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Amikacin Liposome Inhalation Suspension (ALIS) ALIS is a new formulation of the aminoglycoside amikacin, which allows for improved penetration in the lung with reduced toxicity. In the CONVERT study, treatment with amikacin liposome inhalation sus pension in addition to standard background regimen was associated with significantly increased culture conversion (29 vs 8.9%; $p < .0001$) by month 6 in patients with treatment-refractory MAC lung disease compared to standard background regimen alone. It is now approved for treatment of refractory MAC lung infection with persistent sputum positivity at 6 months while on appropriate background regimen. The typical dose is 590 mg (one vial once a day) for 6 months along with the standard three-drug regimen of macrolide, rifampin, and ethambutol. Dosage adjustments in patients with hepatic and renal dysfunction are not required. Half-life elimination typically occurs in ~5.9–9.5 h. Respiratory side effects such as bronchospasm, cough, dysphonia, and dyspnea are common. Monitoring for systemic aminoglycoside toxicity should be considered.

Imipenem Imipenem primarily inhibits cell-wall biosynthesis by binding to the penicillin-binding proteins. It is rapidly gaining impor tance for the treatment of M. abscessus, with a meta-analysis showing improved outcomes with its inclusion in a multidrug regimen. It is dosed at 500 mg to 1 g twice to three times a day as part of a combina tion regimen for the treatment of M. abscessus. Half-life of imipenem is ~1 h, and because it is metabolized in the kidneys, dosing adjustment is needed with renal dysfunction. Adverse effects include anemia, throm bocythemia, and liver dysfunction. Cefoxitin Cefoxitin is a second-generation parenteral cephalosporin with activity against rapidly growing NTM, particularly M. abscessus and M. chelonae. Its mechanism of action against NTM is unknown but may involve inactivation of cell-wall synthesis enzymes. High doses are used for treatment of NTM: 200 mg/kg IV three or four times per day, with a maximal daily dose of 12 g. The half-life of cefoxitin is ~1 h, with primary renal clearance that requires adjustment in renal insufficiency. Adverse effects are uncommon but include gastrointestinal manifesta tions, rash, eosinophilia, fever, and neutropenia. PART 5 Infectious Diseases Newer Drugs Three newer classes of drugs—the oxazolidinones, the glycylcyclines, and the ketolides—are currently being evaluated for possible use in the treatment of NTM infections, especially those caused by M. abscessus. Approximately 50% of M. abscessus isolates have shown some degree of susceptibility in vitro to linezolid, an oxazolidinone. Tigecycline, which is a glycylcycline and a tetracycline derivative, and telithromycin, a ketolide, also appear to have in vitro activity against M. abscessus. These drugs, however, have not yet been prospectively tested for NTM in patients. In addition,

some anti-TB drugs, including clofazimine and beda quiline, are being evaluated as alternative agents for the treatment of refractory NTM infections. In particular, clofazimine appears to act synergistically in combination with amikacin, bedaquiline, or tigecy cline. The exact role of these agents in the treatment of refractory NTM infections remains unclear. Suppressive therapy with periodic parenteral/ oral drugs to limit disease progression and control symptoms may be an appropriate alternative to curative treatment. CONCLUSION Treatment of mycobacterial infections requires multiple-drug regi mens that often exert significant side effects with the potential to limit tolerability. The prolonged duration of treatment has vastly improved results over those obtained in past decades, but drugs and regimens that will shorten treatment duration and limit adverse drug effects and interactions are needed. ■ ■FURTHER READING Collaborative Group for the Meta-Analysis of Individual Patient Data in Mdr-Tb Treatment–2017: Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculo sis: An individual patient data meta-analysis. Lancet 392:821, 2018.

Daley CL et al: Treatment of nontuberculous mycobacterial pulmo nary disease: An official ATS/ERS/ESCMID/IDSA clinical practice guideline. Clin Infect Dis 71:e1, 2020. Nahid P et al: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clini cal practice guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis 63:e147, 2016. Sterling TR et al: Guidelines for the treatment of latent tuberculosis infection: Recommendations from the National Tuberculosis Con trollers Association and CDC, 2020. MMWR Recomm Rep 69:1, 2020. World Health Organization: WHO consolidated guidelines on tuberculosis Module 4: Treatment, Drug-resistant tuberculosis treat ment Geneva: World Health Organization, 2022. Section 9 Spirochetal Diseases Sheila A. Lukehart

Syphilis DEFINITION Syphilis, a chronic systemic infection caused by Treponema pallidum subspecies pallidum, is usually sexually transmitted and is character ized by episodes of active disease interrupted by asymptomatic periods (latency). After an incubation period averaging 2–6 weeks, a primary lesion appears—often associated with regional lymphadenopathy—and then resolves without treatment. The secondary stage, with generalized mucosal and cutaneous lesions and generalized lymphadenopathy, also resolves spontaneously and is followed by a latent period of subclini cal infection lasting years or decades. Central nervous system (CNS) invasion may occur early in infection, and CNS involvement may be symptomatic or asymptomatic. In the preantibiotic era, one-third of untreated patients developed tertiary syphilis, characterized by destructive mucocutaneous, skeletal, or parenchymal lesions; aortitis; or late CNS manifestations. ETIOLOGY The Spirochaetales include five genera that are pathogenic for humans and for a variety of other animals: Leptospira species (leptospirosis, Chap. 189); Borrelia and Borreliella species (relapsing fever and Lyme disease, respectively; Chaps. 190 and 191); Brachyspira species (gastro intestinal infections); and Treponema species (syphilis and the endemic treponematoses; see also Chap. 188). The Treponema pallidum subspe cies include T. pallidum subsp. pallidum (venereal syphilis), T. pallidum subsp. pertenue (yaws), and T. pallidum subsp. endemicum (bejel).

T. carateum (pinta), for which no extant strains are available for molec ular studies, is still classified as a separate species. Historically, the pathogenic Treponema were distinguished by the clinical syndromes they produce, but phylogenetic analyses of whole genome sequences from several strains (excluding T. carateum) yield the three named subspecies groupings. Whether these groupings represent geographi cal variation or actual biological differences is unclear. The crossing of subspecies boundaries by some “molecular signatures” and the recent recognition of

treponemes of the endemicum genotype in sexually acquired genital ulcers (chancres) and secondary rashes (Chap. 188) support the concept of a genetic and clinical “continuum” among strains and subspecies of the pathogenic treponemes. T. pallidum subspecies are thin spiral organisms, with a cell body surrounded by a trilaminar cytoplasmic membrane, a delicate

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