Supplementary Material for Review for "The Impact of Rapid Species Identification on Management of Bloodstream Infections: What's in a Name?" Wu, S., et al., *Mayo Clinic Proceedings*. 2020; Vol. 95.

Haemophilus influenzae

H. influenzae is a small pleomorphic gram-negative coccobacillus. Bacteremia is most commonly associated with pneumonia or less commonly septic arthritis or meningitis. Risk factors for bacteremia are similar to those for *S. pneumoniae*.

Patients with bacteremia should be empirically treated with cefotaxime or ceftriaxone. While cefuroxime and ampicillin/sulbactam have good activity, they are not effective in the treatment of meningitis. Alternatives for penicillin-allergic patients include aztreonam and fluoroquinolones (moxifloxacin is preferred for cases of possible meningitis). Rates of resistance preclude use of trimethoprim/sulfamethoxazole.

Pediatric Perspective: *Haemophilus influenzae can be transmitted to infants via aspiration of amniotic fluid, genital secretions, or nasopharyngeal secretions.[1] Prior to the introduction of the Hib vaccine, Haemophilus influenzae type B was one of the leading causes of pediatric meningitis however since the introduction of Hib vaccine, rates of invasive disease have declined by 99%.[2] Physicians should notify public health of cases of Haemophilus type B and chemoprophylaxis should be considered for household contacts based on immunization status, immune status, and number of cases occurring within a given setting and time period.[1]*

Listeria monocytogenes

L. monocytogenes is a Gram-positive rod most commonly acquired as a consequence of consumption of contaminated foods. It has the ability to grow at low temperatures (e.g., during refrigeration). It most typically affects immunocompromised individuals, the elderly, neonates, and pregnant women. In healthy individuals, *L. monocytogenes* typically causes a self-limiting febrile gastroenteritis. However, in individuals who are at risk, bacteremia may occur and be complicated by meningoencephalitis, fetal loss and overall increased mortality.[3]

High dose ampicillin or penicillin G is first line therapy for bacteremia and neurolisteriosis. Although evidence for aminoglycoside use is somewhat conflicting,[4] on the basis of a large prospective observational cohort study, we recommend usage of both a beta-lactam and aminoglycoside for bacteremia due to listeriosis especially when meningitis or meningoencephalitis is present; of note adjunctive dexamethasone is associated with decreased survival in patients with neurolisteriosis.[3] For patients with penicillin allergy who cannot undergo desensitization, high-dose TMP-SMX is the preferred treatment. If both TMP-SMX and penicillins are not able to be used, meropenem, although possibly less effective, should be administered.[5] If the patient has neurologic symptoms with concurrent bacteremia a lumbar puncture is warranted to evaluate for neurolisteriosis.

Pediatric Perspective: *Listeria infection in the neonatal period is a result of maternal infection at the end of pregnancy. Infection in the pregnant woman can be asymptomatic or a nonspecific febrile illness with associated gastrointestinal symptoms.[1] Infant presentation is similar to that with group B streptococcus: early (first week of life) or late (after the first week of life) and infection can result in premature birth, pneumonia, septicemia and meningitis . Early onset, severely affected newborns may develop a small papular rash, "granulomatosis*

infantisepticum". Infants who present later are more likely to have meningitis. Because cephalosporins have no activity against Listeria, ampicillin should be included in the empiric antibiotic choice for all infants less than 2 months of age, as well as for empiric treatment of meningitis in immunocompromised patients.[1, 6]

Bacteroides fragilis

Bacteroides fragilis is an anaerobic Gram-negative rod that is a part of the normal flora of the terminal ileum and colon; its presence in blood culture usually occurs in the context of intra-abdominal and pelvic infections. *B. fragilis* bacteremia can also occasionally occur in the context of mesenteric or portal vein thrombophlebitis, lung abscess, and complex skin-soft tissue infection (e.g., diabetic foot infection) with or without concomitant osteomyelitis/septic arthritis. *B. fragilis* bloodstream infection without an obvious source should prompt abdominopelvic imaging. Metronidazole, carbapenems, and beta-lactam/beta-lactamase inhibitor combinations (e.g., ampicillin-sulbactam) have the most reliable activity against *B. fragilis*. However, even when *B. fragilis* is found alone in blood culture, other bowel/urogenital flora (e.g., *Enterobacterales,* other anaerobic gut bacteria) may be present at the site of infection, so antimicrobial therapy directed against all these organisms is typically warranted. Cefazolin or ceftriaxone plus metronidazole are reasonable options for patients at low epidemiologic risk of infection with resistant *Enterobacterales;* a carbapenem may be more appropriate for patients at higher risk of *Enterobacterales* resistance. If highly resistant organisms are suspected, it should be noted that ceftazidime-avibactam and ceftolozane-tazobactam have poor anaerobic activity, so metronidazole should be added for *B. fragilis* coverage. Attributable mortality of *B. fragilis* bacteremia is on the order of 20%.[7]

Stenotrophomonas

Stenotrophomonas maltophilia is a Gram-negative bacillus that occurs ubiquitously in the environment.[8] It causes a wide array of infections in humans, particularly in the immunocompromised population. A meta-analysis has reported an attributable mortality rate due to *Stenotrophonomonas* bacteremia of 26.7%.[9]

Detection of Stenotrophomonas in the bloodstream should prompt investigation of a source of infection. Respiratory causes of bacteremia are most common, followed by CVC infection.[10] If a CVC is implicated in infection, prompt removal is associated with a good prognosis.[8] Other less common sources were noted to be gastrointestinal and urinary sources.[10] Rare cases of endocarditis, sinusitis, meningitis, and eye infections have also been described.[8]

Polymicrobial infections have been described in the literature, however, they have not been associated with higher mortality than monomicrobial bacteremia.[8]

Trimethoprim-sulfamethoxazole (TMP-SMX) alone or in combination with another agent is the treatment of choice for Stenotrophomonas infection. Dosing is similar to treatment of *Pneumocytis jirovecii* pneumonia. Levofloxacin and moxifloxacin also have in vitro activity, and retrospective clinical data suggest similar clinical efficacy as TMP-SMX.[11] Limited data suggests that in severe infections (such as bacteremia, endocarditis, or osteomyelitis) combination therapy with 2 active agents may decrease mortality.[9] When combination therapy is indicated, it is reasonable to include co-trimoxazole with another agent, such as ticarcillin-clavulanic acid, ceftazidime, levofloxacin or moxifloxacin.[8]

Acinetobacter

Acinetobacter species are a group of Gram-negative, non-motile, aerobic, bacilli associated with immunocompromised individuals in the intensive care unit.[12] Bacteremia is typically due to infection of the respiratory tract or an intravascular catheter. Wound, abdominal, and urinary sources are also possible.[13] Although all species can cause infection, *A. baumannii* is most often implicated in serious nosocomial bacteremia with increasing rates of resistance.[14] In a recent review, *Acinetobacter* caused 1.3% of all monomicrobial bloodstream infections in the US with a mortality rate of 28%.[12] Bacteremia should prompt treatment and evaluation for a primary source of infection such as the respiratory tract or an intravascular catheter. Wound, abdominal, and urinary sources are also possible.[13]

Multidrug resistance is common with *A. baumannii* infections through a multitude of mechanisms. For serious infections, we recommend empiric therapy with a carbapenem and aminoglycoside. Carbapenems show excellent bactericidal activity and susceptibilities range from 32-90%.[15] Meropenem alone may be appropriate in non-critically ill patients cared for at institutions with antibiograms listing ≤10% meropenem resistance among ≥30 Acinetobacter isolates, as required by CLSI.[16]

. Sulbactam has in vitro activity to Acinetobacter and has been studied in mild to moderate infections. It has also demonstrated efficacy in critically ill patients and patients with multidrug resistant strains of *A. baumannii*.[15] In the United States, sulbactam is only available as combination therapy with ampicillin.[15] Combination therapy also is being studied for particularly resistant strains, however, data on this remains sparse.[15] Newer agents with activity against *Acinetobacter*, most notably eravacycline, are also emerging therapeutic options.[17] We generally

recommend obtaining an infectious diseases consultation if *Acinetobacter* is isolated in blood culture.

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