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PEDIATRIC RHEUMATOLOGY (TJA LEHMAN, SECTION EDITOR)

Diagnosis and Management of Infectious Complications of Childhood Rheumatic Diseases

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Abstract Progress in the diagnosis and management of pediatric rheumatic disease has improved complications from underlying disease and the survival of children. However, as a consequence, infection has now become one of the leading causes of morbidity and mortality. Differentiating between infections and disease flares in children with rheumatic conditions can often pose diagnostic quandaries. Children with rheumatic diseases are at risk of infection, not only because of the use of immune-modulating medications but also because of underlying immune dysfunction associated with their disease. Although bacterial infections are the most common, any organism can potentially be a causative agent and, at times, more invasive measures of diagnosis, for example bronchoscopy and tissue biopsies may be necessary. Maintaining a high index of suspicion of infection with prompt diagnosis and treatment are important to further improve patient outcomes.

Keywords Pediatric rheumatology · Infections · Bacterial · Viral · Opportunistic infections · Management of infections · Rheumatic disease · Treatment · Morbidity · Mortality · Immune dysfunction · Endemic mycosis · Diagnosis · Complications

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Introduction

Infections that occur in childhood rheumatic diseases often pose diagnostic and therapeutic quandaries. The immunologic dysfunction inherent in these autoimmune diseases and use of the immunosuppressive medication required for their treatment increase the risk of infections in these patients. With advances in treatment and improved survival, infection has gained prominence as etiology for morbidity and mortality of these diseases. As such, a high index of suspicion of infection must be maintained at all times in their management. Disease flare and infectious processes may mimic each other with similar clinical presentations and laboratory findings and thus be difficult to distinguish. Infection itself can aggravate the underlying disease and the resulting disease flare can further increase the risk of morbidity and mortality [1–3, 4••].

The most frequent infections are bacterial, but any organism can potentially be a causative agent. Multiple factors are important to consider when identifying a potential causative organism, including travel history, residence in endemic areas, exposure to sick contacts, environmental exposure, and medication use.

There is limited literature, primarily case reports, on infections in this patient population. This review will discuss the risk factors, differential diagnosis, diagnostic tools, and management of infections in pediatric rheumatic diseases.

Morbidity and Mortality

Complications from underlying disease and the survival of children with rheumatic conditions have significantly improved with the earlier recognition and diagnosis of disease, use of a more aggressive therapeutic approach, and the introduction of more effective medications. As a consequence infection has now become one of the leading causes of

morbidity and mortality [1, 2]. Several small cohort disease-specific studies of patients before 1990 revealed high mortality of children with rheumatic conditions, with five-year survival of children with SLE ranging from 83–95 %, and 10-year survival from 76–95 % [3]. However in a more recent large systematic mortality outcome study of pediatric rheumatology patients in the US, Hashkes et al. noted markedly improved survival in several rheumatic conditions, for example SLE, with 5 and 10 year survival of 99.6 % and 99.7 % respectively. It was postulated these results were because of improved treatment and the short follow-up time, but an underestimate of mortality [4••]. Similarly, in their review of systemic vasculitis, Phillip et al. [5] demonstrated falling mortality. Adult studies suggest that intensive care unit (ICU) mortality of patients with rheumatic conditions is primarily attributed to infections [6]. A recent pediatric study [7••] by Radhakrishna et al. analyzing 122 admissions of 90 critically ill pediatric rheumatology PICU (pediatric ICU) patients at a single tertiary center emphasized the importance of infection. Although most PICU admissions (50 %) were rheumatic disease-related, 15 % were for combined infection and rheumatic disease and 21 % were for infection alone. Nine of the admissions involved multiple infections, with nearly all of the infections occurring in patients with SLE. Fifty percent of the 18 deaths were attributed to concomitant infection and rheumatic disease and 22 % to infection. Although survival has improved, morbidity and mortality resulting from infection remain a serious concern.

Infection Risk

Children with rheumatic diseases are at risk of infection, not only because of the use of immune-modulating medications but also because of underlying immune dysfunction associated with their disease, inadequate response to or inability to receive immunizations, and organ damage from disease [8, 9]. In children with juvenile idiopathic arthritis (JIA) the rate of infection is threefold higher than for healthy children. Beukelman et al. compared infection risk in children taking tumor necrosis factor (TNF) inhibitors against children taking only methotrexate, and no significant difference was found amongst the two groups, irrespective of combined use of methotrexate with the TNF inhibitors. In contrast, glucocorticoid use at a dose $\geq$10 mg day^{-1} resulted in a significantly increased rate of infection [10•]. In a large adult cohort study of RA patients, significantly higher risk of infection was demonstrated, with hazard ratios for objectively confirmed infections, infections needing hospitalization, and any documented infection of 1.70 (95 % confidence interval (95 % CI) 1.42–2.03), 1.83 (95 % CI 1.52–2.21), and 1.45 (95 % CI 1.29–1.64), respectively [11]. There may be a difference in the incidence of infection for anti-TNF agents. A Cochrane review in 2011 and the Dutch Rheumatoid Arthritis Monitoring registry (DREAM) both showed a lower risk of serious infections for RA patients treated with etanercept compared with adalimumab or infliximab, for which rates were similar [12, 13]. Additional risk factors for infection among RA patients include high disease activity, leucopenia, comorbid conditions, and use of corticosteroids [14, 15]. Among adult and pediatric SLE (pSLE) patients, predictors of infection are a high SLE disease activity index (SLEDAI) >12, C3 levels below 90 mg dL^{-1}, and positive anti-DsDNA. For children, prednisolone dose, age, and disease duration do not seem to be predictors of infection [16, 17] though infection was more likely to occur in patients receiving cyclophosphamide and a concomitant high dose of prednisolone [9]. Data for adults is more compelling—the incidence of infection increased from 0.43 to 1.63 per 100 hospital days with increasing doses of steroid from zero to more than 50 mg day^{-1} [18].

Immune Dysfunction

Different aspects of the immune system are involved in the increased susceptibility to infections of children with rheumatic conditions. Host immunity is affected by corticosteroids and immunosuppressive therapy, and by an innately aberrant immune system. Children with juvenile arthritis lack the ability to increase specific immunoglobulin levels to respond to their disease, thereby supporting the concept of immunodeficiency in these children [19]. Complement consumption in SLE during active disease impairs bacteriolysis and opsonization, increasing the risk of infection with encapsulated bacteria. Complement deficiency of C2 and less commonly alleles of C4 or C3 have been found more often in patients with SLE. These patients might present with a milder form of disseminated infectious disease, as complement is needed by bacteria to express fulminant disease [20]. The reticuloendothelial system is also dysfunctional in SLE, with overall decreased neutrophil function (chemotactic migration, opsonification, and phagocytosis) [21]. Fc receptor-mediated mononuclear phagocyte system clearance is also impaired. Although Fc receptor ligand binding is increased, Fc-mediated phagocytosis of the receptor ligand is reduced, with the latter seemingly acquired with disease onset. This may contribute to the in-vivo clearance defect seen for these patients [22].

Bacterial Infections

Infections caused by bacteria account for most reported infections of patients with rheumatic conditions. Gram-

positive cocci (*Staphylococcus* sp, *Streptococcus* sp, *Enterococcus*) and Gram-negative bacilli (*Salmonella* sp, *Pseudomona* sp, *E. coli*, *Acinetobacter* sp, *Klebsiella* sp) are the more frequently reported etiologies with the urinary and respiratory tracts the most commonly affected areas, respectively. Bacteremia is the most serious infection frequently reported and has led to sepsis and death of hospitalized pediatric lupus patients [1, 8, 17, 23]. There are no guidelines or recommendations for management of fever in pediatric rheumatology patients. Obtaining blood, urine, and if indicated, throat cultures from these children before initiating use of broad-spectrum antibiotics is important (personal communication). For high-risk individuals, in particular, central line and peripheral cultures should be obtained for a series of three consecutive blood cultures to improve the likelihood of identifying an organism. If fever spikes continue despite antibiotics, a blood culture drawn daily for two or three days may be appropriate. An echocardiogram is essential in the event of unexplained fever of children with rheumatic conditions, because, in our experience, bacterial and fungal endocarditis have been identified in the absence of other findings. Prompt initiation of empiric antibiotics that target the most common organisms can be life saving. Antibiotic coverage can be discontinued after 72 h if cultures are negative, otherwise therapy should be directed by culture results and sensitivity.

Soft tissue is another common site of infection, with microorganisms such as S*taphylococcus aureus*, *Bacteroides* sp and *Enterococcus* sp as causative agents [17]. Direct tissue culture should assist in guiding therapy accordingly.

Use of laboratory studies to differentiate disease flare from infection is difficult. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can both be elevated, although high CRP with a moderately lower ESR, is considered more suggestive of an infection than a disease flare. However, one must be mindful that this can also signify macrophage activation syndrome (MAS). CRP is may be lower in the presence of disease flare, because of defective production of the protein, or in an SLE renal flare, reflective of increased consumption by immune complexes [24, 25]. In a small study of children with fever, limping, and suspicion of osteomyelitis and/or septic arthritis, procalcitonin (PCT) was shown to be more specific than ESR and CRP for identification of infection. Levels of PCT were not elevated in patients ultimately diagnosed with either juvenile idiopathic arthritis (JIA) or reactive arthritis [26]. Larger studies are needed to corroborate these findings. The phagocyte-specific S100 protein family may help differentiate disease flare in rheumatic conditions. In adult SLE, elevated levels of phagocyte-specific S100A8/A9 protein correlate with disease flare and, when used in conjunction with CRP, can assist in differentiating between disease flare and infection [27]. Among children with systemic onset JIA and FMF, S100A12 was 145 and 135-fold higher, respectively, than in healthy controls. It was also comparatively elevated in patients with systemic infections, childhood leukemia, Muckle–Wells syndrome, and neonatal onset multi-inflammatory disorder. It may be a useful tool for differentiation of children with fever of unknown origin [28].

Aspiration pneumonia, particularly in dermatomyositis and limited and/or systemic scleroderma patients with esophageal dysmotility or severe gastroesophageal reflux, should be considered [29]. The abrupt onset of respiratory symptoms with prominent dyspnea, low-grade fever, and infiltrates on chest radiograph, raise suspicion of this entity. Treatment should cover upper airway and gastric bacteria, for example anaerobes and streptococci sp.

Involvement of the central nervous system (CNS) can be particularly difficult to differentiate from a disease flare in patients with different forms of vasculitis, because both can present with seizures, psychosis, headaches, and vomiting [30]. Most cases of meningitis have a bacterial etiology. Several organisms have been implicated, including *Mycobacterium tuberculosis*, *Kingella kingae*, *Listeria monocytogenes*, *S. pneumonia*, and *S. intermedius* [1, 5, 6, 7••, 30]. Cerebral spinal fluid (CSF) analysis with Gram stain and culture is critical for diagnosis, although additional CSF studies may be necessary to differentiate between bacterial infection and a disease flare. Analysis of antibodies and cytokines, for example serum anti-ribosomal P, CSF anti-neuronal antibodies, IgG synthesis, oligoclonal bands, IL-6, and IL-8 may be elevated in patients with autoimmune mediated CNS disorders [31]. Lactate levels may also be helpful in differentiating bacterial meningitis from immune-mediated manifestations, because they can be elevated by bacterial etiologies whereas immune-mediated manifestations do not affect serum levels of lactate. However levels in children can vary with age, and studies of reference values are limited [32].

Pericarditis and pleural effusions are indicative of several rheumatologic conditions and infections can sometimes be overlooked. Worsening chest pain, shortness of breath, and unresponsiveness to standard anti-inflammatory therapy should make one suspect an infectious etiology. *S. pneumonia*, *S. aureus*, and *Klebsiella* are some of the more commonly reported microorganisms causing pericarditis in children with rheumatic conditions [1, 5, 7••]. In sexually active patients, *Neisseria gonorrheae* should be considered. Neisseria pericarditis and endocarditis have seldom been described in the literature [33, 34], but disseminated disease in young women with SLE is well reported. Young females aged 19–25 with renal disease and low complement levels are more commonly affected by *Neisseria* sp. irrespective of corticosteroid dosing. Routine immunization against *Neisseria meningitides* is recommended [21].

Infection with *Mycobacterium tuberculosis* has been associated with the use of several medications used in pediatric rheumatology, but more notably with anti-tumor necrosis factor (TNF) therapy [35]. As such the American College of Rheumatology (ACR) recommends screening of all patients for *M. tuberculosis* before initiation of therapy. Tuberculin skin test is the recommended screening test for tuberculosis (Tb) although, given rates of false negativity in patients with immune dysregulation, other tests, for example the QuantIFERON-TB Gold test and the T spot TB may prove useful aids in further identification of active or latent TB. *M. tuberculosis* can mimic rheumatic diseases and confound diagnosis, especially when the affected organ is extrapulmonary. There are a handful of reports of tuberculosis presenting as oligoarticular arthritis in children without evidence of systemic disease [36, 37]. Sayarlioglu et al. reported that 45 % of their SLE patients with tuberculosis presented with extrapulmonary disease (vertebral, joint, soft tissue, and meningeal [38], suggesting that almost half of patients that present with tuberculosis, can present with atypical manifestations.

Listeria monocytogenes has been reported in several patients with SLE and other forms of vasculitis, for example granulomatosis with polyangiitis. Tobon et al. described five cases of *Listeria monocytogenes* in an SLE cohort of 174 patients with a mean age of 19 years. All patients were well controlled on immunosuppressive therapy with glucocorticoids and a steroid-sparing agent. Two of the five patients presented with headache and nuchal rigidity and one patient presented with new onset seizures without nuchal rigidity. Two presented with fevers and chills only, and *L. monocytogenes* grew on routine blood cultures [39]. History of ingestion of unpasteurized milk or soft cheeses should increase one's suspicion of this infection and prompt empiric antibiotic coverage with ampicillin, or trimethoprin-sulfamethoxazole if the patient is allergic to ampicillin.

Viral Infections

Similar to bacterial infections, new onset viral infections are a concern in pediatric rheumatic diseases. In addition, the potential for exacerbating an underlying viral infection with immunosuppressive therapy exists and may result in recurrent or chronic infections. The advent of biological agents, many of which target pro-inflammatory cytokines, has made an impact in further heightening concern about these infectious complications [40].

Chronic hepatitis B and C infections are worldwide problems that can lead to cirrhosis, hepatocellular carcinoma, and death [40]. Hepatitis A has been reported with macrophage activating syndrome (MAS) in systemic JIA [41]. In rheumatic patients higher prevalence of infectious hepatitis is seen in those living in endemic areas [40]. There is limited literature on the effects of immunosuppression on hepatitis infections in rheumatic diseases in general and pediatric rheumatic diseases in particular, although it has been well described in neoplastic conditions and in transplant patients [40, 42]. Although the occurrence of hepatitis is of most concern with use of biological agents, particularly anti-TNF agents [40, 44], hepatitis B reactivation has also been noted with disease-modifying antirheumatic drug (DMARD) use [43, 44] and before the start of therapy [45]. In the 2011 American College of Rheumatology (ACR) safety monitoring recommendations for treatment of JIA, antibody testing for infection with hepatitis B or hepatitis C was advocated for high-risk patients before initiation of methotrexate or TNF-α inhibitors [46•]. General recommendations for hepatitis screening of patients with rheumatic conditions include HBsAg, anti-HBs, anti-HBc, HBeAg, HBV viral load, anti-HVC, and HCV viral load [44, 45, 47]. In addition, because transaminitis can be seen in reactivation of disease before clinical symptoms or increased viral load, this also must be closely monitored [45, 47]. Treatment has traditionally been with IFN-α though newer oral anti-viral therapy (lamivudine, telbivudine, entecavir, adefovir, and tenofovir) is now available [44, 45, 47]. Prophylaxis to prevent reactivation for patients on immunosuppressive therapy is of crucial importance [44]. The importance of prevention by immunization cannot be underemphasized. Hepatitis A and B vaccination is safe for JIA patients and an adequate response is not affected by immunosuppression except for those with active systemic JIA on anti-TNF treatment [48, 49].

Similar to adults with rheumatic diseases [40], varicella zoster infections that can cause chickenpox or shingles in pediatric rheumatic diseases can be quite devastating. Patients with juvenile-onset SLE seem at most risk. A retrospective review by Lee et al. of 49 children with SLE reported incidence of 58.7 episodes/1000 patient-years and noted that renal involvement and lupus activity, but not high-dose steroids or other immunosuppressive agent use, conferred a higher risk [50]. Although Wu et al. also noted high susceptibility in pediatric SLE, with incidence of 35.7 %, they observed that patients who had received steroids, particularly a high cumulative dose, and cyclophosphamide were more likely to develop the infection [51]. Opastrakul et al. in their study of pediatric SLE patients with lupus nephritis receiving oral and pulse IV cyclophosphamide noted a higher risk for those receiving oral cyclophosphamide (15 %) than IV pulse therapy (5 %) [9]. Infection has also been seen in long-term studies of JIA patients receiving anti-TNF medications, with two of these seen in unvaccinated children [52, 53]. The purpose of therapy is to limit extensive cutaneous involvement or systemic dissemination that could lead to life-threatening complications. Ideally anti-viral therapy should commence within a week of the development of the rash. Intravenous acyclovir is indicated for those with disseminated

disease and ophthalmic complications and for those who are significantly immunosuppressed or unable to take oral medications. Oral acyclovir, valacyclovir, and famciclovir are usually sufficient for localized disease if close outpatient follow-up is possible. In acyclovir-resistant cases foscarnet is recommended. Traditional analgesics and medications to specifically address neuropathic pain are important in the management of varicella zoster infections [54]. Novel VZV treatments (bicyclic nucleoside analog FV-100, helicase-primase inhibitor ASP2151, and valomaciclovir) which have been evaluated in adult clinical trials, may be more effective and be future treatment options for pediatric rheumatic diseases [55]. Vaccination is not recommended for patients receiving immunosuppressive medications as the live attenuated virus may pose a risk of infection. Measurement of serum antibody levels and, when possible, varicella immunization of un-immunized or seronegative children and adolescents should be attempted three weeks before the start of immunosuppressive therapy.

Primary infection of Epstein–Barr virus (EBV) occurs in childhood and adolescence and reactivation in children with rheumatic diseases is of concern for several reasons. EBV infections can have a clinical course that itself can lead to significant morbidity, exacerbate the underlying rheumatic disease, and be associated with MAS [43, 56, 57]. Immunosuppressed patients are also at increased risk of EBV-associated lymphoproliferative disorder. An increased viral load has been demonstrated for adult patients with RA and SLE, suggesting impaired T-cell-mediated control of EBV infection [40, 56]. In contrast, an increased viral load was not seen during prospective monitoring of EBV among JIA patients treated with methotrexate and tocilizumab or among adolescents with SLE on immunosuppressive medications [58, 59]. EBV-associated lymphomas have been reported for RA patients primarily receiving methotrexate [40, 60]. Similarly there are case reports of EBV-associated lymphomas in JIA patients treated with methotrexate and other immunosuppressive medications [61, 62]. Diagnosis of primary EBV infection is defined by a serologic response of a positive IgM antibody titer to the viral capsid antigen (VCA) or an elevated IgG antibody titer ≥1:320 in the setting of a negative EBNA (Epstein–Barr nuclear antigen) antibody. Antibodies to early antigens (EA) can also be observed. The serologic response in EBV reactivation includes elevated IgG antibody to VCA, EA, and EBNA. Individuals with past infection have a positive EBNA titer with a low positive VCA antibody titer [63]. However, traditional serologic testing for EBV infections may be difficult to interpret for pediatric SLE patients [59, 64] for whom an altered immune response to EBNA 1 has been demonstrated [64] and for whom serologic patterns are indicative of primary or reactivated EBV infection without a corresponding increased viral load [59]. Because EBV infection and active SLE may present with similar symptoms, establishing the appropriate diagnosis is imperative. Increasing immunosuppressive therapy to address SLE disease activity could result corresponding aggravation of EBV infection [59]. EBV detection by quantitative DNA PCR measurements on serum, plasma, and tissue, or RNA PCR in lymphoid cells or tissue, provides more definitive diagnosis in pediatric rheumatic conditions [63]. Although cessation or decrease of immunosuppressive medications is important when addressing EBV infections, this may often be difficult because EBV infections precipitate flares in disease [56, 63]. Additional therapeutic strategies include corticosteroids, anti-viral therapy (acyclovir, ganciclovir, or valacyclovir) and passive antibody therapy with IVIG. Monoclonal antibodies (anti-CD20, anti-CD21, anti-CD24, anti-IL6, and antiTNF), cyclosporine, and etoposide may sometimes be necessary [56, 63].

The exact involvement of parvovirus B19 in chronic arthritis and the pathogenesis and onset of JIA [65, 66] is uncertain, although its association with acute juvenile arthritis and with other autoimmune conditions is well described. Severe persistent anemia, thrombocytopenia, neutropenia, and papulopurpuric gloves-and-socks syndrome can also be seen with infections [67]. It has also been postulated that persisting viral infection, as evidenced by amplifiable parvovirus DNA in sera years after the acute infection, in children with rheumatic diseases may perpetuate immune dysfunction in the infected child [68]. Furthermore there are reports of parvovirus B19-associated antiphospholipid antibodies in JIA [69, 70]. In the immunocompetent host the preferred diagnostic test for acute infection is detection of parvovirus B19 IgM in the serum. In the immunocompromised patient, however, the optimum way of detecting chronic infection is by nucleic acid hybridization or by parvovirus B19 DNA PCR assays [67]. Supportive care is important for treatment and at times a severe aplastic crisis may require transfusion. IVIG is indicated and can be effective for immunocompromised individuals [67, 71].

Children and adolescents with rheumatic disease, particularly those receiving immunosuppressive medication, are at great risk of serious complications of influenza infections [72, 73]. Upper respiratory infections are common adverse events [45, 52, 72, 73] and infection with influenza has been noted with anti-TNF use. Of greater concern, influenza pneumonia in a pediatric SLE patient was one of the 11 deaths noted in the 15 year PICU study of pediatric rheumatic diseases [7]. A heightened index of suspicion, particularly during the flu season is imperative, although vigilance even before reported cases of influenza infection is important. Particular attention must also be paid to the development of an influenza pandemic, which is the emergence and global spread of a new influenza sub-type, because this is a

significant cause of morbidity and mortality [74]. During the first 72 hours of illness nasopharyngeal secretions, nasal specimens, or endotracheal aspirate should be obtained for viral cultures, immunofluorescent, rapid diagnostic tests, and/or RT-PCR (reverse transcription-polymerase chain reaction) [74, 75]. Serologic testing may also be performed but is of limited benefit in the acute setting when rapid diagnosis and initiation of appropriate treatment is vital. Supportive measures and surveillance for invasive secondary infections, especially group A streptococcus, MRSA, and *Streptococcus pneumoniae* are integral to the plan of care [74]. Anti-viral medications for influenza include the adamantanes (amantadine, rimantadine) and neuroaminidase inhibitors (zanamivir, oseltamivir). Drug resistance has been noted and recommendations for prophylactic and treatment medication choices for the season are updated and can be reviewed at www.cdc.gov/flu. Vaccination with inactivated trivalent influenza vaccines is recommended and has been found to be safe and efficacious in pediatric rheumatic diseases [72–75].

Opportunistic Infections

Opportunistic infections pose a unique risk for children with rheumatic conditions. They are often diagnosed late in their course when dissemination has already occurred, leading to greater mortality. In addition, they can be difficult to identify with routine tests and at times require more invasive studies to establish diagnosis. The use of multiple immunosuppressive drugs increases the risk of development of these types of infections.

Aspergillosis has become one of the most common invasive fungal infections [76, 77]. Since 1980, a 357 % increase in invasive aspergillosis (IA) has been observed in individuals with malignancy, organ transplant, primary immunodeficiencies, and rheumatic conditions [78]. In a report of five cases of IA in SLE by Silva et al., leucopenia, primarily lymphopenia, and immunosuppressive medications led to a higher risk of aspergillosis [79]. Retrospective analysis of 139 cases of IA (malignancy, organ transplant, immunodeficiency, and other) in six medical centers by Burgos et al., also noted that immunosuppressive medications and neutropenia were a major risk factor [77]. In another retrospective study of lupus nephritis pediatric patients with treated with IV cyclophosphamide, Laoprasopwattana et al., noted opportunistic infections in 12/31 patients, with seven contracting fatal Aspergillosis infection [80]. The lungs are the most common site of infection, but any organ system can be affected [77, 79, 80]. Patients with IA often present with non-specific symptoms that are easily confused with disease activity. Clinicians should have heightened suspicion of continued pulmonary symptoms and infiltrates on chest X-ray (CXR) after treatment of patients with broad-spectrum antibiotics. IA mortality is 50 % [77], and prompt diagnosis may lead to improved outcomes. Evaluation of IA often begins with noninvasive studies, for example chest computed tomography, which may reveal nodules and/or cavities [81]. In 2003, the US Food and Drug administration approved the galactomannan enzyme immunoassay (GM EIA) for detection of IA [81]. Bronchoalveolar lavage may yield a positive culture or a positive GM EIA. If CT is suggestive of IA, but cultures and detection of antigen are negative, a lung biopsy may be needed to confirm the diagnosis. Current recommendations from the Infectious Disease Society of America (ISDA) is treatment with 7 $mg kg^{-1}$ IV voriconazole every 12 h. Duration of therapy has yet to be established but the IDSA guidelines recommend a minimum of 6–12 weeks liposomal amphotericin B, caspofungin, posaconazole, or itraconazole for patients who are unable to tolerate or who are refractory to voriconazole [82].

Cryptococcal infection has been reported among pediatric and adult patients with SLE [83, 84]. In a retrospective review by Jeng-Juh Hung et al., 17/3165 inpatient SLE patients were found to have proved CNS infections, 10 of which were *Cryptococcus neoformans* [83]. Abnormalities of cell-mediated immunity and immunosuppressive medications conferred an increased risk of cryptococcal infection [83]. A case report by Liou et al. also confirmed that immunosuppressive medications and possibly cell-mediated immunity posed an increased risk of cryptococcal infection [84]. Most patients who developed Cryptococcus were receiving glucocorticoids [83–85]. The common presenting symptoms of headache, vomiting, seizures, and altered mental status are similar to those of active SLE CNS disease and can delay diagnosis. Mortality is 54 % for SLE patients with cryptococcal meningitis. Suspicion should be a high for patients with CNS symptoms, persistent fever, and elevated CRP [83, 84]. A lumbar puncture for CSF analysis should be obtained. Diagnosis of Cryptococcus can be made by India ink stain and/or cryptococcal antigen test. Amphotericin B with or without flucytosine or fluconazole has been used in the treatment of cryptococcosis. For immunocompromised patients the National Institute of Allergy and Infectious Diseases mycoses study group recommends treatment with amphotericin B for 2 weeks followed by fluconazole 400–800 mg for 8-10 weeks and fluconazole 200 mg for 6–12 months [86].

Norcardia has been documented in children with SLE and JDMS. Similar to other opportunistic infections, multiple immunosuppressive agents (glucocorticoids in combinations with DMARDs and/or cytotoxic agents) and intrinsic immunological defects, seem to confer increased risk of developing norcardiosis [87–89]. Common presenting symptoms are cough, chest pain, dyspnea, and fever. The primary site of infection is the lung, followed by the skin and brain. Although rare, widespread dissemination may occur [88, 90]. Diagnosis requires the isolation of the species from sputum, blood, CSF,

or abscess material. Current treatment is trimethoprim–sulfamethoxazole for 12 months [91].

Pneumonia secondary to *Pneumocystis jiroveci* (PCP) is a common opportunistic infection of immunocompromized individuals with rheumatic conditions. PCP occurs in pediatric patients with SLE, scleroderma, vasculitis, arthritis, and myositis [92–96]. There may be an increased risk of granulomatosis with polyangiitis (GPA) compared with other rheumatic conditions [96]. Other risk factors for the development of PCP are immunosuppressive medications (cyclophosphamide, glucocorticoids, methotrexate, azathioprine, and TNF agonists) and lymphopenia [92–95]. Most individuals who develop PCP have recently been or are currently receiving glucocorticoids [97]. PCP mortality ranges from 30 to 60 %, and is highest for GPA and inflammatory myopathies [98]. Symptoms that should induce high suspicion include significant respiratory distress, hypoxemia, and fever. Prompt diagnosis may lead to improved outcomes. CXR may reveal infiltrates that can be difficult to distinguish from other bacterial and fungal infections whereas chest CT reveals ground glass opacifications. Diagnosis occurs with isolation of Pneumocystis via bronchoalveolar lavage (BAL). Treatment of PCP depends on disease severity. Mild to moderate disease is treated with oral trimethoprim–sulfamethoxazole for 3 weeks. Severe disease requires IV trimethoprim–sulfamethoxazole. Currently the effect of PCP prophylaxis on patients with connective tissue disorders is unclear and there are no guidelines. In clinical practice, many rheumatologists use prophylaxis for patients receiving high doses of glucocorticoids and immunosuppressive agents.

Endemic Mycosis

Histoplasma capsulatum is endemic to the Midwest and Southeastern United States. Histoplasmosis has been reported in individuals with RA, JIA, and SLE [99, 100]. In a retrospective review by Olson et al., individuals who developed histoplasmosis tended to be on multiple immunosuppressive medication [101].

Coccidiodes is endemic to the deserts of the western hemisphere, particularly the American Southwest, and infection develops after inhalation of coccidioidal arthroconidia. Initial clinic presentation includes fever, malaise, cough, and dyspnea. Pulmonary involvement with pneumonia is the most common site but dissemination to the skin, bones, joints and CNS may occur [102]. Bergstrom et al. [103] evaluated adult RA patients treated with TNF therapy for development of coccidioidomycosis and found an increased risk, particularly in those receiving infliximab rather than with etanercept. Yorgin et al., reported two adolescents with lupus nephritis treated with IV cyclophosphamide and glucocorticoids who developed coccidioidomycosis [104]. Prednisone itself has also has been shown to be associated with an increased risk of coccidioidomycosis [102]. In our personal experience disseminated coccidioidomycosis has presented as monoarticular and polyarticular arthritis in children without systemic symptoms. Visual loss occurred in another patient with systemic onset JIA with disseminated coccidioidomycosis. Diagnosis of endemic fungal infections requires laboratory and tissue testing. Methods of detections are serology, culture, and urine antigen. Biopsy of an affected area can lead to rapid diagnosis. Amphotericin B, fluconazole, or itraconazole, for 6–12 months, are used for treatment of symptomatic coccidioidomycosis and histoplasmosis. In a recent study of coccidiomycosis in adult patients receiving biological response modifiers (BRMs) and DMARDs, Taroumian et al. proposed a treatment strategy in which all patients with pulmonary or disseminated coccidiomycosis were treated with antifungal therapy for 6–12 months for the former and indefinitely in the latter. For patients with pulmonary involvement it was believed prudent to discontinue BRM and DMARD therapy, with the decision to restart therapy when the coccidiomycosis was asymptomatic and rheumatic disease, only, was active. Although guidelines for treatment in pediatric rheumatic disease are not defined, disseminated infection will require life-long treatment [105•].

Because of increased risk of endemic fungal infections with TNF antagonists, Crum et al. recommend screening for histoplasmosis and coccidioidomycosis before initiation of treatment. The authors recommend CXR and antigen testing every 3–4 months for those living in endemic areas [106].

Conclusions

With advances in the management of pediatric rheumatic diseases, morbidity and mortality of the underlying conditions have improved and infections have gained further prominence. Differentiating between infections and active disease flare can be challenging and requires a high suspicion of both common and uncommon pathogens. A detailed history of exposure and diagnostic laboratory and imaging studies are important to obtain a diagnosis. If suspicion of infection is high, more invasive measures, for example bronchoscopy and tissue biopsies are warranted for identification of a pathogen. Early treatment that targets the specific etiologic agent is paramount, although immunization to prevent or attenuate disease is also important.

Conflict of Interest Rhina D. Castillo declares that she has no conflict of interest.

Wendy De la Pena declares that she has no conflict of interest.

Katherine A.B. Marzan declares that she has no conflict of interest.

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- •• Of major importance

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