SHC De-escalation Guide for Uncomplicated Enterobacterales Bacteremia from a Urinary Source

Purpose: To provide guidance on IV to oral stepdown options, dose optimization and appropriate treatment durations (~7 days) for uncomplicated Enterobacterales bloodstream infection secondary to a urinary source, including those caused by resistant organisms (e.g. ESBL and ampC producers).

Definition: To meet the definition of uncomplicated, ALL 3 conditions below must be met:

1. *Urinary source AND adequate source control*
    - Removal/exchange of urinary catheters, nephrostomy tubes or stents present when the infection developed, and resolution of any known obstruction
    - These guidelines do not apply to patients with undrained abscesses, bacterial prostatitis, epididymitis or orchitis
2. *Patients without risk for opportunistic infections*
    - Recent solid organ transplant recipients (within 6 mos); expected prolonged neutropenia with ANC <500 cells/mL; CD4 cell count <200 cells/mL; chronic corticosteroids and/or immunomodulator therapy where opportunistic infection prophylaxis would be considered)
3. *Clinical improvement within 72 hours of effective antibiotic treatment*
    - at minimum includes afebrile x48 hrs without antipyretics AND hemodynamically stable

Repeat Blood Cultures: Follow-up blood cultures are generally not indicated to confirm culture clearance.

- Repeat cultures may be indicated if concerned for treatment failure (e.g. ongoing fever at 72 hours) and/or inadequate source control. These patients would not meet criteria for uncomplicated infection.

De-escalation: De-escalate to the narrowest spectrum antibiotic to complete treatment.

- Refer to Table 1 for preferred treatment options and dosing recommendations.
- Refer to Supplemental Table 2 for patient specific considerations/tolerability.
- Consider IV to PO switch when clinically stable, able to take other PO medications and if there is no concern for absorption issues.

Table 1. Recommended Agents for IV to PO Stepdown

Note: An IV beta-lactam x3-5 day lead-in is recommended prior to narrowing to a PO beta-lactam

Preferred Agents for de-escalation if susceptible	**Duration of Therapy**
Amoxicillin[a] 1g PO TID Amoxicillin-clavulanate 875/125mg PO TID Cephalexin[b] 1g PO QID Ciprofloxacin[c] 750mg PO BID Levofloxacin[c] 750mg daily SMX/TMP[c] 1-2 DS tabs PO BID - <80 kg: 1DS PO BID - >= 80kg: 2 DS PO BID	**7 days total** (Day 1 counted from 1st day active therapy) (Stone-related urinary obstruction: Day 1 counted from urinary decompression)
Alternative beta-lactams (lower bioavailability)	
Cefuroxime 500mg PO w/ food BID Cefpodoxime 400mg PO w/ food BID	

a. Infer susceptibility from ampicillin

b. Infer from cefazolin susceptibility in blood cultures

c. IDSA endorses quinolones or SMX/TMP as options for treatment of ampC producing organisms or ESBL infections with a urinary source

The above recommendations are based on available literature, national guidelines and expert opinion. They are not intended to replace clinical judgement. Please contact your ID/ASP Pharmacist with questions.

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- Historically, ciprofloxacin and SMX/TMP were preferred PO stepdown options due to their high bioavailability and lower recurrence rates compared to PO beta-lactams. Available literature suggests a higher incidence of recurrent bacteremia with use of PO beta-lactams may be due to suboptimal dosing used in prior studies. **Beta-lactam dose-optimization for uncomplicated GN BSI is provided in Table 1**.
    - IV beta-lactam x3-5 day lead in is recommended prior to narrowing to a PO beta-lactam
    - Use of the narrowest spectrum beta-lactam is recommended as agents like amoxicillin, amoxicillin/clavulanate and cephalexin have more reliable target attainment
        - NOTE: Cefuroxime use should be reserved for patients with resistance to alternative beta-lactams OR if PCN allergy precludes use of cephalexin (d/t side chain similarity)
        - NOTE: PO 3rd generation cephalosporins (cefdinir and cefpodoxime) are not routinely recommended because of PK limitations, please contact your ID/ASP pharmacist
- **IDSA endorses quinolones or SMX/TMP stepdown for treatment of ESBL infections with a urinary source. These are also suitable options for ampC producing organisms (e.g. *E. cloacae*, *C. freundii*, *K. aerogenes*).**
    - Use of a highly bioavailable oral option (over IV) maintains efficacy, reduces risk for line-related complications, reduces healthcare costs and improves patient satisfaction.
    - Avoid quinolones or SMP/TMP if prior PO treatment failure or h/o recurrence within 30 days

Duration:

- Multiple randomized controlled trials and meta-analyses have demonstrated that **7 days of antibiotic therapy is non-inferior to 14 days for the treatment of uncomplicated Enterobacterales bacteremia with a urinary source**, provided that source control has been achieved and the patient is clinically stable.
    - The recently published BALANCE trial comparing a 7 vs 14 day treatment duration for uncomplicated bacteremia in n=3,608 hospitalized patients (including 55% ICU patients at enrollment) found no difference in 90d mortality or secondary outcomes (including hospital mortality ICU LOS, relapsed bacteremia).
- Duration should be 7 days starting from the first day of microbiologically active treatment for most infections with adequate source control
    - Note: patients with stone related urinary obstruction should have a duration of 7 days from urinary decompression (percutaneous nephrostomy or stent)

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Supplemental Table 2. Consider risk factors to select appropriate agents:

Fluroquinolones	TMP/SMX[1]	Beta-lactams
▫ C. difficile (hypervirulent strain) ▫ Increased colonization & infection rates with MDRO ▫ QTc prolongation ▫ Tendonitis/tendon rupture ▫ DDIs (ex: corticosteroids) ▫ Dysglycemia ▫ CNS effects ▫ Aortic dissection and aneurysm	▫ Sulfa allergy reaction ▫ Renal insufficiency ▫ Falsely elevated Scr ▫ Hyperkalemia ▫ Hypoglycemia ▫ DDIs (ex: warfarin, digoxin, phenytoin, ACEi, cyclosporine, etc.)	▫ May have more frequent dosing (ensure compliance) ▫ PCN allergy (amox-clav and cephalexin)

1. SMX/TMP can cause both a false elevation in Scr (10-30% increase) as well as true AKI. A short course of treatment (to complete 7 days), with dose adjustment for renal function and adequate hydration is generally well tolerated.

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