Treatment of infections caused by nocardia
ANTIBIOTIC SUSCEPTIBILITY

- Sulfonamides have been considered the standard of therapy for more than 50 years

- Variable antimicrobial susceptibility
  - different studies, countries and species.

- 42% resistance to TMP-SMX and 61% were resistance to sulfamethoxazole reported in a US study [6]

- 16% resistance to TMP-SMX in Switzerland [7]
susceptibility test is always necessary

- **N. asteroides sensu stricto**
  - typically susceptible to TMP-SMX and amikacin.
  - variable resistance to third-generation cephalosporins imipenem [2,8].
- **N. farcinica**
  - variably susceptible to TMP-SMX and minocycline [2,6].
  - uniformly susceptible to amikacin
  - resistant to other aminoglycosides and third-generation cephalosporins [6,9,10].
- **N. nova**
  - Most isolates remain susceptible to imipenem, and amikacin [6,11].
  - variable susceptibility to TMP-SMX and third-generation cephalosporins [6,11]
- **N. brasiliensis**
  - typically susceptible to TMP-SMX and amikacin.
  - high levels of resistance (81 percent) to ceftriaxone and imipenem [6,8,12].
- **N. transvalensis**
  - susceptible to TMP-SMX (88 percent), imipenem (90 percent), and third-generation cephalosporins (50 percent) [8].
  - usually resistant to amikacin and other aminoglycosides [13-15].
- **N. otitidiscaviarum**
  - generally resistant to TMP-SMX, but is usually susceptible to amikacin and minocycline [2].
trimethoprim-sulfamethoxazole as part of first-line therapy

- All sulfonamides appear to be equally efficacious.

- The majority of break-through isolates in patients on low-dose TMP-SMX remain susceptible [19].

- TMP and SMX are synergistic against Nocardia in vitro studies.
  - Controversy exists over the optimal synergistic ratio [20,22].
  - Achieved ratio is not the same within serum and tissues.
  - No clinical evidence of benefit by this combination [22].
Carbapenem utilization

- varies among the carbapenems
  - In an in vitro study [16].
    - Imipenem = Meropenem × 4 = ertapenem × 16

- BBB penetration is far more adequate comparing with Amikacin
Other antimicrobial choices

- All of the Nocardia species are described to be susceptible to linezolid [6,16,17].
- linezolid > 2 weeks is associated with neurotoxicity and hematologic toxicity [30,31]
- unlikely to become a widely used in this setting.

- Co-amoxiclavé, minocycline, moxifloxacin, tigecycline, and dapsone [16,24-27, 29].
Level of evidence in nocardia infection treatment

- No prospective randomized trials have determined
- Unlike to be ever performed
  - relative rarity diversity of clinical presentations in different patients.

- choice is based upon:
  - cumulative retrospective experience, investigations in animal models, and in vitro antimicrobial activity
treatment of non-severe infections

- Empiric oral monotherapy regimens
  - TMP-SMX
    - (2.5 to 5 mg/kg of the TMP orally twice daily)
  - minocycline (100 mg orally twice daily)
  - amoxicillin-clavulanate, doxycycline, macrolides, and fluoroquinolones.
    - if the isolate proves susceptible
Duration of treatment in non-severe infections

- Immunocompetent patients with cutaneous disease
  - oral therapy for 3 to 6 months
  - mycetoma requires 6 to 12 months.

- Immunocompromised patients with cutaneous disease
  - treated for a minimum of 12 months.
Severe infection definition

- Severe nocardiosis includes cases of:
  - pulmonary disease
  - disseminated disease
  - central nervous system disease
  - all infections involving more than one site in immunocompromised patients.
Choice of treatment in severe cases

• Initial treatment should be intravenously for at least 3 to 6 weeks
  • and/or until clinical improvement is documented.

• 2 drug regimens prior to the availability of susceptibility results [1,2].

• in cases of life-threatening infection, 3 drug regimens may be considered [1].
Therapy modification in CNS involvements

- Severe infection without CNS involvement
  - TMP-SMX plus amikacin
  - imipenem plus amikacin

- patients with CNS disease
  - TMP-SMX plus imipenem
    - TMP-SMX (15 mg/kg/day IV of the TMP in 2-4 divided doses)
    - amikacin (7.5 mg/kg IV every 12 hours).
    - imipenem (500 mg IV every 6 hours)
Switch to oral therapy

- **Uncomplicated cases**
  - Clinical improvement with induction IV therapy
  - Switched to oral monotherapy after 3 to 6 weeks

- **Complicated cases**
  - CNS or multiorgan involvement, immunocompromised
  - 2 drug oral therapy after a min of 6 weeks
    - Some infectious diseases experts recommend exclusive intravenous treatment for patients with central nervous system (CNS) disease.
Oral antibiotic choice is based on susceptibility tests

- **TMP-SMX**
  - 10 mg/kg/day of the TMP in 2-3 divided doses)

- **Minocycline**
  - (100 mg twice daily)

- **Amoxicillin-clavulanate**
  - (875 mg twice daily)
prolonged course of treatment because of the relapsing nature

- 3 to 6 months
  - for isolated cutaneous infection in immunocompetent patients

- 6 to 12 months
  - in immunocompromised patients.

- 6 to 12 months or longer
  - in serious pulmonary infection,

- at least 12 months
  - All immunocompromised patients (except those with isolated cutaneous infection) as well as CNS involvement [2].
Monitoring

- Patients with nocardiosis should be monitored for the response to therapy and possible drug toxicity.
- at least monthly visits following discharge
- follow-up imaging studies (eg, chest radiographs and/or CT scans for pulmonary disease, and brain CT or MRI scans for CNS disease) after 1, 3, 6, and 12 months of treatment.
Relapse

- Depending on duration of therapy [35] and resolving the risk factors.
- The radiologic studies could be repeated at 6 and 12 months after clinical cure.
Treatment failures

- Clinical improvement is usually seen within two weeks after initiation of appropriate therapy.

- Poor response may represent:
  - primary drug resistance
  - poor penetration of drug into the infected tissue,
  - presence of an abscess requiring surgical drainage.

- Surgical intervention may be necessary in:
  - Cerebral and large soft tissue abscesses, empyemas, mediastinitis and pericarditis, [37,38, 39,40].
Patients on immunosuppressive therapy

- Immunosuppressive therapy predisposes patients to *Nocardia* infection.

- In patients who have undergone transplantation,
  - immunosuppression the dose should be decreased as much as possible.

- It is ideal to discontinue the immunosuppressive agent if alternatives are available.
Maintenance suppressive therapy

- in patients who continue to be immunosuppressed
  - prolonged oral maintenance therapy may be necessary [18,42].

- TMP-SMX one single strength tablet daily
  - TMP-SMX given 2 or 3 times a week do not prevent nocardiosis [19,44-46].
Brain abscess Complications: Vasogenic edema

- Glucocorticoids should be used when substantial mass effect can be demonstrated on imaging.

- Dexamethasone is administered at a loading dose 10 mg IV followed by 4 mg every six hours; the drug should be discontinued as soon as possible.
Corticosteroid disadvantages

- Reduction in contrast enhancement on CT scan
- Slowing of capsule formation
- Increasing the risk of ventricular rupture
- Decreasing the penetration of antibiotics into the abscess

STEROID WITHDRAWAL SYNDROME
- Symptoms not caused by recurrence of brain headache and lethargy that may mimic recurrence of brain edema as well as myalgias and arthralgias (steroid pseudorheumatism)
- All of the symptoms respond to raising the dose slightly and tapering more slowly.
Brain abscess Complications: seizure

- Anticonvulsant therapy should be instituted if seizures are suspected

- Prophylactic treatment may be warranted in some cases
  - There are no clear guidelines
  - High-risk mass lesions near cortex