<tr>
<td>12</td>
<td>Estimate total daily dose need to achieve target AUC\text{24}</td>
<td>[ \text{New TDD} = \frac{\text{Current TDD} \times AUC_{0-24} \text{ (desired)}}{AUC_{0-24} \text{ (calculated)}} ]</td>
</tr>
<tr>
<td>13</td>
<td>Calculate predicted steady state C_{\text{max}} for new dosing regimen</td>
<td>[ C_{\text{ss, max}} = \frac{\text{New dose}}{\text{CL} \times t} \times \frac{1 - e^{-k t}}{1 - e^{-k \text{tau}}} ]</td>
</tr>
<tr>
<td>14</td>
<td>Calculate predicted steady state C_{\text{min}} for new dosing regimen</td>
<td>Same as step 5</td>
</tr>
<tr>
<td>15</td>
<td>Calculate predicted AUC based on new dosing regimen</td>
<td>Same as steps 9-11</td>
</tr>
</tbody>
</table>


**Abbreviations**

- t: infusion time; Tau: dosing interval; Ke: elimination rate constant; Vd: volume of distribution; C_i: concentration at time t_i (i.e. first of 2 levels drawn following dose); C_{\text{ss}}: concentration at time t_{\text{ss}} (i.e. second of 2 levels drawn following dose) t_i: time at which C_i is drawn t_{\text{ss}}: time at which C_{\text{ss}} is drawn
- CL_{\text{van}}: vancomycin clearance
- TDD: total daily dose
- AUC: area under the concentration-time curve
- AUC\text{24}: 24 hour area under the concentration-time curve
I: Discharge on vancomycin

General approach: specify desired vancomycin trough range based on prior trough levels associated with therapeutic AUC

- Select a trough range as approximately +/- 2 of the trough level corresponding to target AUC, assuming the AUC is not already at the upper or lower limits. Please use clinical discretion.

Goal vancomycin troughs for discharge

<table>
<thead>
<tr>
<th>Description</th>
<th>Target trough range</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior therapeutic AUC available</td>
<td>Individualized: select a 5-point range</td>
<td>Ex 1. if trough was 12 with AUC 500, discharge target trough range 10-15 mg/L.</td>
</tr>
<tr>
<td></td>
<td>close to trough associated with</td>
<td>Ex 2. if trough was 12 with AUC 400, discharge target trough range 12-17 mg/L.</td>
</tr>
<tr>
<td></td>
<td>therapeutic AUC (400-600 mg*h/L)</td>
<td>Option to calculate:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calculate lower (x) and upper (y) limits of target range using linear proportionality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Using Ex 1 above:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Lower limit: 12/500=x/400 = 9.6 ≈ 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Upper limit: 12/500 = y/600=14.4 ≈ 15</td>
</tr>
<tr>
<td>No prior therapeutic AUC available</td>
<td>12-17 mg/L</td>
<td></td>
</tr>
<tr>
<td>Intermittent hemodialysis</td>
<td>15-20 mg/L</td>
<td></td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>Random level: 17-25 mg/L</td>
<td>• Logistical barriers: requires advanced planning with case management for insurance approval, ensure outpatient pharmacy or SNF feasibility, etc.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Related info: see Section G for how to transition off continuous infusion</td>
</tr>
</tbody>
</table>

I. DOCUMENT INFORMATION

A. Original Author/Date
   Emily Mui, Pharm.D. BCPS: 08/2013

B. Gatekeeper
   Pharmacy Department

C. Distribution
   This procedure is kept in the Pharmacy Policies and Procedure Manual

D. Review/Revision History:
   Lina Meng, Pharm.D., BCPS: 06/2015
   Janjri Desai, Pharm.D., MBA, BCPS: 10/2015, 03/2016, 08/2016
   Lina Meng, Pharm.D., BCPS, BCCCP: 08/2016, Emily Mui, Pharm.D., BCPS: 08/2016
   Calvin Diep, Liz Keil, Jamie Kuo, Lina Meng 5/2021

E. Approvals
   Pharmacy and Therapeutics Committee: 11/2015, 03/2016, 6/2021 pending

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