



GOVERNMENT OF KERALA

Abstract

Health & Family Welfare Department - Management of Leptospirosis disease in the State - Treatment Guidelines For Leptospirosis - Orders issued.

HEALTH & FAMILY WELFARE (F) DEPARTMENT

G.O.(Rt)No.2108/2022/H&FWD Dated,Thiruvananthapuram, 25-08-2022

ORDER

Government are pleased to issue the "Treatment Guidelines for Leptospirosis" detailing the clinical management of the patients at the level of PHC/CHC/THQH/Tertiary Care Centres, as annexed to this order.

(By order of the Governor)
TINKU BISWAL
PRINCIPAL SECRETARY

To:

The State Mission Director -National Health Mission,
Thiruvananthapuram.

The Director of Health Services, Thiruvananthapuram.

The Director of Medical Education, Thiruvananthapuram.

The Managing Director, Kerala Medical Services Corporation Ltd

All District Medical Officers (Health)

All Superintendents of Government Medical Colleges

Principal Accountant General (A&E/Audit) Kerala.

Information & Public Relations (Web & New Media) Department

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Forwarded /By order

Signed by Savitha M V

Date: 25-08-2022 10:58:38

Section Officer

TREATMENT GUIDELINES FOR LEPTOSPIROSIS

AT THE PHC/CHC LEVEL

All people coming from flood-affected areas or those who have visited flood-affected areas presenting with fever, headache, and myalgia with or without diarrhea to be immediately started on **Tab. DOXYCYCLINE 100 1-0-1 for 7 days**.

Those patients with red flag signs like tachypnoea [$>24/\text{min}$], tachycardia out of proportion to fever [IF $\text{HR}>10$ for every 1°F rise in temp], hypotension [sys BP <100 mm of Hg], cold clammy extremities, altered sensorium, jaundice, oliguria or hemorrhagic manifestations need to be referred to higher centers.

Those patients without red flag signs send back on Doxycycline, should be followed up daily and asked to report back in case of red flag signs.

All pregnant women and those with co-morbidities like uncontrolled diabetes mellitus, cirrhosis, chronic kidney disease, coronary artery disease, COPD, HIV, malignancies, hematologic disorders, and those on steroids or other immunosuppressants must be referred to a higher center.

AT THE THQ LEVEL

Inj. Crystalline Penicillin is to be started immediately at a dosage of 20 L Q6H intravenous after a test dose. [For a child 3 to 4 lakh units/kg/day divided into 6 hours intravenously]. The first dose of Inj. CP is to be given as a supervised dose with the patient in the supine position [ie with emergency drugs, cannula, AEFI kit etc in place]

In case of a past history of penicillin anaphylaxis or in case of a positive skin test, the alternative is Inj Ceftriaxone 1 gm IV BD, after negative skin test [for a child, Inj Ceftriaxone 100 mg/kg/day divided into 2 doses, at 12 hourly intervals].

In the case of positive skin test to ceftriaxone, alternatives are IV Azithromycin 500 mg for 5 days or IV Doxycycline 200 mg IV loading dose and 100 mg IV twice daily for 7 days.

From THQH, patients should be referred to higher centers in case of

1. Hypotension [SBP <100 mg/Hg] with a disproportionate increase in heart rate [HR >10 FOR every 1°F rise in temperature], cold clammy extremities, diaphoresis—consider Myocarditis and refer.

2. Tachypnoea [$>30/\text{min}$], hypoxemia [$\text{spo}_2 <90\%$ despite continuous oxygen], chest signs—consider ARDS and refer.
3. Progressively deepening jaundice or if INR >1.5 —refer.
4. Oliguria not responding to fluid challenge [1 L NS to be infused over 30 min provided there is no clinical evidence of myocarditis]—consider AKI and refer.
5. Hemoptysis, melena, hematemesis, menorrhagia, spontaneous gum bleed—need to be referred.
6. Alteration of sensorium persisting after correction of electrolytes and after ruling out CNS hemorrhage—to be referred.

INVESTIGATIONS TO BE DONE AT CHC/THQH LEVEL.

1. Hb, TC, DC, ESR, PLC.
2. RBS, LFT, RFT, Na^+ , K^+
3. In case of oliguria and severe myalgia—send CPK.
4. Routine Urine Examination
5. In case of worsening jaundice—send PT/INR.
6. In case of hemorrhagic manifestations—PLC, Peripheral smear, PT/INR, APTT.
7. Thrombocytopenia with altered sensorium—CT BRAIN PLAIN.
8. In case of hypotension with relative tachycardia — Troponins [TROP T, TROP I in case of kidney injury].
9. Severe epigastric pain — send Lipase to rule out pancreatitis.
10. Rule out other Tropical fever syndromes [Dengue, malaria, scrub typhus, Enteric fever, H1N1].

[In the post-flood scenario, treatment of leptospirosis has to be based on clinical features alone. Lab testing is only for surveillance purposes. Moreover, Lepto ELISA/card test will become positive only after 7 days.]

LEPTOSPIROSIS TREATMENT GUIDELINES FOR TERTIARY CARE CENTERS

1. Any patient coming to the OPD/Emergency department with acute febrile illness with myalgia, headache $\pm$ diarrhea especially in patients from flood-affected area or those who have visited flood-affected area should be provisionally diagnosed as possible leptospirosis and should be started empirically on Tab DOXYCYCLINE 100 mg 1-0-1 for 7days.

2. If there are red flag signs or symptoms like tachypnoea [$>24/\text{min}$], tachycardia disproportionate to fever [rise in HR >10 for 1°F rise in temperature], hypotension [SBP <100 mm of Hg], jaundice, alteration of the sensorium, oliguria, hemorrhagic manifestation –patients should be admitted and initiated on INJ CRYSTALLINE PENICILLIN 20 L Q6H FOR 7DAYS after negative skin test.

RED FLAG SIGNS

1	Tachypnoea [$>24/\text{min}$]
2	Tachycardia disproportionate to fever [rise in HR >10 for 1°F rise in temperature]
3	Hypotension [SBP <100 mm of Hg]
4	Jaundice
5	Alteration of sensorium
6	Oliguria
7	Hemorrhagic manifestation

3. In case of previous history of anaphylaxis to Inj Crystalline penicillin or in case of positive skin test, Inj Ceftriaxone 1 gm IV twice daily for 7 days may be used instead of Crystalline penicillin after skin test.
4. In case of positive skin test to Inj Ceftriaxone, intravenous doxycycline or IV azithromycin [500 mg IV daily for 5 days] can be used as an alternative.

ONCE ADMITTED

Focused investigations should be done to rule out

1. Myocarditis
2. ARDS
3. Hepatitis
4. Acute kidney Injury.
5. Pancreatitis
6. Myositis/Rhabdomyolysis.

7. Aseptic Meningitis.

8. Acalculous cholecystitis.

9. DIC

Investigations to rule out other tropical fever syndromes must be sent [Dengue, malaria, enteric fever, scrub typhus, H1N1].

Two sets of blood cultures must be sent to rule out bacterial sepsis.

Patients with myocarditis, ARDS/Severe pulmonary hemorrhage syndrome [pulmonary leptospirosis] should ideally be admitted to an ICU/HDU.

[In the post-flood scenario, treatment of leptospirosis has to be based on clinical features alone. Lab testing is only for surveillance purposes. Moreover, Lepto ELISA/card test will become positive only after 7 days.]

CRITICAL CARE

FLUID RESUSCITATION:

IVC ASSESSMENT FOR FLUID RESPONSIVENESS

In spontaneously breathing patients, the following measurements suggest fluid responsiveness

- a. IVC measuring <2 cm in diameter coupled with IVC collapse >50% with each breath or
- b. IVC collapsibility >12%

In mechanically ventilated patients, IVC distensibility index >18% suggests fluid responsiveness.

COAGULOPATHY, THROMBOCYTOPENIA

Coagulopathy and thrombocytopenia need to be corrected in case of spontaneous bleeding manifestations.

PULMONARY:

Presentation vary from subtle clinical features to deadly Alveolar hemorrhage and ARDS.

Pulmonary complications are more in patients with Thrombocytopenia, hemoptysis, anuria, those requiring Renal replacement therapy, diabetes and those having shortness of breath.

Use NIV only for mild ARDS [P/F 200-300].

Invasive ventilation for P/F < 200 or low GCS

Intubation and mechanical ventilation.

Volume control or pressure control lung protective ventilation—

Plateau pressure <30 cm H₂O. Start with tidal volume of 6ml per Kg—decrease to 4 ml/kg if plateau pressure is >30 cm H₂O.

Set FIO₂ to keep spO₂ 88 to 94.

Adjust respiratory rate according to PaCO₂ [max RR 35].

PEEP: According to ARDS net protocol or adjust to a PEEP with good oxygenation and no adverse hemodynamic effects.

Ventilatory management of diffuse alveolar hemorrhage in Leptospirosis.

1. Identify acute respiratory failure early, Consider Pulse dose of Methyl prednisolone.
2. Clinical: Tachypnoea, use of accessory muscles, intercostals indrawing, diaphoresis
ABG: PaO₂ <60 with FiO₂>0.5: CO₂ retention with respiratory acidosis.
3. Manage as ARDS
4. Care of endotracheal tube— frequent suctioning to clear hemorrhage (preferably with closed suction.)
5. Consider muscle relaxants if Pplat >30 cm of H₂O in spite of optimal ventilator settings.
6. Prone ventilation—consider prone ventilation if P/F <150 in spite of optimal ventilator settings.
7. Permissive hypercapnia with pH> 7.2 .

STERIODS IN LEPTOSPIROSIS

For severe Leptospirosis with multiorgan failure Pulse steroids with Inj Methylprednisolone 1gm IV stat.

ACUTE KIDNEY INJURY

Pre-renal AKI should be corrected by Normal saline, if there is no clinical/echo/biochemical evidence of myocarditis.

In order to shorten door- to dialysis time, early Nephrology consultation should be sought.

Definition and classification of Acute Kidney Injury (AKI)

- AKI is defined as any of the following
 - Increase in Serum Creatinine by 0.3 mg/dl within 48 hours.
 - Increase in S. Cr to X 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.
 - Urine volume <0.5 ml/kg/h for 6 hours.

Hypercatabolic AKI is defined as acute renal shut down with an increase of urea >60mg/dL/day and creatinine >1 mg/dL/day with one of the following: an increase in serum potassium >1 mEq/L/day from baseline, serum uric acid >15 mg/dL, serum phosphate >8 to 10 mg/dL and a decrease of serum bicarbonate > 2 mEq/L/day from baseline.

Management of AKI

General considerations

- Evaluate patients with AKI promptly to determine the cause and correct them, with special attention to reversible causes.
- Pre-renal factors have to be identified and corrected. In case of hypotension, consider fluid resuscitation after ruling out myocarditis [relative tachycardia/bradycardia, elevated JVP, basal crepitations, muffled heart sounds, ECG-ST-T changes, preferably ECHO].
- If there is no hyperkalemia, Ringer Lactate is preferred over normal saline for fluid resuscitation. If Potassium >5.0 meq/L or in case of liver failure, Normal saline is to be preferred over Ringer Lactate.
- Fruits, fruit juices, tender coconut water and ORS to be avoided if serum potassium is >5.0 meq/L or in case of oliguria [if urine output is less than 30 ml/kg/hr for 6 hours or <400 ml/day]
- “Salted kanji water” is to be used if there is no evidence of hypervolemia.
- Oral /intravenous bicarbonate supplementation is to be considered if there is no evidence of hypervolemia.
- In the case of rhabdomyolysis [CPK > 3000], bicarbonate infusion is to be considered.
- If there is no evidence of fluid overload or myocarditis, Fluid challenge with 500 ml NS followed by Inj Frusemide 40 mg IV may be tried once.

Fluid challenge should not be repeated.

- **Do not** use diuretics to prevent AKI or to treat AKI, except in the management of volume overload.
- **Do not** use low-dose dopamine to prevent or treat AKI.
- Avoid nephrotoxic medications in patients with AKI.
- Withhold ACE Inhibitors and ARBs temporarily if patient is already on these drugs.

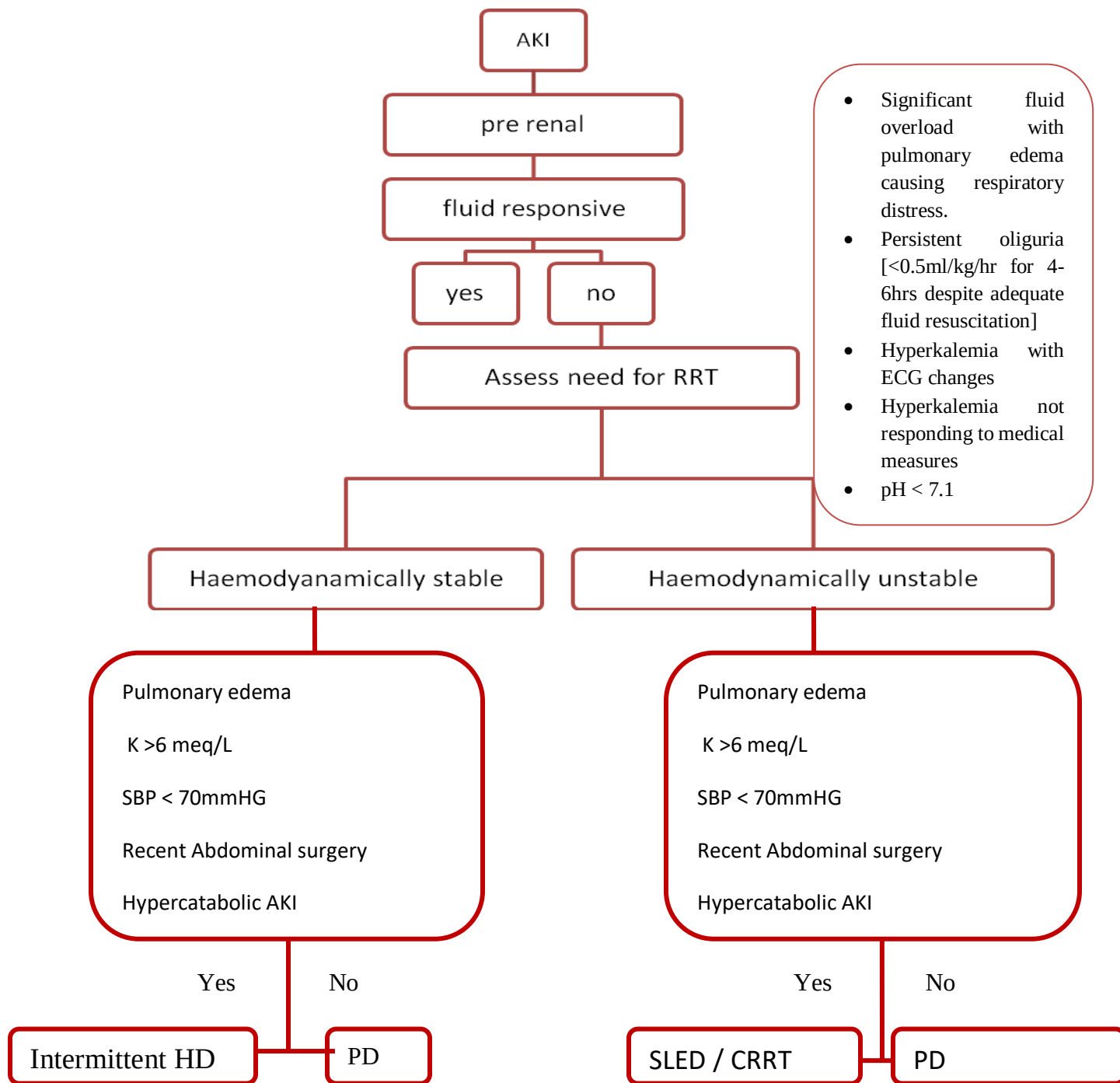
Renal Replacement Therapy

Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. Aim must be to minimize time to dialysis as far as possible.

Indications for initiation of RRT are

1. Significant fluid overload with pulmonary edema causing respiratory distress.
 2. Persistent oliguria [<0.5 ml/kg/hr for 4-6hrs despite adequate fluid resuscitation]
 3. Hyperkalemia with ECG changes
 4. Hyperkalemia not responding to medical measures
 5. pH < 7.1
- The decision to discontinue RRT is taken when kidney function has recovered to the point that it is adequate to meet the patient's needs.
 - Do not use diuretics to enhance kidney function recovery, or to reduce the duration or frequency of RRT.

Antibiotic	Dose for normal renal function	Dose for renal failure Estimated creatinine clearance ml/min		
		50-90	10-50	<10
Amoxicillin	500mg Q6h or 1gm Q8h	Q8h	Q12h	Q24h
Ampicillin	0.5-1gm Q8h	Q6h	Q6-12h	Q12-24h
Azithromycin dehydrate	500mg OD	No dose adjustment		
Cefotaxime	1gm Q6h	Q 8-12h	Q12-24	Q24h
Ceftriaxone	1gm Q12h	No dose adjustment		
Doxycycline	100mg BID	No dose adjustment		
Penicillin G	2 MU Q6h	No dose adjustment		



- The following **advantages of peritoneal dialysis** should be considered while deciding on the modality of RRT
 - Acute PD using semi rigid acute PD catheter is comparatively cheaper when compared to other modalities of RRT used in AKI.
 - PD does not need a vascular access hence advantageous in patients having difficulty in securing a vascular access.
 - PD can be easily performed in remote areas where hemodialysis machine and RO water system is not available.
 - Nursing staff with minimal training can initiate and continue PD.
 - PD is useful in critically ill patients with hypotension (SBP>70mmHG) as it is a hemodynamically friendly procedure.
 - Patients on mechanical ventilation can be considered for PD if hemodialysis machine or CRRT machine is not available in the ICU as shifting a mechanically ventilated patient to a dialysis unit is risky.
 - PD is useful in patients with increased bleeding risk as there is no requirement for anticoagulation.
- PD is **not preferred** when there is life-threatening pulmonary edema or severe hyperkalemia.
- PD is **less preferred** in patients with hypercatabolic AKI.
- CRRT or PD is preferred over intermittent HD, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema.
- When choosing a vein for insertion of a dialysis catheter in patients with AKI, consider these preferences- First choice: right jugular vein; Second choice: femoral vein; Third choice: left jugular vein; Last choice: subclavian vein with preference for the dominant side.
- Use ultrasound guidance for dialysis catheter insertion when available.
- Obtain a chest radiograph promptly after placement and before the first use of an internal jugular or subclavian dialysis catheter. Chest radiograph may be delayed in emergency situations if vein cannulation was easy, and good flow was present in both limbs of the catheter.

Prevention of AKI

- Identify patients at high risk for AKI.
- In a patient with dehydration, withhold ACE Inhibitors and ARBs temporarily if patient is already on these drugs. All patients on ACE Inhibitors and ARBs should be advised to temporarily stop these drugs at the time of significant vomiting or diarrhoea.
- Avoid prescribing NSAIDs in patients who are on ACE Inhibitors or ARBs.
- Avoid prescribing NSAIDs in patients who are fluid depleted.

Dialysis in Special situations

- Thrombocytopenia $< 50,000/\text{mm}^3$ with bleeding tendency, consider low dose heparin, heparin free or Peritoneal dialysis.
- If INR > 1.5 , consider low dose heparin, heparin free or peritoneal dialysis.
- Pancreatitis is not a contraindication to peritoneal dialysis

Protocol for bicarbonate infusion in rhabdomyolysis

- To be given for Serum CPK $> 3000 \text{ U/L}$ or increasing values
- Seventy-five ml of soda bicarbonate to be added to 500ml 5% dextrose and given at 200ml/hr to maintain urine pH above 6.5
- Bicarbonate infusion should be given only if serum pH < 7.5 , S bicarbonate $< 30 \text{ meq/L}$, hypocalcemia is absent, patient has adequate urine output and there is no evidence of LV dysfunction
- If a diuresis is established, bicarbonate therapy may be discontinued once CPK falls below 5000 U/L or if symptomatic fluid overload develops

DIRECTIVE FOR DOXYCYCLINE PROPHYLAXIS IN FLOOD AFFECTED AREAS IN KERALA

CATEGORY	EXPOSURE	RISK	ACTION
0	<u>No contact*</u> with flood waters, muddy, polluted water or dead/sick animals.	No risk	No need for doxycycline
1	<u>One time contact*</u> (with intact skin) with flood waters, muddy, polluted water or dead/sick animals	Low risk	Doxycycline [^] 200mg (100 mg x 2 tablets) once weekly for 2 consecutive weeks [#] .
2	<u>Continuing contact*</u> (with intact skin) with flood waters, muddy, polluted water or dead/sick animals. (eg: rescue/relief personnel, local residents with similar contact)	Moderate risk	Doxycycline 200mg once a week as long as the exposure continues.
3	<u>Any contact*</u> with flood waters/soil/mud when there are wounds/cuts/ open lesions of the skin or accidental ingestion of contaminated water.	High risk	Doxycycline 100 mg twice daily for 5 days. Ensure weekly prophylaxis as long as exposure continues ^{**} .

*Contact- walking, swimming, bathing, washing in flood waters, mud, polluted water, soil or contact with sick or dead animals, cleaning flood affected materials like furniture, utensils, floor, walls, personal belongings etc

[^]Doxycycline should be consumed with a full glass of safe drinking water after food.

[#] Considering the possibility of ongoing exposure. Directives may be revised as needed based on reassessment of the situation.

^{**}As far as possible reduce the risk of exposure by using personal protective equipment like rubber boots, heavy duty/utility gloves.

SPECIAL SITUATIONS:

Category	Chemoprophylaxis	Remarks
Pregnant and Lactating Mothers	Azithromycin 500mg once a week	Doxycycline is Contraindicated in pregnancy and lactation
Children 2-12 yrs	Doxycycline* 4mg/kg body weight once weekly.	-
Children <2 yrs	Azithromycin 10mg/kg body weight, once weekly.	-

NB: There is no upper age limit for consumption of doxycycline.

No dose modification is required for doxycycline in patients with kidney disease.

*Doxycycline can be used for children of all age groups as it binds less readily to calcium, teeth staining is not seen with duration of treatment < 21 days.