AMIKACIN, IV

- Amikacin, IV, 15 mg/kg daily given slowly over 30 minutes.
  - If BMI is >40 kg/m^2 use ideal body weight* + 40% of the difference between ideal and actual body weight.
  - In severe sepsis or septic shock, a loading dose of 25 mg/kg should be given (irrespective of renal function).
  - If eGFR is 40–60 mL/minute, adjust maintenance dose to 15 mg/kg every 36 hours (check trough amikacin level and give the next dose when level is <5 mg/L or be guided by local laboratory cut off trough value).
  - Maximum daily dose 1.5 g, usually for a maximum of 10 days.
  - Amikacin is nephrotoxic and ototoxic – monitor creatinine three times per week and discontinue if vestibular or cochlear symptoms develop. Regular audiometry is essential with longer term use in patients with drug-resistant TB.
  - Therapeutic drug monitoring: pre-dose amikacin trough levels after the third dose. Aim for a trough level of <5 mg/L or be guided by local laboratory cut off trough value.
    - Normal renal function: do not wait for the amikacin level before giving the next dose. The level should be used to adjust the dose for the next day if applicable.
    - Impaired renal function: wait for the amikacin level and give the next dose when level is <5 mg/L.
    - In obese patients or in patients with resistant Gram-negative bacteria also measure peak concentrations (0.5–1 hour after infusion). Aim for peak of >30 mg/L (or ten times higher than the MIC for resistant organisms).

      ** Ideal body weight calculator:* https://www.mdcalc.com/ideal-body-weight-adjusted-body-weight

AMIODARONE, ORAL

- Amiodarone, oral, 800 mg daily for 7 days.
  - Then 600 mg daily for 3 days.
  - Hypotension may occur, especially during the loading dose phase
  - Titrate to maintenance dose of 200–400 mg daily.
  - May cause hypothyroidism or thyrotoxicosis - monitor thyroid function every 6 months.
  - Monitor for pulmonary symptoms and perform baseline CXR before starting long-term therapy and annually thereafter to monitor for interstitial pulmonary fibrosis.
  - In chronic use, liver function tests and tests for hypokalaemia (if on diuretic) should be conducted periodically.

AMOXICILLIN/CLAVULANIC ACID, ORAL

- Amoxicillin/clavulanic acid, oral, 875/125 mg (containing 875 mg amoxicillin trihydrate and 125 mg clavulanic acid) 12 hourly.
  - When treating pneumonia in areas where there is a confirmed high prevalence (≥ 5%) of *Streptococcus pneumoniae* with intermediate resistance to penicillin: dose 8 hourly
    ADD: Amoxicillin 1 g, oral, daily between the amoxicillin/clavulanic acid doses (i.e. 8 hours after the morning dose of amoxicillin/clavulanic acid).

AMOXICILLIN/CLAVULANIC ACID, IV

Amoxicillin/clavulanic acid IV is not suitable for intramuscular or subcutaneous administration.

- Amoxicillin/clavulanic acid, 1.2 g powder vials for intravenous injection containing amoxicillin sodium equivalent to 1 g of amoxicillin and potassium clavulanate equivalent to 200 mg clavulanic acid.
  - **Dosage Recommendation:** Amoxicillin/clavulanic acid, 1.2 g, IV, 8 hourly.
  - **Directions for use:**
    - Powder vials for injection can be reconstituted by dissolving in 20 mL water for injection.
    - Reconstituted vials can be administered intravenously by injection over 2 minutes or slow intravenous infusion over 30 minutes.
    - For intravenous infusion, the reconstituted vial should be further diluted with the desired volume of a suitable infusion fluid (e.g. Sodium chloride 0.9%, 100 mL).
    - **The contents of the vials must be used within 20 minutes.**
  - **Precautions:**
    - Allergy to penicillins.
    - Drug-induced cholestatic hepatitis may occur, typically a few weeks after starting therapy. Use with caution in patients with evidence of hepatic dysfunction.
    - Dosage adjustments required in renal impairment:
      - CrCl >70 mL/minute: no dose adjustment required.
      - CrCl 10–30 mL/minute: 1.2 g as a single dose followed by 600 mg 12 hourly.
      - CrCl <10 mL/minute: 1.2 g as a single dose followed by 600 mg daily.

AMPHOTERICIN B DEOXYCHOLATE, IV

- Amphotericin B deoxycholate, IV, 0.7–1 mg/kg daily, dose and duration of therapy depend on indication for use and infecting organism. Daily dose must not exceed 1.5mg/kg.

  - Reconstitue in 5% dextrose only (as incompatibile with saline solution). Do not reconstitute or dilute with saline or administer through an

intravenous line that has previously been used for saline, unless first flushed with dextrose solution (5 %,10 % or 20 %) for infusion.
  - Administer over a period of 2–6 hours.
  - Ensure adequate hydration, by loading with 0.9% normal saline, to minimise the risk of nephrotoxicity.
- Treat infusion reactions with hydrocortisone 25mg IV. In such cases, premedicate with hydrocortisone 25mg IV and paracetamol 1g orally, half an hour before each dose, until tolerance develops.

Monitoring

- Serum potassium, magnesium and creatinine (baseline and twice weekly). Monitoring of serum potassium and creatinine should occur more frequently in neutropenic patients (3 times a week).
- Monitor haemoglobin (baseline and weekly).
- Careful attention to fluid monitoring of intake and output.
- For management of hypokalaemia, see section 7.2.2: Hypokalaemia.
- Monitor drip sites and replace if any evidence of phlebitis.

Management of elevated creatinine in cryptococcal meningitis

If creatinine increases by ≥2 fold from baseline value, stop amphotericin B deoxycholate, increase pre-hydration to 1 litre 8 hourly (watch for fluid overload), and switch to fluconazole 600mg daily and flucytosine 25mg/kg (with the flucytosine dosing interval adjusted for eGFR).

- Once improved, restart to complete 7 days amphotericin B deoxycholate in total
- (Adapted from: WHO. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: Prevention, monitoring and management of amphotericin B toxicity. 2011 [Online] [Accessed March 2016] http://www.ncbi.nlm.nih.gov/books/NBK299520/pdf/Bookshelf_NBK299520.pdf

Management of elevated creatinine for fungal infections other than cyptococcal meningitis

If creatinine increases by ≥2 fold from baseline value, either omit an amphotericin B dose, or increase pre-hydration to 1 litre 8 hourly.

- Once improved, restart at 0.7 mg/kg daily and consider alternate day amphotericin B.
- If creatinine remains elevated i.e. ≥2 fold from baseline value, discontinue amphotericin B and continue with fluconazole, oral, 800 mg daily (for fungal infections known to be responsive to fluconazole, e.g. *Cryptococcus*).

  (Adapted from: WHO. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: Prevention, monitoring and

management of amphotericin B toxicity. 2011 [Online] [Accessed March 2016] http://www.ncbi.nlm.nih.gov/books/NBK299520/pdf/Bookshelf_NBK299520.pdf

LIPOSOMAL AMPHOTERICIN B, IV

- Liposomal amphotericin B, IV, 10 mg/kg single dose for cryptococcal meningitis
  - Reconstitue in 5% dextrose only (as incompatibile with saline solution). Do not reconstitute or dilute with saline or administer through an intravenous line that has previously been used for saline unless first flushed with dextrose solution (5 %,10 % or 20 %) for infusion.
  - Administer over a period of 2 hours.
  - Liposomal amphotericin B contains soya oil. Patients allergic to peanut or soya should not be given liposomal amphotericin B.

Monitoring in patients with cryptococcal meningitis

- Anaphylaxis and anaphylactoid reactions have been reported in association with liposomal amphotericin B. If a severe anaphylactic/ anaphylactoid reaction occurs, the infusion should be immediately discontinued and the patient should not receive further infusion.
- Monitor blood glucose levels in diabetic patients - each vial of liposomal amphotericin B contains 900mg of sucrose. Furthermore, liposomal amphotericin B must be reconstituted with dextrose 5%.

CEFEPIME, IV

- Cefepime IV/IM, 1–2 g 12 hourly.
  - Renal adjusted dosing:
    - eGFR >50 mL/minute: 100% of daily dose
    - eGFR 10–50 mL/minute: 50–100% of daily dose
    - eGFR <10 mL/minute: 25–50% of daily dose

      (Source: *Bennet, WM. Drug prescribing in renal failure. Fifth edition*).

CLINDAMYCIN, IV

- Clindamycin IV, 600 mg, 8 hourly (maximum of 4.8 g/day)
  - Dilute the contents of the vial in 100 mL of diluent prior to infusion.
  - Infuse over 20 minutes.
  - **Note:** Rapid infusion can cause flushing, pain, thrombophlebitis, hypotension and cardiopulmonary arrest.
  - Local pain at injection site may be minimised by deep IM injection. Not more than 600mg should be injected into a single IM injection site.

DIGOXIN, ORAL

- Digoxin, oral, 0.125 mg daily, adjust according to rate response, if in atrial fibrillation, and trough plasma level.
  - Digoxin trough plasma levels (before the morning dose) should be maintained between 0.6–1 nmol/L. Monitor after 7 days and periodically thereafter.
  - Patients at high risk of digoxin toxicity are:
    - the elderly,
    - patients with renal dysfunction,
    - hypokalaemia,
    - hypomagnesaemia,
    - hypercalcaemia and
    - patients with low lean body mass.

FLUCYTOSINE, ORAL

- Flucytosine, oral, 25 mg/kg 6 hourly for 14 days for cryptococcal meningitis.

Monitoring

- Flucytosine is partially metabolised to 5-fluorouracil which is potentially teratogenic. Women of childbrearing age should be counselled on effective contraception during treatment and up to one month following discontinuation of treatment. Male patients should be counselled to use effective contraception during treatment and for 3 months following discontinuation of flucytosine treatment.

Management of elevated creatinine

Dosage adjustment is required in patients with renal impariment as tabulated below:

Creatinine Clearance	Single Dose	Dosing Interval
CrCl >40mL/min	25mg/kg	6 hourly
20 ≤ CrCl < 40mL/min	25mg/kg	12 hourly
10 ≤ CrCl < 20mL/min	25mg/kg	24 hourly
CrCl <10mL/min*	25mg/kg	48 hourly

***Adopted from:** Flucytosine | Johns Hopkins ABX Guide (hopkinsguides.com) https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540227/all/Flucytosine?q=flucytosine#3.2 and *Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal*

disease among HIV-infected persons: 2019 update. South Afr J HIV Med. 2019 Nov 8;20(1):1030. https://pubmed.ncbi.nlm.nih.gov/32201629/ Source: The Sanford guide to antimicrobial therapy 2019 / editors, David N, Gilbert MD, George M, Eliopoulos MD, Henry F, Chambers MD et al. Sperryville, VA, USA: Antimicrobial Therapy, Inc., [2019]).

GENTAMICIN, IV

- Gentamicin, IV, 5–6 mg/kg once daily.
  - If BMI is >40 kg/m^2 use ideal body weight* + 40% of the difference between ideal and actual body weight.
  - Administer slowly over 3 minutes or infused over 20–30 minutes up to 2 hours, diluted in 5% dextrose or 0.9% sodium chloride solution.
  - For streptococcal endocarditis: 1.5 mg/kg 12 hourly (in combination with penicillin).
  - Renal impairment dosage adjustment (eGFR <60 mL/minute):
    - Administer 3–4 mg/kg loading dose and adjust further dosing according to plasma concentrations.
  - Gentamicin is potentially nephrotoxic and ototoxic – monitor creatinine three times per week and discontinue if vestibular or cochlear symptoms develop.
  - Therapeutic drug monitoring: Sample after the third dose;
    - Draw trough concentrations immediately before dose; peak concentrations 0.5–1.0 hours after dosing from the drip-free arm.
    - Therapeutic ranges: Peak >8 mcg/ml, trough <1 mcg/ml
    - Reduce the dose per kg or consider omitting a dose if concentration is supratherapeutic. If the plasma concentration is subtherapeutic but the patient has signs of toxicity, change to an alternative agent.

      ** Ideal body weight calculator:* https://www.mdcalc.com/ideal-body-weight-adjusted-body-weight

LABETALOL, IV

- Labetalol, IV infusion, 2 mg/minute to a total of 1–2 mg/kg.
  - Initial dose: 2 mg/minute
  - Titrate to response up to 300 mg total cumulative dose (e.g. discontinue after 2.5 hours of 2 mg/minute).
  - Usual total dose required is 50–200 mg (1–2 mg/kg).
  - Commence an oral antihypertensive regimen as soon as the infusion is discontinued.

LITHIUM, ORAL

- Lithium, oral, 400mg at night.
  - Check eGFR and thyroid function before starting lithium. Lithium may be used once hypothyroidism is treated. Adjust doses if renal function is impaired and, in the elderly, as below.
  - Start with 400mg (200mg in the elderly) at night. Check the plasma level after 7 days and adjust dose as needed (usually by 200–250mg). Check plasma levels 7 days after each dose adjustment until desired plasma

level is reached. *(Adopted from: Maudsley prescribing guidelines in psychiatry / David M. Taylor, Thomas R. E. Barnes, Allan H. Young. 13th edition. | Hoboken, NJ : Wiley, 2019.)*

- Dose-adjust in renal impairment:
  - CrCl ≥ 60 mL/minute: Normal daily dose (see above).
  - CrCl 30 to < 60 mL/minute: Initiate at low doses (e.g., 150 to 300 mg/day) in 1 to 2 divided doses, titrate slowly based on clinical response and tolerability, monitor levels frequently.
  - CrCl < 30 mL/minute: Avoid Use.

Adapted from Up to Date: Dosing: Kidney Impairment: Adult (Lithium). Available at: https://www.uptodate.com/

- Lithium has a narrow therapeutic window. The therapeutic range is 0.4–0.8 mmol/L for maintenance therapy, and 0.8–1.0 mmol/L in acute mania.
- Measure serum concentrations at 12 hours after the last dose. Note the time of blood specimen collection and the time of the last dose on the laboratory request form to facilitate accurate reference range and interpretation.
- Maintain therapeutic blood levels of lithium for as long as the patient is on lithium. Monitor lithium levels and renal function monthly for the first 3 months of therapy.
- Monitoring once stable levels have been achieved: Lithium levels, eGFR and TSH 6-monthly. Serum calcium (for lithium-induced hyperparathyroidism) annually.
- Lithium induced hypothyroidism is treated with thyroxine (note that TFTs usually normalise if lithium is discontinued).
- **Beware of combining lithium with ACE-inhibitors, NSAIDs and thiazide diuretics, as they all potentiate the risk for lithium toxicity**.
- Pregnancy - Lithium has been associated with congenital abnormalities in the newborn with first trimester exposure. Women of child-bearing potential should be on contraception. Risk-benefit assessment required for indication of maternal use during pregnancy.
- Discontinuation: abrupt discontinuation may precipitate a manic episode in the first few months after stopping lithium. Adherence support is important. Planned discontinuation should be gradual, over at least a month, with reductions of plasma levels by about 0.2 mmol/L at a time.

METFORMIN, ORAL

- Metformin, oral, 500 mg twice daily with meals.
  - Titrate dose slowly depending on HbA_{1c} and/or fasting blood glucose levels to a maximum dose of 850 mg 8 hourly.
  - Monitor renal function.
  - Dose-adjust in renal impairment as follows:
    - eGFR > 60 mL/minute: Normal daily dose (see above).

  - eGFR < 60 mL/minute: Half of the daily dose.
  - eGFR < 30 mL/minute: Stop metformin.
- Contra-indicated in:
  - renal impairment i.e. eGFR < 30 mL/minute,
  - uncontrolled congestive cardiac failure,
  - severe liver disease,
  - patients with significant respiratory compromise, or
  - peri-operative cases.
- Drug-drug interaction with dolutegravir (DTG): DTG may increase the serum concentration of metformin. Limit maximum dose of metformin to 1000 mg daily if concomitant use with DTG.

MORPHINE, IV

- Morphine, IV, to a maximum dose of 10 mg.
  - Morphine, IV, 3–5 mg as a single dose then further boluses at intervals of 5–10 minutes and monitor all vitals closely.
  - Dilute 10 mg up to 10 mL with sodium chloride 0.9%.
  - Repeat after 4 hours if necessary.
  - Monitor response to pain and effects on respiration and blood pressure.
  - Onset of action: 5–10 minutes. Duration of action: 4-5 hours.

PHENYTOIN, IV

- Phenytoin, IV, 20 mg/kg diluted in sodium chloride 0.9% **(not dextrose)** administered not faster than 50 mg/minute, with cardiac monitoring. Elderly patients and patients with impaired liver function, require lower doses initially with subsequent adjustment. IV administration in the elderly and patients with impaired liver function should not exceed 25mg/minute (possibly as little as 5-10mg/minute).
  - Mixing instructions: For preparation of the infusion, the contents of a vial of phenytoin should be well mixed in 0.9% sodium chloride at a concentration of less than 4 g/L and be completely administered within 1 hour of mixing to avoid precipitation.
  - Cardiac monitoring should be done during the infusion.
  - If dysrhythmias occur, interrupt the infusion temporarily and reintroduce slowly, once rhythm becomes stable.
  - Continue with, IV, 5 mg/kg/day (300 mg daily for most adults).

POTASSIUM CHLORIDE, IV

Must always be diluted before infusion.

- Potassium chloride, IV, diluted in 1 L sodium chloride 0.9%.
  - Rapid infusion of potassium chloride can cause fatal dysrhythmias.
  - Infusion rates > 20 mmol/hour are very irritating to peripheral veins.
  - Potassium chloride 15% for intravenous use, contains 20 mmol K+ per 10 mL ampoule.

- Potassium chloride infusion – see diabetes section for the administration of potassium infusion in DKA (Section 8.6.2: Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS)).
- Non DKA; Dilute potassium chloride in a non-glucose containing solution (e.g. 0.9% sodium chloride) to a concentration not exceeding 40 mmol/L. Maximum rate of infusion should not exceed 20 mmol/ hour. Total daily dose should not exceed 3mmol/kg/day (max 400mmol/day).
- As large volumes of solution may need to be given, monitor the patient for fluid overload.
- For preparation of the infusion, the contents of an ampoule of potassium chloride should be well mixed in 0.9% sodium chloride.

An example prescription might be: '*dilute two 10 ml ampoules of 20 mmol KCl in 1 litre of 0.9% sodium chloride, and mix thoroughly. Infuse at a rate of 125 ml/hour, and repeat 8 hourly (i.e. give three litres of the solution containing 40 mmol KCl per litre as a constant infusion over a 24 hour period)*'.

PREDNISONE, ORAL

Prednisone tapering - generally required after prolonged use (i.e. >1 week)

- Example of a dose reduction regimen: for an initial dose of 60 mg daily, reduce initial dose to 2/3 the original dose, and continue as follows:
  - » 40 mg/day in week 2,
  - » 25 mg/day in week 3,
  - » 20 mg/day in week 4,
  - » 15 mg/day in week 5,
  - » 10 mg /day in week 6 and
  - » thereafter 5 mg daily for 1 week and then discontinue.

Note: Weaning should be adjusted according to clinical context. If control deteriorates on weaning return to the previous effective dose.

VANCOMYCIN, IV

- Vancomycin, IV, 25-30 mg/kg as a loading dose. Follow with 15-20 mg/kg/dose 12 hourly. Duration depends on the organism & site of infection: for methicillin-resistant *Staphylococcus aureus* duration is 2 weeks after first negative blood culture, or 4 weeks for complicated infections (e.g., endocarditis).
  - The rate of infusion should not exceed 1 g/hour (i.e., at least 2 hours for a 2 g infusion).
  - **Note:** Rapid infusion can cause flushing, pain, thrombophlebitis, hypotension and cardiopulmonary arrest.
  - Weigh patients and estimate eGFR (see chapter 7: Nephrological/ urological disorders).

- See table for dosing interval and measurement of trough concentrations.
- Aim for trough concentration of 10–20 mcg/mL except in osteitis or endocarditis or if MIC > 1 when trough should be 15–20 mcg/mL.
- If trough is too low, increase dose (specialist consultation if unsure how much to increase) and/or shorten dose interval to 8 hourly.
- If trough too high, decrease dose or increase dosing interval (specialist consultation if unsure how much to adjust).
- Vancomycin is not significantly removed by conventional intermittent haemodialysis. Dosing and monitoring as for those with eGFR <25 mL/minute.

Dosing intervals and when to measure trough concentrations of vancomycin:

eGFR (mL/minute)	**Dosing interval (hours)**	**Measurement of trough concentrations**
>80	12	Before 3rd dose
50-79	24	Before 3rd dose
35-49	36	Before 2nd dose
25-34	48	Before 2nd dose
<25 **or** haemodialysis **or** CAPD	When trough level <15	3 days after loading dose

(Adapted with permission from Groote Schuur hospital's protocol).

WARFARIN, oral

- Warfarin, oral, 5 mg daily adjusted to maintain INR between 2 and 3.
  - *Warfarin interactions:*
    A large number of medicines interact with warfarin leading to under- or over-anticoagulation, and careful evaluation of all new medicines, herbal and over-the counter products is critical. This includes (but is not an exhaustive list):
    - Medicines altering platelet function e.g., NSAIDs, aspirin, clopidogrel, etc.
    - Food (e.g. cruciferous vegetables) or medicines (e.g. antibiotics) altering vitamin K synthesis
    - Medicines interfering with warfarin metabolism e.g. efavirenz, rifampicin, macrolide antibiotics, simvastatin, phenytoin, carbamazepine, Imidazoles (ketoconazole, fluconazole, itraconazole, miconazole) quinolones, co-trimoxazole, selective serotonin reuptake inhibitors (SSRIs), glibenclamide etc.

- Grapefruit juice St John's wort (commonly used herbal preparation), Ginkgo biloba and garlic

Unless INR is markedly out of range the modest adjustments recorded below should be followed:

Initiation

Warfarin initiation dosing protocol (week 1) with INR target: 2–3		
Day therapy	**INR Value**	**Total daily dose**
Day 1		5 mg daily (2.5 mg daily for high sensitivity)
2 to 3 days after initiation	< 1.5 1.5 – 1.9 2.0 – 2.5 > 2.5	5–7.5 mg daily 2.5–5 mg daily 2.5 mg daily Hold warfarin and recheck INR next day
2 to 3 days after last INR check	< 1.5 1.5 – 1.9 2.0 – 3.0 > 3.0	7.5–10 mg daily 5–10 mg daily 2.5–5 mg daily Hold warfarin and recheck INR in1–2 days

Frequency of INR monitoring after initiation of warfarin	
Check INR	
Every 2–3 days	Until INR within therapeutic range on 2 consecutive INR checks
Then every week	Until INR within therapeutic range on 2 consecutive INR checks
Then every 2 weeks	Until INR within therapeutic range on 2 consecutive INR checks
Then every 4 weeks	When dose is stable, check monthly

Maintenance

Warfarin maintenance dosing protocol to maintain an INR 2-3:

INR<1.5	INR: 1.5-1.9	INR: 2.0-3.0	INR: 3.1-4.0	INR: 4.1-5	INR: 5.1-9.0	INR>9.0
Extra Dose. Increase **weekly** dose 10%.	Increase **weekly** dose 5%.	No change.	Decrease **weekly** dose 5%.	Withhold 1 dose. Decrease **weekly** dose 10%.	*Withold 2 doses. Decrease **weekly** dose 20%.	Admit.

*History and examination to exclude bleeding. Admit persons with additional risks for bleeding.

Frequency of INR monitoring for maintenance of warfarin	
Check INR	
Every 3–5 days	If start/stop interacting medication, change in diet, change in activity level or other change that could affect INR.
Every 1–2 weeks	Once INR within therapeutic range on 2 consecutive INR checks.
Every 4 weeks	If maintained on same stable dose < 6 months and INR stable.
Every 6–8 weeks*	If maintained on same stable dose ≥ 6 months and INR stable.

*A stable INR is when a patient is maintained on the same dose of warfarin for ≥6 months. INR would require to be checked every 6-8 weeks.

Time in therapeutic range (TTR)

The Rosendaal method is commonly used for monitoring and is validated to assess the time in therapeutic range (TTR). A TTR < 65% is associated with poorer outcomes and may signal a re-assessment of patient adherence and dosing.

Source: Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993 Mar 1;69(3):236-9. https://pubmed.ncbi.nlm.nih.gov/8470047/

Rosendaal calculation procedure (preferred method)

Example:

A patient has an INR reading of 2.4 on 1 October and a follow up INR measurement of 3.2 on 17 October.

If the patient's INR moves linearly from 2.4 to 3.2 throughout the 16-day interval, then we can estimate that the patient was within the INR therapeutic range (2 – 3) for approximately 75% of the time interval.

See calculation steps below:

Calculation steps:	Example:
1. Calculate the duration of the time interval between 2 INR values*	1 October to 17 October = 16 days
2. Calculate the amount of total INR shift in the time interval.	INR on 1 October: 2.4 INR on 17 October: 3.2 Total INR shift: 0.8
3. Calculate the amount of INR shift that is within the therapeutic range.	Upper INR threshold = 3.0 INR measurement in range = 2.4 Amount of INR shift within range: 3.0 - 2.4 = 0.6
4. Calculate the percent of total shift that is within therapeutic range. This is the %TTR for this specific time interval.	$\frac{\text{Amount of INR shift within range}}{\text{Total INR shift}}$ = 0.6 /0.8 = 75%
5. Estimate the number of days in the interval that were within the therapeutic range	Duration of INR measurement interval X % TTR = 16 days X 75% = 12 days in therapeutic range
6. To calculate overall %TTR over multiple INR measurements, add total days in range for each time interval and divide by the total period of therapy.	A follow-up INR measurement on 30 October was 2.7. The %TTR for the interval of 17-30 October is 60% and days in therapeutic range is 8 days. The overall days in therapeutic range is 12 days + 8 days and the overall therapeutic period is 16 + 13 days. $\frac{\text{20 days in therapeutic range}}{\text{29 days in treatment period}}$ = 69% cumulative TTR

Adapted from the *Rosendaal Method for % INR in range [Internet]. Using the ROSENDAAL method for calculating therapeutic time in range (TTR). INRpro.com; [cited 2022Nov29]. Available from: https://www.inrpro.com/rosendaal.asp*.

Note:

» The Rosendaal method for calculating TTR is not advised for intervals longer than 56 days/2 months between INR measurements.

» For step 3, if both INR measurements above or if both INR measurements are below the therapeutic range, time spent in therapeutic range is 0 and %TTR is also 0% for that time interval. E.g. first INR = 1.5 and second INR = 1.7

» For step 3, if one INR measurement is below therapeutic range and one is above the therapeutic range, then the INR shift within the therapeutic range will be 1. E.g. first INR = 1.5 and second INR = 3.2.

» For a TTR <65% adherence with warfarin therapy should be assessed and

reinforced with the patient. Adjust the dose of warfarin only once it is established that poor adherence is not the cause of the sub-therapeutic TTR.

Frequency in range (FIR) (alternative to the preferred Rosendaal method, when a simple manual calculation is required).

Warfarin anticoagulation may also be monitored using the frequency in range (FIR) method which performs comparably to the TTR method. FIR should be maintained at a level greater than 54% as this was found to be a good predictor of optimal anticoagulation (TTR >/= 65%).

Soure: Parboo P et al. A comparison between TTR and FIR as a measure of the quality of anticoagulation in patients with atrial fibrillation. Wits Journal of Clinical Medicine, 2019, 1(1) 23–30

The FIR is calculated using the following formula:

$$\text{Frequency in range (\%)} = \frac{\text{Number of tests within therapeutic range}}{\text{Total number of tests performed}}$$

Note:

» The FIR method is less reliable when INR levels are measured at irregular intervals

The South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022 was used in the update of sections in Appendix II prescribing information for specific medicines.