UWTASP

tele-antimicrobial stewardship program

New Drugs for MDROs

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Multitude of New Abx

- Ceftolozone- tazobactam
- Ceftazidime- avibactam
- Imipenem- relebactam
- Meropenem-vaborbactam
- Cefiderocol
- Plazomicin

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citations

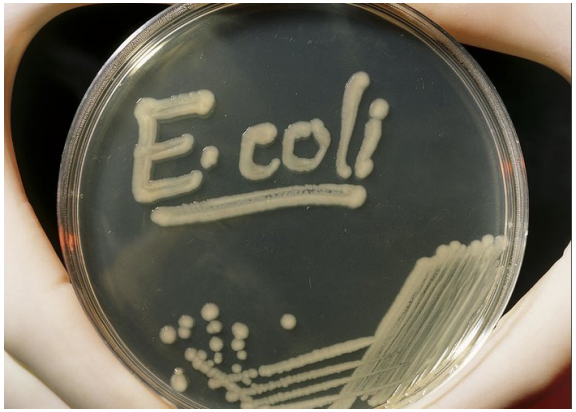
Patient Case

- 81 yo female, DM, HTN, otherwise healthy
  - Presents from LTCF with some flank pain, foul smelling urine, pain on urination
  - Fever, WBC count elevated, Cr 1.2 (baseline 0.9)
  - Hemodynamics stable, mental status normal
- Presumed Urinary tract infection/pyleonephritis

citations

…On day 3

Patient is receiving cefepime

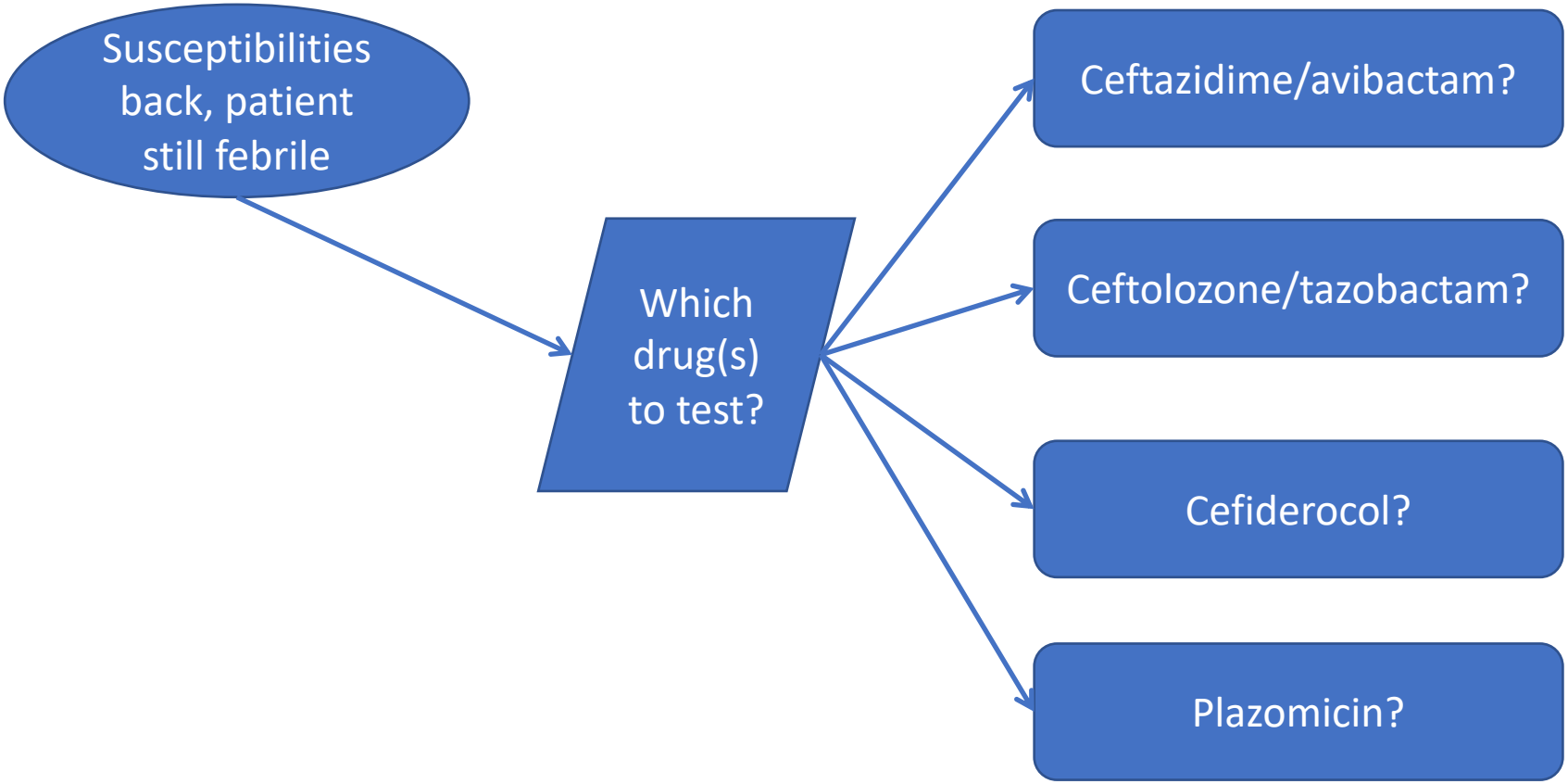


Urine growing ***E.coli*** with following susceptibilities:

Amoxicillin R
Amox/clav R
Cefazolin R
Cefoxitin R
Ceftriaxone R
Ceftazidime R
Cefepime R
Ertapenem R
Gentamicin S
Levofloxacin R
Meropenem R
Pip/tazo R
TMP/sulfa R
Tobramycin S

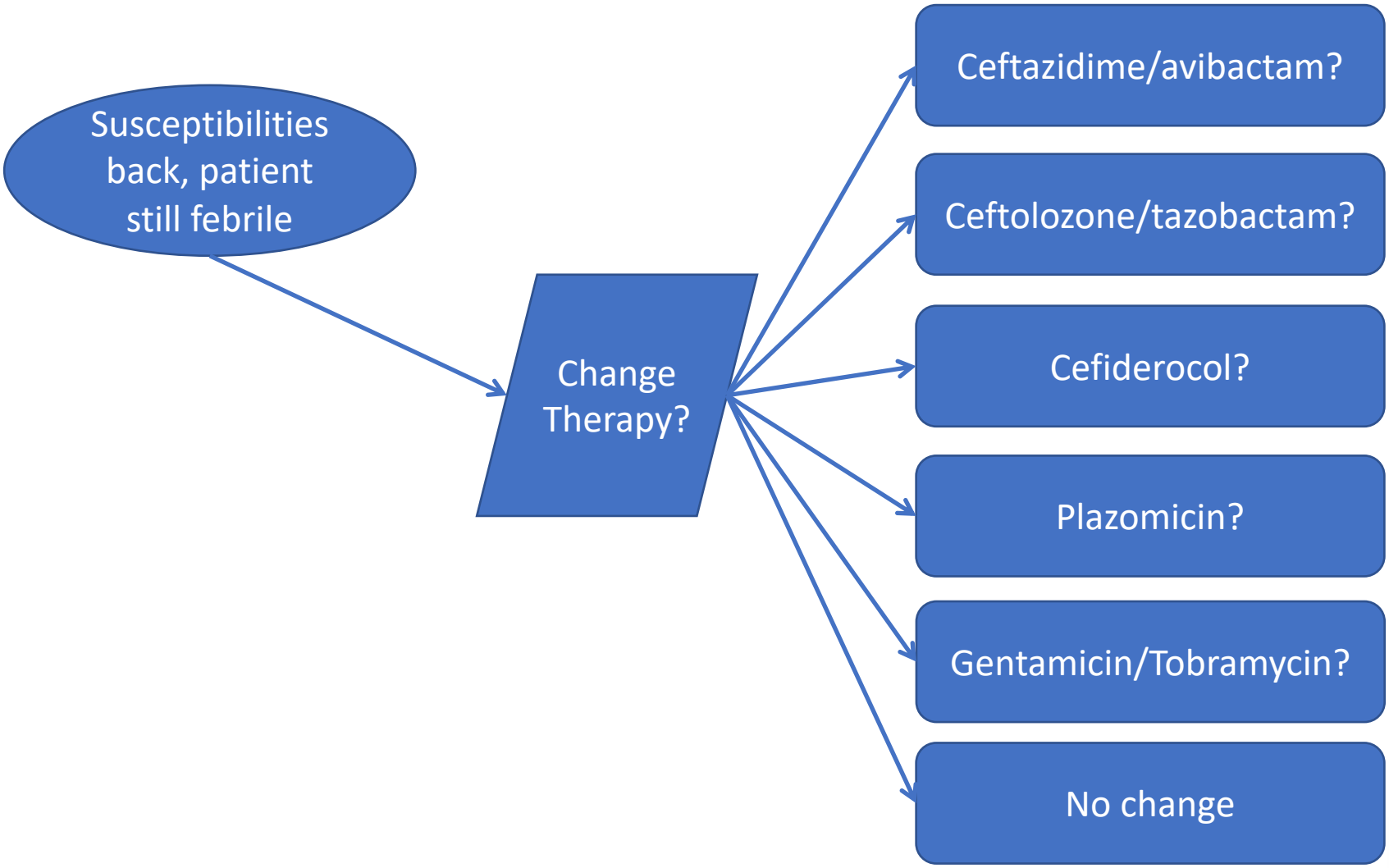
citations

What do you test for?



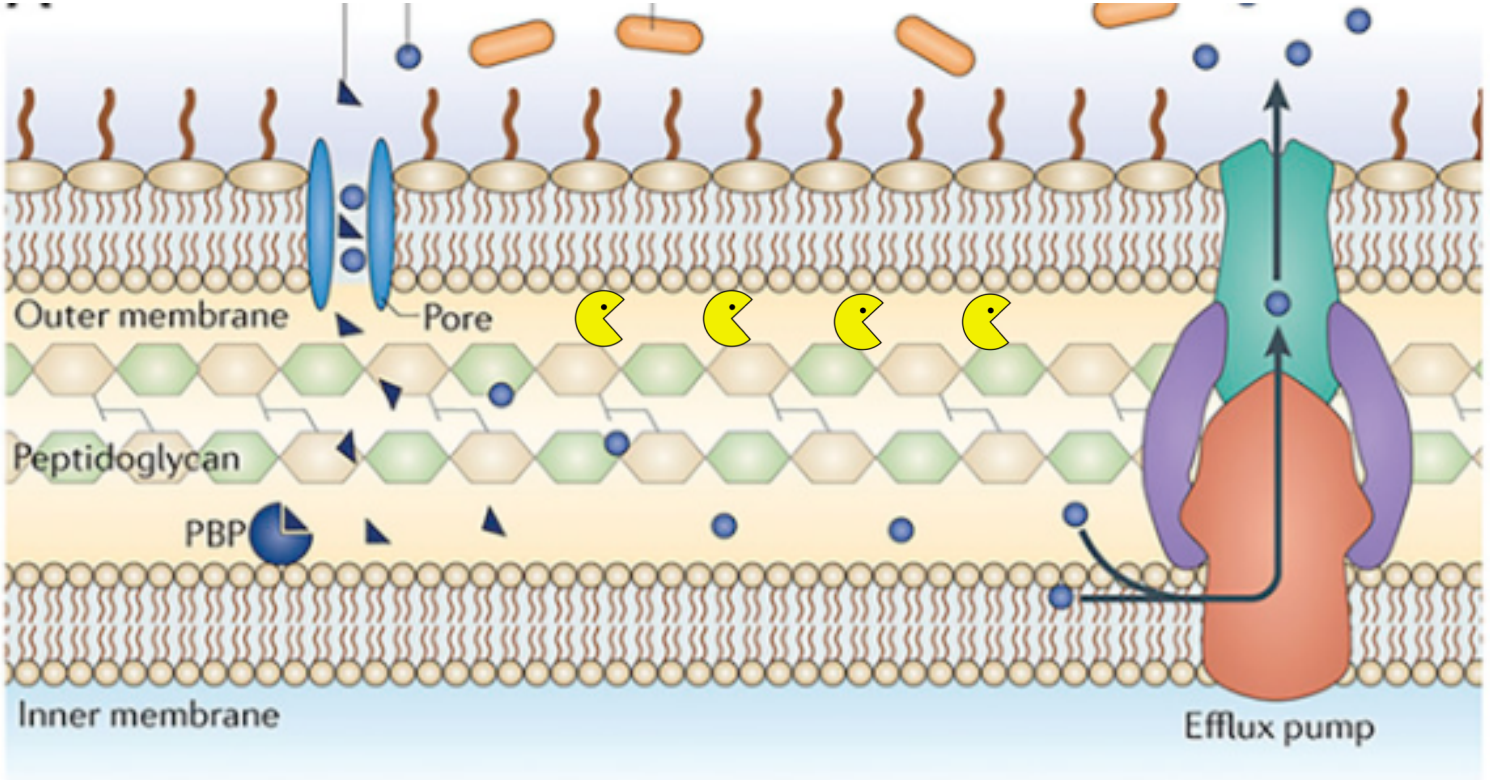
citations

What do you do with regimen?



citations

Visual of GNR Resistance

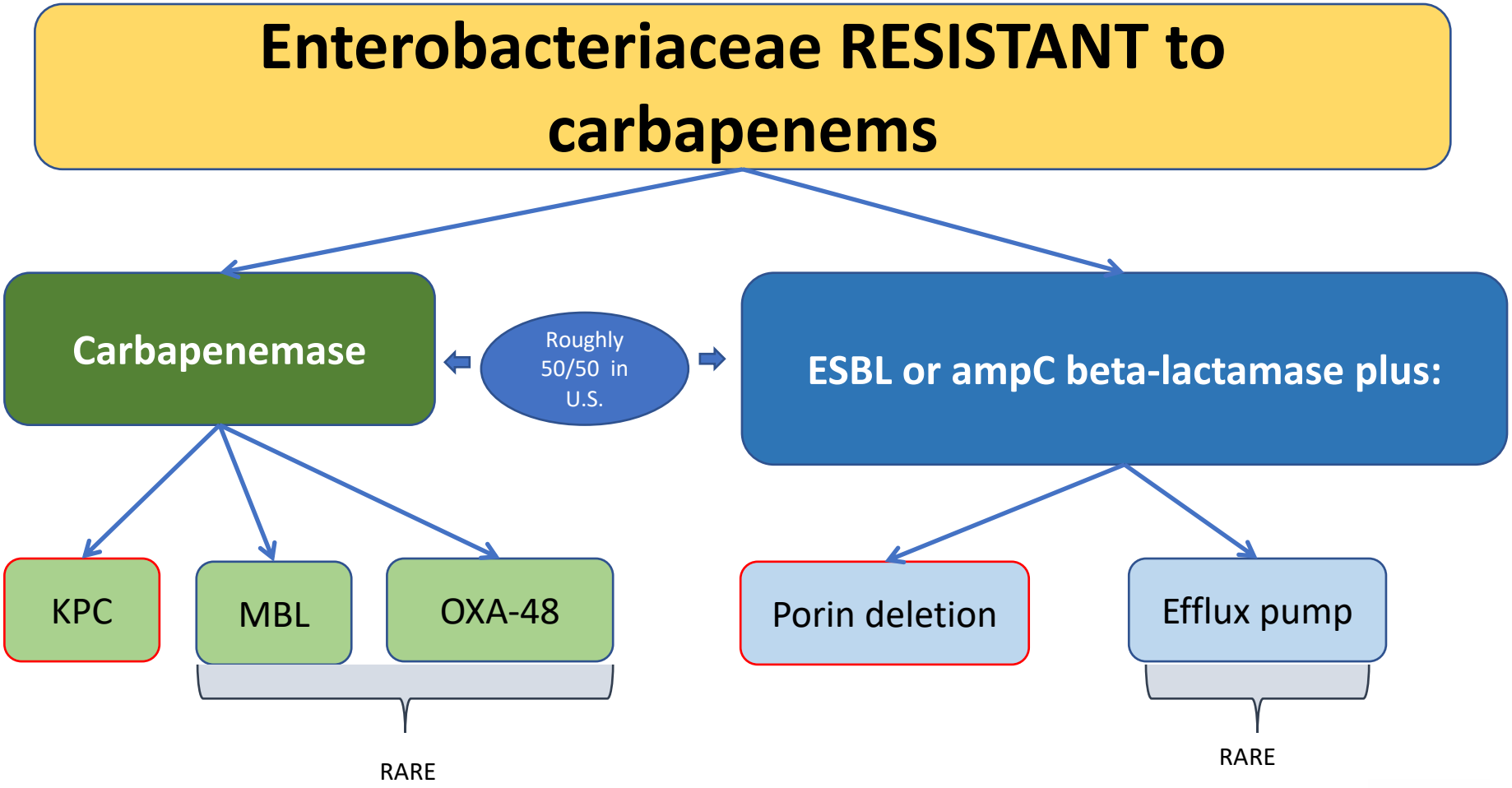


= beta-lactamase

citations

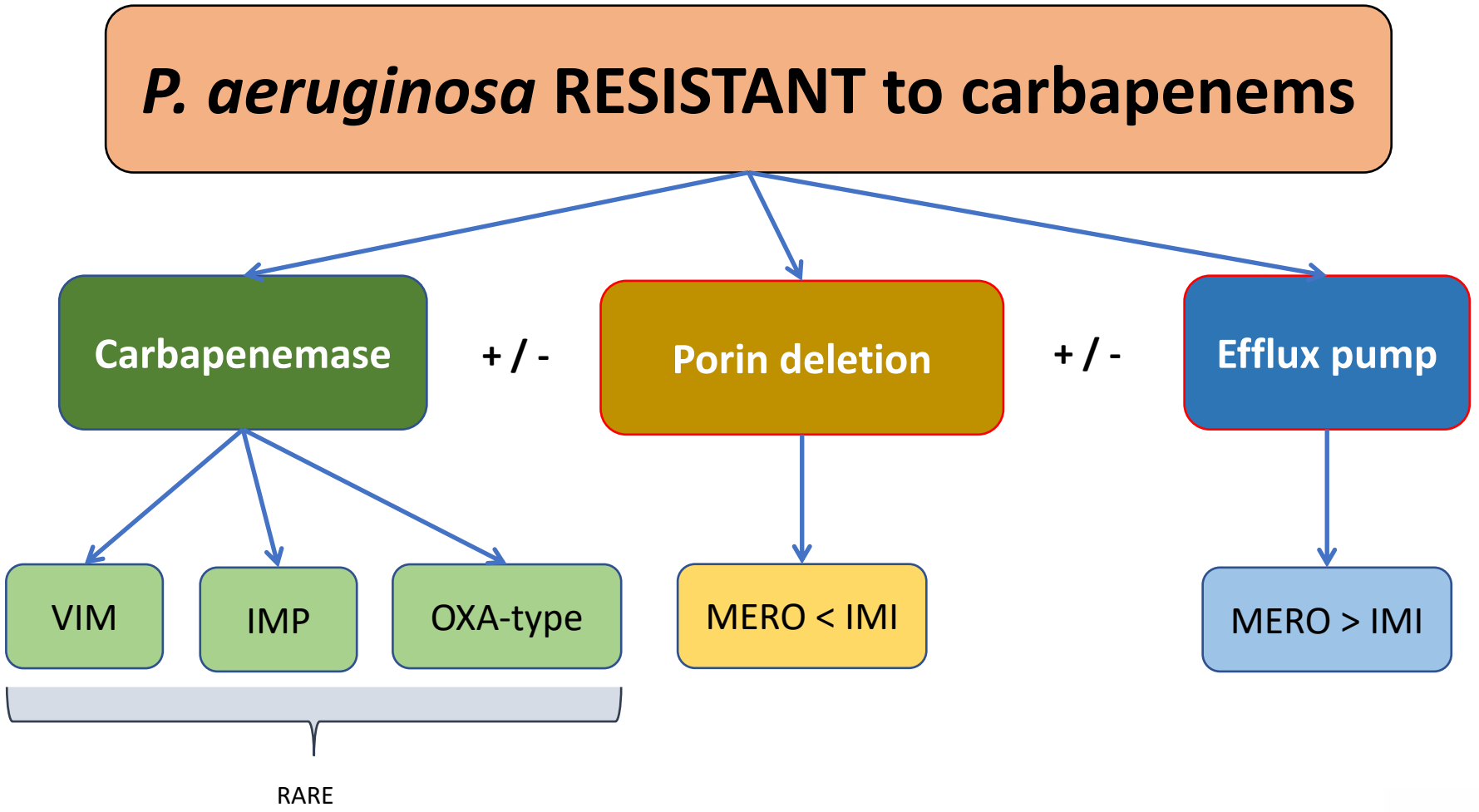
Chellat MF. 2016. Targeting antibioticresistance. Angew Chem Int Ed Engl 55:6600–6626

Mechanism of Resistance



citations

Mechanism of Resistance



citations

Option #1 Ceftazidime- avibactam

- Older 3rd gen ceph with new inhibitor which impairs variety of beta-lactamases (ESBL, ampC, KPC, OXA), effective against porin + ESBL/ampC
- FDA Indications:
  cUTI, cIAI, HABP/VABP
- Safety:
  Similar to other beta-lactams
- Considerations:
  - Avibactam is *only* an inhibitor, no intrinsic activity
  - Limited improvement in susc. in MDR *P. aeruginosa*
  - Limited anaerobic activity
  - Growing evidence for efficacy in MDR (CRE) infections

citations
Van Duin D. Clin Infect Dis . 2016 Jul 15;63(2):234-41.

Option #2 - Ceftolozane/tazobactam

- New ceph with *old* inhibitor which impairs variety of beta-lactamases (ESBL, ampC); ceftolozane less affected by porin deletion/efflux/ampC resistance mechanisms
- FDA Indications:
  cUTI, cIAI, HABP/VABP
- Safety:
  similar to other beta-lactams
- Considerations:
  - ESBL activity is not uniform, especially for *K. pneumoniae*
  - Given as a prolonged infusion
  - Limited anaerobic activity
  - Growing evidence for efficacy in MDR *P. aeruginosa* infections

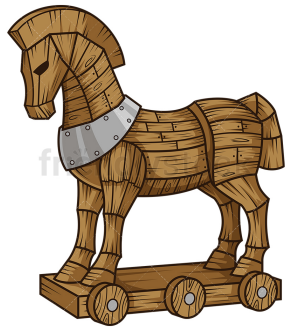
citations
Takeda S. Antimicrob Agents Chemother. 2007 Mar; 51(3): 826–830.
Van Duin D. Clin Infect Dis . 2016 Jul 15;63(2):234-41.

Option #3 - Cefiderocol

- New ceph with novel method of entry into cell (siderophore), structure resilient to all beta-lactamases
- FDA Indications:

  cUTI, HABP/VABP
- Safety:

  similar to other beta-lactams
- Considerations:
  - Porin/efflux mechanisms of resistance don't impair cefiderocol
  - Despite circumvention of most resistance mechanisms, bacteria can be resistant via alterations in iron transport system
  - Limited anaerobic activity
  - Concerns for poor in-vivo performance in MDR infections (did not meet clinical endpoints for efficacy)



citations

Tamma PD. JPIDS. 2019:8(3): 251-60

Option # 4 - Plazomicin

- New aminoglycoside with modifications that get around conventional aminoglycoside resistance mechanisms
- FDA Indications:
  cUTI
- Safety:
  Similar to other aminoglycosides
- Considerations:
  - Despite its modified structure and mitigation of various mechanisms of resistance, resistance still documented
  - Showed better outcomes in cUTI (vs meropenem) due to less recurrence in sub-group analysis
  - Phase 3 study in treatment MDR infections failed FDA approval due to too small of numbers

citations

Shaeer KM. Pharmacotherapy 2019;39(1):77–93

Option #5 Older Aminoglycosides

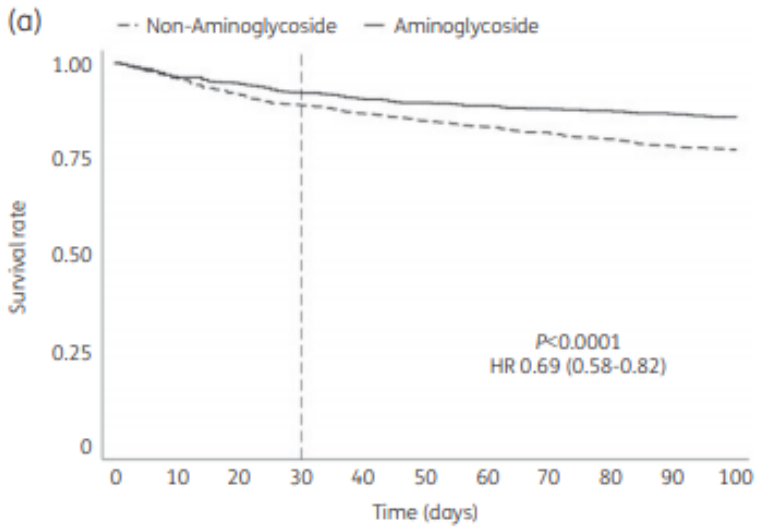
Effectiveness and safety of an institutional aminoglycoside-based regimen as empirical treatment of patients with pyelonephritis

Meital Elbaz[1], Hila Zadka[2], Ahuva Weiss-Meilik[2] and Ronen Ben-Ami[3,4]*

[1]Internal Medicine, Tel Aviv Medical Center, Tel Aviv, Israel; [2]Data Science and Quality Division, Tel Aviv Medical Center, Tel Aviv, Israel; [3]Infectious Diseases Unit, Tel Aviv Medical Center, Tel Aviv, Israel; [4]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

- Retrospective study from large hospital in Israel

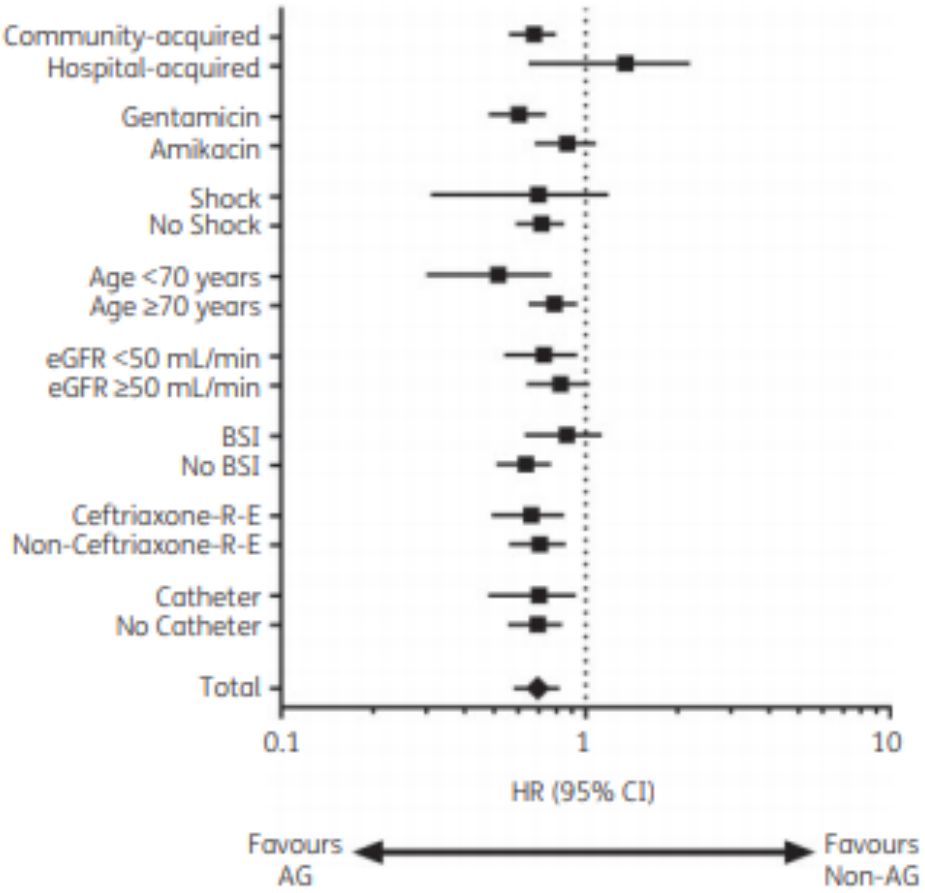
- Stewardship program promoted **aminoglycosides as first-line therapy for adult pyelonephritis**
  - Bacteremia included
  - Neutropenia excluded
  - Oral step down allowed
- N=2026; 715 AG, 1311 non-AG
- **Median age 82**
- Median duration 3 days (IQR 2-5)
- **Primary endpoint, death within 30 days: 7.6 vs. 11%**
- AKI occurred in 2.5% vs. 2.9%



citations

Elbaz M et.al. J Antimicrob Chemother 2020; 75: 2307–2313

Primary Outcome by SubGroup



citations

Elbaz M et.al. J Antimicrob Chemother 2020; 75: 2307–2313

Alternate Reality on day 3

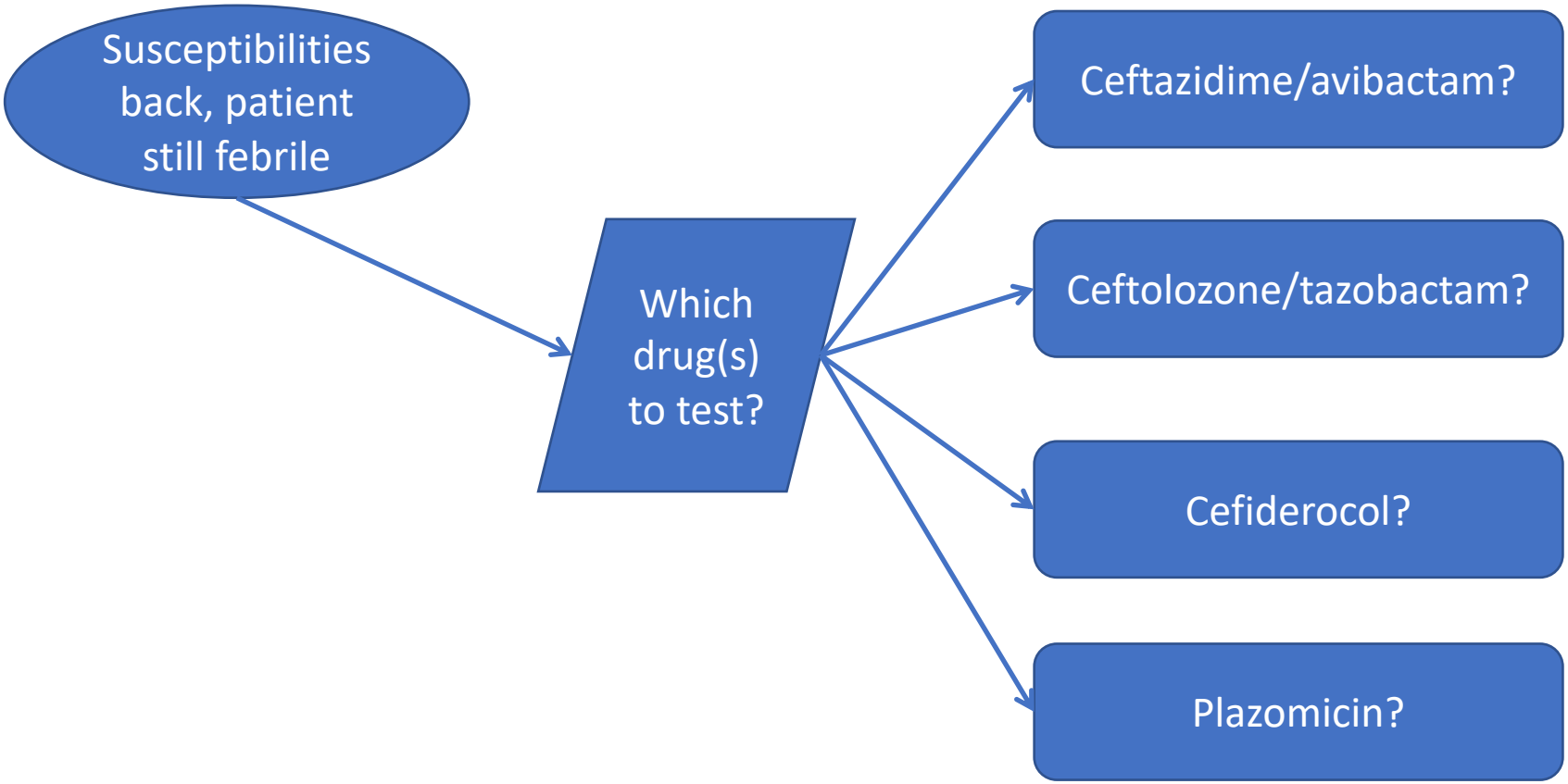
Patient is receiving cefepime

Urine growing ***P. aeruginosa*** with following susceptibilities:

- Ceftazidime R
- Cefepime R
- Gentamicin S
- Levofloxacin R
- Meropenem R
- Pip/tazo R
- Tobramycin S

citations

What do you do?



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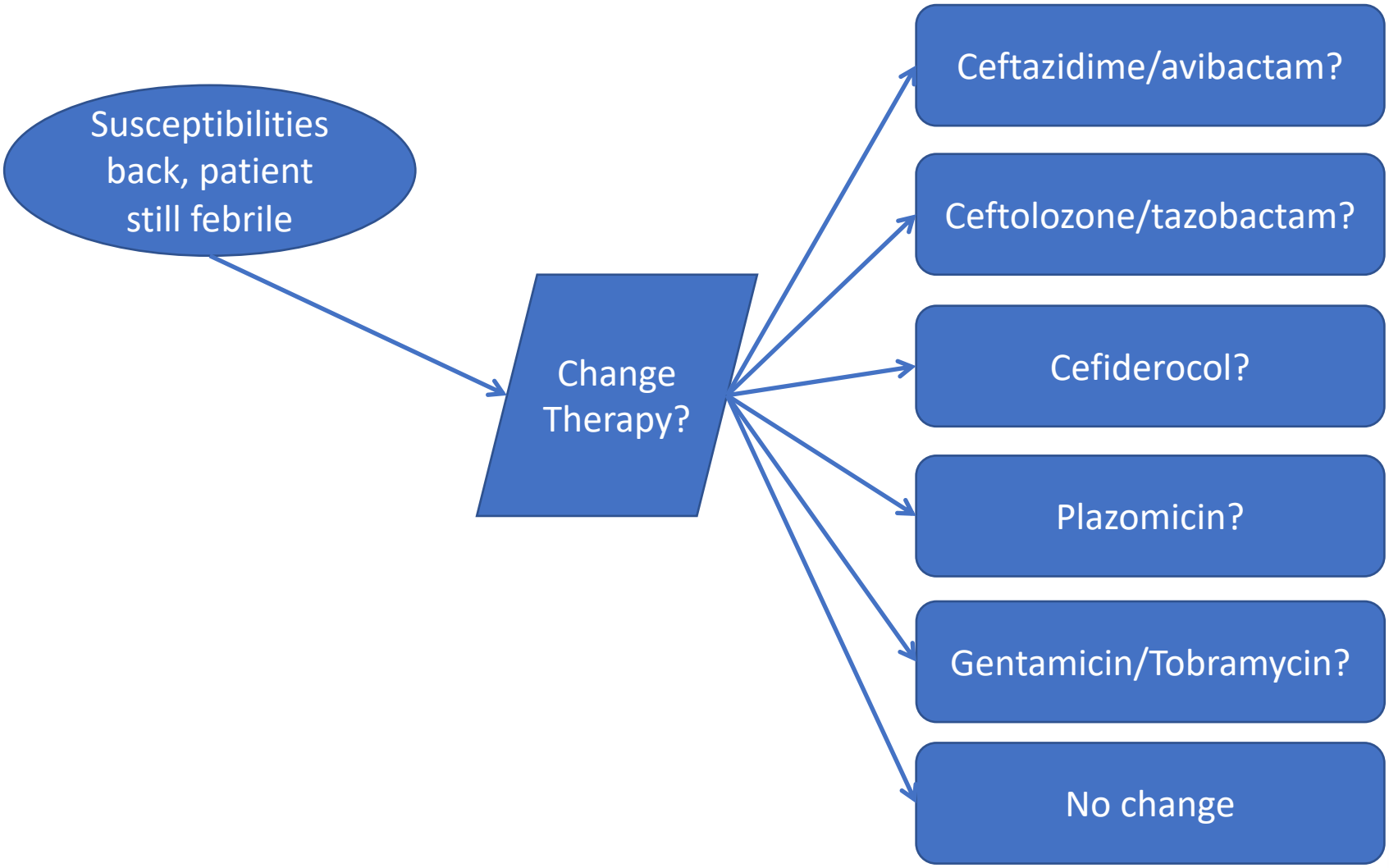

citations

New Abx in the Toolbox

- Ceftolozane – tazobactam
  - Multi-drug resistant *P.aeruginosa*
- Ceftazidime – avibactam
  - Carbapenem-resistant Enterobacteriaceae
- Plazomicin
  - Drug of last resort, MDR GNR in which amik/tobra/gent are resistant AND you would otherwise use an aminoglycoside
- Cefiderocol
  - Drug of last resort, MDR including resistance to newer agents

citations

Tamma PD. JPIDS. 2019:8(3): 251-60