Use of Metagenomic Next-Generation Sequencing to Identify Pathogens in Pediatric Osteoarticular Infections

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Background. Osteoarticular infections (OAIs) are frequently encountered in children. Treatment may be guided by isolation of a pathogen; however, operative cultures are often negative. Metagenomic next-generation sequencing (mNGS) allows for broad and sensitive pathogen detection that is culture-independent. We sought to evaluate the diagnostic utility of mNGS in comparison to culture and usual care testing to detect pathogens in acute osteomyelitis and/or septic arthritis in children.

Methods. This was a single-site study to evaluate the use of mNGS in comparison to culture to detect pathogens in acute pediatric osteomyelitis and/or septic arthritis. Subjects admitted to a tertiary children’s hospital with suspected OAI were eligible for enrollment. We excluded subjects with bone or joint surgery within 30 days of admission or with chronic osteomyelitis. Operative samples were obtained at the surgeon’s discretion per standard care (fluid or tissue) and based on imaging and operative findings. We compared mNGS to culture and usual care testing (culture and polymerase chain reaction [PCR]) from the same site.

Results. We recruited 42 subjects over the enrollment period. mNGS of the operative samples identified a pathogen in 26 subjects compared to 19 subjects in whom culture identified a pathogen. In 4 subjects, mNGS identified a pathogen where combined usual care testing (culture and PCR) was negative. Positive predictive agreement and negative predictive agreement both were 93.0% for mNGS.

Conclusions. In this single-site prospective study of pediatric OAI, we demonstrated the diagnostic utility of mNGS testing in comparison to culture and usual care (culture and PCR) from operative specimens.

Keywords. metagenomics; mNGS; next-generation sequencing; osteomyelitis; septic arthritis.

Osteoarticular infections (OAIs) are commonly encountered in children, with an incidence of up to 80 per 100 000 [1]. There are significant practice variations in both the diagnosis and treatment of OAI, with some institutions foregoing routine procurement of operative cultures [1–3]. However, in up to 20% of cases, the empiric antibiotic regimen inadequately treats the organism isolated from culture [4, 5]. This is further complicated by low diagnostic yield from operative cultures when obtained (as low as 50% in some studies) [2, 4, 5]. Therefore, there is an opportunity to validate new diagnostic methods to identify a pathogen in pediatric OAI. Identifying a pathogen may allow for narrower-spectrum treatment and a lower chance of treatment failure due to an inappropriate antimicrobial regimen.

Metagenomic next-generation sequencing (mNGS), testing for pathogen-specific nucleic acids (RNA and DNA), allows for sensitive sampling of body compartments and encompasses the broad range of organisms that can be identified by culture as well as fastidious organisms that may be difficult to isolate by culture [6, 7]. Turnaround times for mNGS have been shortened to 24–48 hours, thereby enhancing the utility of mNGS for timely and clinically relevant diagnoses [8–10]. This study sought to evaluate the diagnostic utility of mNGS in comparison to culture and usual care (both culture and polymerase chain reaction [PCR]) to detect a pathogen from operative specimens in children with suspected/clinically diagnosed acute osteomyelitis and/or septic arthritis.

METHODS

This was a single-site prospective study to evaluate the diagnostic utility of mNGS in comparison to operative culture to detect a pathogen in children with presumed OAI. The members of the research team had final responsibility for the trial design, clinical protocol, and trial oversight. The University
of California, San Diego Institutional Review Board provided human subjects protection oversight of this study. Written consent was obtained from all subjects or their guardians.

Eligible subjects were children with a clinical diagnosis of acute osteomyelitis and/or septic arthritis admitted to Rady Children's Hospital from July 2019 through July 2020. We excluded any subjects with bone or joint surgery within 30 days of admission or with a known diagnosis of chronic osteomyelitis. Subjects with osteomyelitis and/or septic arthritis in their problem list were screened using an automated alert system with notification of the investigators at the time of hospital admission through the electronic medical record (EMR). Operative samples were obtained at the surgeon's discretion (joint aspirate, synovium, or bone) based on operative and imaging findings. For bone or synovial tissue, the orthopedic surgeon, using a flocked swab, swabbed the area that was suspected to be infected and placed the flocked swab in phosphate-buffered saline media. Joint aspirate was collected in a sterile collection tube. All samples were frozen at –80°C prior to shipping. Samples were shipped on dry ice. Extraction was done upon receipt at IDbyDNA from the swab or from joint aspirate. We compared mNGS testing to culture from the same site. We also compared mNGS to usual care testing, defined as culture and pathogen-specific PCR from a College of American Pathologists/Clinical Laboratory Improvement Amendments–approved laboratory licensed to perform high-complexity testing by state and federal authorities [11]. Pathogen-specific PCR testing was mostly for *Kingella kingae* (Quest Diagnostic, San Juan Capistrano, California), and when sent, was always done in addition to culture. Subjects were ideally enrolled before surgery, but for subjects identified postoperatively, remnant operative samples were obtained from the microbiology laboratory after usual care testing had been performed. mNGS results were disclosed to the treating clinician.

**Study Outcomes**

The primary objective of this study was to compare the diagnostic yield of pathogen detection in operative samples between mNGS and culture from the same site. Fluid (abscess or synovial fluid) or tissue specimens were obtained intraoperatively and sent to the hospital laboratory, and residual matched samples were sent for study purposes after standard care testing had been performed. Standard cultures were obtained on all operative specimens, and PCR for specific pathogen identification was only obtained when the surgeon and/or infectious disease consultant dictated. This study used the Explify mNGS platform (IDbyDNA, Salt Lake City, Utah) [12, 13]. A panel of 5 pediatric infectious diseases faculty reviewed the mNGS results in comparison to culture and usual care testing (both PCR and culture) in the context of the clinical presentation to determine the likelihood that the identified organism was indeed a true pathogen (Supplementary Table 1) [8, 14–16]. Each result was identified as a true positive (TP), false positive (FP), true negative (TN), or false negative (FN) based on the determination by unanimous consensus of the aforementioned study members. The determination of TN was made when a putative organism was not identified by any diagnostic modality. Determination of TP was made when mNGS and usual care testing were concordant. When results were discordant, results from usual care and mNGS were independently adjudicated to determine if an identified organism was likely pathogenic in that subject’s specific clinical context. If an organism was identified as a TP by that test modality, then the other modality by which that organism was not identified was deemed an FN. If an identified organism was not thought to explain the clinical presentation (eg, a commensal organism or environmental contaminant), this was considered an FP. There were no instances of discordance where 2 different organisms were identified by different testing modalities. We reviewed clinical data extracted from the EMR to describe the demographics of our cohort.

**Sequencing**

Operative samples were tested at IDbyDNA with research use–only next-generation shotgun DNA and RNA sequencing protocols, and the resulting data were analyzed with the Explify Platform (IDbyDNA). DNA and RNA were extracted separately from residual clinical samples [13, 17]. Next-generation DNA sequencing libraries were prepared with the Nextera DNA Flex Library Prep kit (Illumina, San Diego, California) and sequenced on a NextSeq550 instrument (Illumina) to a median depth of 4.9 × 10⁷ single-end, 150-bp sequencing reads per library. Sequencing reads were adapter-trimmed and quality-filtered as part of the Explify analysis. Quality control included positive and negative external controls for each batch of samples, spike-in (internal) controls added at the lysis step, and minimum thresholds for sequencing data quality and quantity. A research use–only antimicrobial resistance (AMR) pipeline was used to evaluate for the presence of *mecA* (most salient for *Staphylococcus aureus*).

**Statistical Analysis**

Positive predictive agreement (PPA) and negative predictive agreement (NPA) with 95% confidence intervals (CIs) were calculated for mNGS, culture result, and usual care (both PCR and culture) from the reference standard derived by the adjudication scheme described above (Supplementary Table 2). Means were reported with standard deviation and medians with interquartile range.

**RESULTS**

The EMR automated alert identified 166 subjects from July 2019 to July 2020, from which we enrolled 45 subjects (Figure 1). Many of the patients screened were for improperly triggered alerts through the EMR for subjects with remote history of
OAI or who were incorrectly characterized as having OAI by the EMR problem list. Of the 45 enrolled subjects, 42 subjects had samples that were adequate for analysis (Table 1). mNGS of the operative samples identified a putative organism in 26 (61.9%) subjects as compared to 19 (45.2%) identified by operative culture. Eighteen subjects were enrolled postoperatively, and mNGS identified a pathogen in 12 (67%) of these cases (culture was positive in 8 [44%] of these subjects). PCR for *K. kingae* was positive from the joint aspirate of 5 subjects, and PCR for *Borrelia burgdorferi* from the joint aspirate was positive in another subject. mNGS was concordant with all positive *K. kingae* PCR results. Cultures for all of the subjects with a positive PCR result were negative. In 3 subjects, a blood culture was positive, for which both the operative culture and mNGS result were concordant. *Staphylococcus aureus* accounted for 57% of positive results, 2 of which were methicillin-resistant *S. aureus* (MRSA) (Figure 2). In both MRSA cases, the AMR detection pipeline in the mNGS assay identified mecA, concordant with

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**Figure 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Abbreviation: OAI, osteoarticular infection.

**Table 1. Clinical Characteristics of All Enrolled Subjects**

| Characteristic                        | All (Organism Isolated) | No Organism Isolated | P Value |
|---------------------------------------|-------------------------|----------------------|---------|
| No. of subjects                       | 42 (28 [66.7])          | 14 (33.3)            |         |
| Average age, y (SD)                   | 9.1 (5.7)               | 9.7 (6.5)            | 0.3     |
| Duration of symptoms <1 wk            | 29 (69.1)               | 17 (60.7)            | 0.2     |
| Length of hospitalization, d, median (IQR) | 4.5 (3.0–6.0)       | 5.0 (4–6.3)          | 0.2     |
| Average admission CRP, mg/dL (SD)     | 6.7 (7.7)               | 7.8 (8.5)            | 0.2     |
| Average admission ESR, mm/h (SD)      | 39.6 (20.0)             | 39.5 (21.0)          | 0.1     |
| Osteomyelitis                         | 21 (50.0)               | 17 (60.7)            | 0.1     |
| Septic arthritis                      | 21 (50.0)               | 11 (39.3)            | 0.1     |
| Positive blood culture                | 3 (71)                  | 3 (10.7)             | 0.5     |
| Subperiosteal abscess                 | 8 (19.1)                | 7 (25.0)             | 0.2     |
| Received antibiotics prior to surgery | 33 (78.6)               | 22 (78.6)            | 0.1     |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; SD, standard deviation.

*Reference range: 0.00–0.99 mg/dL.

*Reference range: 0–15 mm.
The mNGS analysis of samples from 42 subjects with OAI demonstrated a similar diagnostic yield compared to culture and usual care (culture and PCR), with mNGS of the operative samples identifying a pathogen in 26 (61.9%) subjects as compared to 19 (45.2%) identified by operative culture and 24 (57.1%) by usual care testing. In 4 subjects, mNGS detected a likely pathogen where usual care was negative. One of these cases was a subject with *K. kingae* osteomyelitis for which culture was negative (PCR for *K. kingae* is not commercially available from bone). An FP result by mNGS from an operative sample was identified in 1 subject. In 2 subjects, mNGS was falsely negative. In 1 case, Lyme arthritis was diagnosed by PCR from synovial fluid. Both culture and mNGS failed to detect *B. burgdorferi*. It is possible that PCR is a more sensitive test for Lyme disease than mNGS, which is an important consideration in endemic areas.

Operative sampling is often part of the management of pediatric OAI [1–3]. The most common pathogens in pediatric osteomyelitis include *S. aureus*, group A Streptococcus, *Streptococcus pneumoniae*, and *K. kingae* [1]. Determining empiric treatment to cover these organisms, including MRSA, can be challenging, and the result may be unnecessarily broad, inappropriate, or prolonged antibiotic therapy. Furthermore, cultures are often falsely negative. In 1 of these cases, a subject with septic arthritis was found to have a positive PCR for *B. burgdorferi* from the same sample (this subject was also found to be positive for *B. burgdorferi* by serology). Culture for this subject was negative. In the other case, tissue culture identified methicillin-sensitive *S. aureus*. Further investigation of this discrepancy revealed a possible sampling error (mNGS may have been sent from a different site than the tissue culture). Using the adjudication scheme described above, PPA was 93.0% (95th CI, 77%–99%) and NPA was 93.0% (95th CI, 66%–99%) for mNGS of the operative samples versus 66.0% (95th CI, 46%–82%) and 85.0% (95th CI, 55%–98%) respectively for culture and 86.0% (95th CI, 67%–96%) and 86.0% (95th CI, 57%–96%) respectively for usual care (culture and PCR) (Table 2).

All enrolled children achieved clinical cure without readmission, osteonecrosis, or pathologic fracture within the 2-month follow-up period.

**DISCUSSION**

Table 2. Positive Predictive Agreement and Negative Predictive Agreement of Metagenomics Next-Generation Sequencing Versus Culture and Usual Care (Culture and Polymerase Chain Reaction)

| Method                   | All (N = 42) | Bone (n = 21) | Joint (n = 21) |
|--------------------------|--------------|--------------|---------------|
|                          | % Positive   | PPA (95% CI) | NPA (95% CI)  | % Positive | PPA (95% CI) | NPA (95% CI)  | % Positive | PPA (95% CI) | NPA (95% CI)  |
| mNGS                     | 61.9         | 0.93 (.77–.99) | 0.93 (.66–.99) | 76.2       | 0.94 (.71–.99) | 1.0 (.40–1.0) | 50.0       | 0.91 (.59–.99) | 0.90 (.55–.99) |
| Culture                  | 45.2         | 0.66 (.46–.82) | 0.85 (.55–.98) | 61.9       | 0.76 (.50–.93) | 1.0 (.40–1.0) | 25.0       | 0.45 (.17–.77) | 0.80 (.44–.97) |
| Usual care (culture + PCR)| 57.1         | 0.86 (.67–.96) | 0.86 (.57–.98) | 66.7       | 0.82 (.57–.96) | 1.0 (.40–1.0) | 50.0       | 0.91 (.59–.99) | 0.80 (.44–.97) |

Abbreviations: CI, confidence interval; mNGS, metagenomic next-generation sequencing; NPA, negative predictive agreement; PCR, polymerase chain reaction; PPA, positive predictive agreement.
Pathogen-specific PCR testing may be useful as obtained operatively may be negative in up to 50% of cases [2, 4, 5, 20–23]. Identification of a pathogen may be important in guiding therapeutic decision making, and positive culture data may result in a change in management in up to 85% of cases [4]. Metagenomic next-generation sequencing, testing for pathogen-specific RNA and DNA, allows for broad and sensitive sampling of sterile sites [6, 7, 14, 15, 26, 27]. Few studies to date, however, have examined use of mNGS for OAI specifically. Thoenel et al, in a study examining 213 subjects with prosthetic joint infection (PJI), found that mNGS performed on joint aspirate was able to identify a pathogen in 43 of 98 (43.9%) subjects with culture-negative PJI [7]. A similar study done by Huang et al examined an adult cohort of 103 subjects with OAI (70.8% of whom had PJI), identifying an organism by mNGS alone in 23.8% of samples [28]. Our data show that mNGS from operative samples offers a similar diagnostic yield in pediatric OAI, with the added benefit of detecting fastidious organisms that culture slowly and/or poorly such as *K. kingae*. The concordance of mNGS AMR detection for *mecA* (which correlates with methicillin resistance) with culture susceptibility testing adds further relevance to mNGS in the management of OAI. However, an additional consideration is cost of mNGS, which can range from $300 to $2000 depending on sample type, methodology, and turnaround time, and has been a limiting factor in its adoption for regular clinical use [29]. As mNGS techniques evolve to provide similar results to usual care testing in a shorter time and at a similar price point, mNGS testing may become more clinically applicable [30].

This study has several limitations, including a modest sample size. As a single site, the epidemiology of pathogens causing OAI may reflect local geographic distribution and incidence rates, hampering generalizability of our cohort. We were also unable to enroll many subjects before surgery; however, in this cohort, the detection rate of mNGS in the subjects enrolled postoperatively was similar to that of those enrolled preoperatively. Separately, many subjects received antibiotics prior to surgery, which additionally may further limit sensitivity of culture. Surgeons were moreover afforded discretion in determining the optimal sampling sites based on their preoperative and intraoperative findings. Though this reflects real-world clinical practice, it does introduce potential sampling error and variability to the data set. PPA and NPA were determined based on adjudication of results by a panel of infectious disease specialists, which allows for possible bias in cases where mNGS and usual care results were discordant. For the determination of a TN specifically by using the criteria of no organism detected by any method, we may have excluded some subjects with organisms that were either in low abundance or intrinsically difficult to isolate or sequence. Conversely, some subjects with suspected infection may have had an autoimmune or autoinflammatory phenomenon masquerading as infection [31–34]. Importantly, while the data presented suggest a similar diagnostic yield for mNGS testing in comparison to usual care testing, we are unable to demonstrate an impact on clinical care.

**CONCLUSIONS**

In this single-site prospective study of pediatric OAI, we demonstrated similar diagnostic utility of mNGS testing in comparison to culture and usual care (culture and PCR) from operative specimens. However, further prospective studies are needed to better characterize the best diagnostic and clinical use of mNGS in pediatric OAI.

**Supplementary Data**

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

**Notes**

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**Patient consent statement.** Written consent was obtained from all subjects or their guardians. The members of the research team had final responsibility for the trial design, clinical protocol, and trial oversight. The University of California, San Diego Institutional Review Board provided human subjects protection oversight of this study.

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**Potential conflicts of interest.** L. F. is now the Chief of Medical Affairs at IDbyDNA. B. B. is the Associate Director of Medical and Scientific Affairs at IDbyDNA. R. S. is the Associate Director of Clinical Studies at IDbyDNA. IDbyDNA provided support for sample shipment and for the cost of the mNGS assay. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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