disease severity and predict the risk of long-term sequelae (see XIV) [66, 69]. CRP elevation was also a key variable in another model predictive of severity of musculoskeletal infection in children, with risk of disseminated disease increasing steadily across a continuum of increasing CRP concentrations [215], but without clear cutoffs for specific risks being identified in terms of sensitivity, specificity, and predictive values.

CRP elevation is not specific to AHO and its complications. Initial and persistent elevation sometimes may be seen in other disease processes, including malignancy and autoimmune and autoinflammatory disorders [82, 83]. Persistent elevation during the course of documented AHO also can be the result of concurrent or intercurrent viral infections or intercurrent bacterial infections, such as intravascular catheter-related phlebitis or bacteremia, or *C. difficile* infection. Postsurgical increases in CRP after orthopedic procedures, on the order of 3 to 15 mg/dL (30 to 150 mg/L), may be seen, usually peaking on the second to third postoperative day [84, 85, 219].

ESR normalization over time also has been used as a guide to the duration of antimicrobial therapy for optimal outcomes [86]. The ESR peaks similarly to CRP but normalizes more slowly [43, 65, 87, 220]. ESR normalization in uncomplicated cases usually occurs within 3 to 4 weeks [18, 65]. Time to normalization for ESR is longer for complicated vs uncomplicated clinical courses of AHO [18, 42, 220]. Like the CRP, normalization of the ESR is typically slower in children with AHO with concurrent septic arthritis than with AHO alone [13, 65]. Intercurrent infections or diseases during the course of treatment for AHO may lead to increases in ESR or more prolonged time to normalization, especially with longer courses of therapy for complicated cases. The utility of ESR normalization as a guide to the duration of therapy in complicated courses remains uncertain.

Rationale for Recommendation

Physical examination has limited potential for harm and generally provides the necessary information for clinical decision-making. Measurement of serum CRP concentration is widely available in a timely manner, is relatively inexpensive, and is an objective, adjunctive data point that supports clinical decision-making. Pain and discomfort can occur from venipuncture that may not otherwise be required, but these are usually mild.

The relatively rapid normalization of CRP has been interpreted as providing useful clinical guidance for both early switch to oral therapy and avoidance of prolonged antibiotic therapy for uncomplicated disease. Although higher CRP peaks and prolonged time to normalization correlate in general with various aspects of the extent and severity of infection in children with AHO, no specific thresholds of CRP concentration have been well validated for specific clinical interventions or decisions regarding the duration of therapy.

As fever abates and local signs of inflammation begin to resolve, there usually is a concurrent fall in serum CRP concentration. Persistent elevation of CRP from what is expected in a typical uncomplicated course, especially when associated with slower than expected clinical improvement, can raise concerns that lead to (1) additional imaging to better define the extent of the infection (eg, persisting abscess) and its complications (eg, associated DVT) or (2) surgical intervention(s) that may optimize short- and long-term outcomes, and (3) reconsideration of the differential diagnosis (eg, infection vs cancer). The interpretation of persistent elevation of the CRP in the face of apparent clinical improvement is uncertain. This discordance can raise concerns about the need for more evaluation or intervention but acting on such data reflexively could lead to unnecessary actions and associated risks. Such discordance can be caused by intercurrent infection or other issues unrelated to the underlying musculoskeletal infection.

Within the limitations outlined above, the panel suggests sequential monitoring of CRP as an adjunctive measure in children with AHO that can be taken into account with other clinical factors in management decision-making. There are no data to support a particular frequency of CRP monitoring during the course of AHO in children. Measurement every 2 to 3 days during the early therapeutic course, rather than daily, followed by weekly or other periodic measurement until normalization (or a clear trend toward normalization is evident) is an acceptable approach.

Research Needs

More detailed analyses of the clinical utility of serial serum CRP concentrations or other markers of systemic inflammation, including PCT, the ESR, or various biosignatures, especially when elevation persists in the context of apparent clinical improvement, would be useful. Identification of specific CRP or other biomarker cutoff values would be helpful for specific clinical situations, such as the need for additional surgery vs observation for persisting small abscesses or fluid collections or as a guide to the duration of thrombolytic therapy for DVT associated with AHO. Multicenter studies using iterative protocols may be a way forward to gain insight into some of these questions.

X. In hospitalized children with suspected or documented AHO responding well to initial intravenous therapy and deemed ready for hospital discharge, should they be (1) be transitioned to oral therapy or (2) OPAT?

Recommendations:

1. For children with suspected or documented AHO who respond to initial intravenous antibiotic therapy, we recommend transition to an oral antibiotic regimen rather than OPAT when an appropriate (active against the confirmed