HK23: Does the pH of infected synovial fluid vary from that of uninfected synovial fluid?

Ayesha Abdeen, Javad Parvizi, Tsed Alex, Michael Kheir, Thomas P Schaer

Response/Recommendation: No, the pH in the synovial joint has been reported to range from acidic to alkalotic, regardless of infectious status. The pH is a diagnostic parameter of interest. Much work is needed to disentangle host-microbial interactions in synovial structures and their impact on pH. We, therefore, recommend that the current knowledge is insufficient to support pH as a diagnostic biomarker to differentiate between septic and aseptic synovial fluid.

Level of Evidence: Limited

Delegate Vote:

Rationale:

The pH scale is used to determine the acidity or alkalinity of a solution; a lower pH is consistent with increased acidity. Studies regarding the pH of synovial fluid date back to 1959, when Jebens et al. demonstrated the average pH of synovial fluid to be significantly higher than that of serum (7.7 +/- 0.04 versus 7.38 +/- 0.01) and that the pH of synovial fluid is lower in the setting of joint trauma (7.56 +/- 0.03) and osteoarthritis (7.55 +/- 0.04).[1] A 1975 study of human synovial fluid revealed a direct correlation between increased synovial fluid white blood cell count and decreased pH in human synovial fluid[2]. Additional studies underscored the relationship between increasing inflammation and synovial fluid acidity: synovial fluid in inflammatory conditions such as rheumatoid arthritis has lower pH values than osteoarthritis[3].

The pH of infected synovial fluid has been shown to be lower than that of non-infected synovial fluid[2,4–6]. This is most likely due to increased inflammation and lactic acid production in the setting of an infection.[5] Treuhaft et al. demonstrated that the pH of synovial fluid correlates strongly with the presence of lactate and to increasing severity of clinical inflammation in the setting of inflammatory arthritis[3]. Recent studies have revealed decreased pH in the setting of both native and periprosthetic joint infections (PJI) of the hip and knee[6–8]. Judl reported that patients who have a PJI of the hip and knee had a significantly lower synovial fluid pH (6.98 +/- 0.48) than non-infected hip and knee arthroplasties (7.82 +/- 0.29) and that a threshold pH of 7.4 had a sensitivity of 88.6% and specificity of 95.5% for the diagnosis of PJI[8]. Conversely, while Theil et al. also demonstrated synovial fluid pH to have reasonable specificity (89% at a threshold of pH = 7.11) the authors report poor sensitivity (53%) of synovial pH for the diagnosis of chronic PJI of the hip and knee[6].

In order to answer the above question, we conducted a comprehensive systematic literature review, consistent with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). MeSH terms were utilized to identify relevant studies. The primary databases used were PubMed and Scopus, with Web of Science being utilized to ensure all possible citations were identified. Of the literature reviewed, only articles containing original research for the direct measurement of synovial fluid pH were included for analysis. Species included for review were humans and clinically relevant animal species, including equine, porcine, and canine. The

pH data was either reported as recorded or calculated for normal joints, septic conditions, osteoarthritis, and arthroplasty. Conditions such as gout, rheumatoid arthritis, and traumatic and soft tissue injury were excluded.

The initial search generated 2,959 studies across all three databases. Of these, 20 studies met the inclusion criteria. Species distribution was 15 human, five equine, one canine, and one porcine. There were nine papers published after 2010. There were 50% of the papers that included a direct measurement of pH for normal synovial fluid. There were five papers that included a direct measurement for pH in conditions relating to septic arthritis. There were ten papers that included a direct measurement for pH in osteoarthritic conditions. There were four papers that reported pH for cases of septic arthroplasty, and five papers included pH for cases of aseptic arthroplasty. There were two papers that included the causative organism with pH, and two papers mentioned the use of antibiotics with pH. The methodologies of measuring pH varied greatly from digital pH meters to commercial blood gas analyzers to pH papers. Overall, the rigor of preserving sample integrity from collection to analysis was low and varied substantially. Furthermore, there is a concern for pH changes as a function of time, as well as the temperature at which it is stored if samples are not fresh when analyzed.

There is some consensus that the pH of synovial fluid is lower in the setting of an infection. Additionally, the low pH of synovial fluid in infection may explain why certain antibiotics (such as aminoglycosides) are rendered less effective when used for gram-negative infections[2]. White blood cells, metabolic products, and inflammatory mediators have been shown to influence the pH of synovial fluid, which may explain why infected synovial fluid has a different pH than non-infected fluid[2,9]. The impact of NSAIDspell out therapy and /or systemic or local antimicrobials on the synovial milieu is not well defined. Only two studies mentioned the use of antimicrobials, both of which considered the impact of specific antimicrobials on the joint environment. There is very little published data addressing the impact of antimicrobials on the *in vivo* environment when measuring pH, and vice versa. The causative organism in septic conditions may also affect the degree to which pH shifts, especially when comparing organisms of different phyla. There were two studies that measured the pH of the infectious organism; however, both papers used experimentally induced models of septic arthritis. The other papers that listed causative organisms in the clinical population did not correlate those organisms to pH. Also, the environment created by arthroplasty is unique and understudied and may have a direct impact on pH. Metal ions in the joint fluid were shown to have a buffering effect in a physiologic simulation study[10]. Metallosis, synovectomy, and arthrotomy have all been reported to change the pH of the native joint to favor a more alkalotic environment[10]. Advanced age may also have an impact on synovial fluid pH. Milosev et al. demonstrated synovial fluid pH to be higher in octogenarian patients who have native osteoarthritis of the hip and knee as well as a revision for the aseptic failure of hip and knee arthroplasties compared to those aged 40 to 49 years[10]. There were no studies that interrogated pH in the immediate postoperative surgical wound milieu.

Conclusions: The current systematic review revealed that the pH of synovial fluid in the setting of infection differs from that of non-infected joints. However, there are multiple factors that can affect the synovial fluid environment, such as inflammation, renal failure, metallosis, and administration of drugs like NSAIDs. Therefore, pH is not a reliable stand-alone diagnostic metric for PJI. Synovial fluid pH shows promise as an adjunctive measure for diagnosis of PJI, but its role as a diagnostic measure and potential to guide antibiotic selection need to be further refined. Original *in vivo* research of high translational fidelity and/or clinical research using

standardized analytical methods is needed to better understand host-microbial interactions and their impact on the environments created in different states of joint pathology.

References Fix references as per JOA

1. JEBENS EH, MONK-JONES ME. On the viscosity and pH of synovial fluid and the pH of blood. *J Bone Joint Surg Br*. 1959;41-B(2):388-400. doi:10.1302/0301-620X.41B2.388
2. Ward TT, Steigbigel RT. Acidosis of synovial fluid correlates with synovial fluid leukocytosis. *Am J Med*. 1978;64(6):933-936. doi:10.1016/0002-9343(78)90446-1
3. Treuhaft PS, MCCarty DJ. Synovial fluid pH, lactate, oxygen and carbon dioxide partial pressure in various joint diseases. *Arthritis Rheum*. 1971;14(4):475-484. doi:10.1002/art.1780140407
4. Lloyd KC, Stover SM, Pascoe JR, Adams P. Synovial fluid pH, cytologic characteristics, and gentamicin concentration after intra-articular administration of the drug in an experimental model of infectious arthritis in horses. *Am J Vet Res*. 1990;51(9):1363-1369.
5. Lenski M, Scherer MA. Diagnostic potential of inflammatory markers in septic arthritis and periprosthetic joint infections: a clinical study with 719 patients. *Infect Dis (Lond)*. 2015;47(6):399-409. doi:10.3109/00365548.2015.1006674
6. Theil C, Ackmann T, Gosheger G, et al. Synovial fluid pH is as specific as synovial leukocyte count but less sensitive for the diagnosis of chronic prosthetic joint infection. *Journal of Orthopaedics and Traumatology*. 2022;23(1). doi:10.1186/s10195-022-00672-5
7. Wijayaratna UN, Kiridena SD, Adams JD, Behrend CJ, Anker JN. Synovial Fluid pH Sensor for Early Detection of Prosthetic Hip Infections. *Adv Funct Mater*. 2021;31(37). doi:10.1002/adfm.202104124
8. Judl T, Popelka S, Tomšík E, et al. Acidity Is an Excellent Marker of Infection in Hip and Knee Arthroplasty. *J Clin Med*. 2024;13(3). doi:10.3390/jcm13030688
9. Wang Y, Che M, Zheng Z, et al. Animal Models for Postoperative Implant-Related Spinal Infection. *Orthop Surg*. 2022;14(6):1049-1058. doi:10.1111/os.13238
10. Milošev I, Levašič V, Vidmar J, Kovač S, Trebše R. pH and metal concentration of synovial fluid of osteoarthritic joints and joints with metal replacements. *J Biomed Mater Res B Appl Biomater*. 2017;105(8):2507-2515. doi:10.1002/jbm.b.33793