Received: 25 May 2020 | Revised: 27 August 2020 | Accepted: 30 September 2020

DOI: 10.1111/ijlh.13370

ORIGINAL ARTICLE

ISLH International Journal of Laboratory Hematology WILEY

Clinical assessment of the utility of metagenomic next-generation sequencing in pediatric patients of hematology department

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Abstract

Introduction: Metagenomic Next-Generation Sequencing (mNGS) is an emerging technique for microbial identification and diagnosis of infectious diseases. The clinical utility of mNGS, especially its real-world impact on antimicrobial treatment and patient outcome has not been systematically evaluated.

Methods: We prospectively assessed the effectiveness of mNGS in 70 febrile inpatients with suspected infections at Hematology department of the Children's Hospital, National Clinical Research Center for Child Health. 69/70 patients were given empirical antibiotics prior to mNGS. A total of 104 samples (62 plasma, 34 throat swabs, 4 bone marrow, 4 bronchoalveolar lavage) were collected on day 1-28 (mean 6.9) following symptom onset and underwent mNGS testing.

Results: Traditional microbiological tests discovered causal microorganisms in 5/70 (7.14%) patients, which were also detected by mNGS. In addition, mNGS reported possible pathogens when routine tests were negative. Antibiotics were adjusted accordingly in 55/70 (78.6%) patients that led to improvement/relief of symptoms within 3 days. In contrast, mNGS results were considered irrelevant in 15/70 (21.4%) patients by a board of clinicians, based on biochemical, serological, imaging evidence, and experiences.

Conclusion: mNGS expanded the capacity of pathogen detection and made a positive impact on clinical management of suspected infections through (a) differential diagnosis which may rule out infectious diseases and (b) adjustment or de-escalation of empirical antibiotics.

KEYWORDS

diagnosis, hematological malignancy, infectious disease, metagenomic next-generation sequencing, pediatric

1 | INTRODUCTION

Clinical management of infection is a leading factor that influences prognosis of pediatric patients with hematological malignancies, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), non-Hodgkin lymphoma (NHL), aplastic anemia (AA), blastic plasmacytoid dendritic cell neoplasm (BPDCN).[1-3] Early diagnosis and intervention of infectious diseases would drastically reduce the risk of complications and improve patients' long-term survival.[4] As a result, diagnostic tests play a critical role in the clinical care

of patients, especially when empirical antibiotics are not effective. However, conventional microbiological tests such as culture, staining, and serology often have low sensitivity and can only cover a small fraction of potential pathogens.[5]

Due to the advances in Massively Parallel Sequencing (MPS) technique, nucleic acid sequencing-based diagnostics such as the metagenomic Next Generation Sequencing (mNGS) are increasingly applied in clinical settings. mNGS is "culture-free" and "hypothesis-free" that can detect a wide range of potential pathogens.[6] Notably, mNGS is superior to traditional tests in diagnosing polymicrobial infections, fastidious/unculturable or novel pathogens within a time frame of 24-48 hours.[7] It is also less-affected by prior antibiotic use when compared to culture.[8,9]

Despite its vast potential, mNGS has a number of drawbacks that might hinder its clinical use. These include, but are not limited to high cost, slow turnaround-time (TAT), lack of assay standards and challenges in interpretation of results. Current opinions toward mNGS are quite polarized. While many studies pointed out its value in diagnosing infections in immunocompromised cohort, a number of studies suggested limited utility of mNGS as currently used in routine clinical practice.[10,11] The disagreement partly reflects the complexity in management of infectious diseases and in what way this technology is used in clinical care. There are many factors at play, such as the sample type, transportation, prior use of antibiotics, prevalence of antimicrobial resistance, patient's age, ethnicity, gender, underlying illness, *etc*.[12]

To assess whether and how mNGS can benefit patient outcomes, we incorporated it as a routine microbiological test in the Department of Hematology at Children's Hospital in Zhejiang Province, China. We enrolled 70 febrile pediatric patients with hematological disorders in this study. Most patients were immunocompromised due to chemotherapy, hematopoietic stem cell transplantation and underlying illness.

2 | METHODS

2.1 | Subject recruitment

From May 2019 to October 2019, 70 patients (43 males, 27 females) at Hematology department of the Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health were recruited for this study. All participants were suspected of having infectious diseases due to fever and/or respiratory/gastrointestinal symptoms such as cough, shortness of breath, chest pain, diarrhea, and abdominal pain *etc*. All subjects have provided informed consent for participation and publication of the de-identified data.

2.2 | Traditional microbiological tests

Routine clinical examinations such as CT scan, microbiological culture, blood cell count, biochemistry (procalcitonin (PCT), C-reactive protein (CRP) and cytokines), serology (influenza A (Flu A), influenza B (Flu B), parainfluenza viruses (HPIV), adenovirus (AdV), respiratory syncytial virus (RSV), Epstein–Barr virus (EBV) and cytomegalovirus (CMV)) and molecular (*Mycoplasma pneumoniae* (MP)) tests were also performed.

2.3 | Sample collection and mNGS testing

For each patient, 10 mL of peripheral blood was drawn into EDTA tube. Sample collection took place on day 1-28 (mean 6.9) following onset of fever. One throat swab or 10 mL of BALF was collected when respiratory symptoms were evident. In four patients, bone marrow aspiration was performed, and 2 mL of bone marrow was obtained. All samples were transported within four hours to Hangzhou Matridx Biotechnology Co., Ltd. for mNGS testing. Whole blood was centrifuged at 1600 *g* for 10 min and supernatant was centrifuged at 16 000 *g* for 10 min to separate plasma. For plasma and bone marrow, DNA sequencing was performed. For throat swabs and BALF, RNA sequencing was also performed in order to detect RNA viruses. DNA or RNA sequencing library was prepared by reverse transcription (for RNA), enzymatic fragmentation (except for plasma), end repairing, terminal adenylation and adaptor ligation (NGSmaster™ library preparation, Matridx, Cat# MAR002). Concentration of libraries was quantified by real-time PCR (KAPA) and pooled. Shotgun sequencing was carried out on illumina Nextseq™ platform. Approximately 20 million of 75bp single-end reads were generated for each library. Bioinformatic analysis was conducted as described in a previous report [13] in which sequences of human origin were filtered (GRCh38.p13) and the remaining reads were aligned to reference database (NCBI nt database and GenBank) in order to identify microbial species. For each run, one negative control (artificial plasma mixed with fragmented human genomic DNA) and one positive control (a mixture of inactivated bacteria, fungi and pseudoviral particles containing synthesized DNA or RNA fragments of adenovirus and influenza A virus, respectively) were included for quality control.

2.4 | Interpretation of mNGS results

Clinical samples were collected and sent out for mNGS and analyzed results typically came back within 24 hours. For 38 patients who showed respiratory symptoms (cough, shortness of breath, chest pain *etc*), both respiratory sample [throat swab or bronchoalveolar lavage (BALF)] and peripheral blood were tested. Prior to mNGS, 69/70 patients were empirically administered broad-spectrum antibiotics, but no apparent symptom alleviation was observed. The antibiotics included meropenem, linezolid, and voriconazole that target gram-negative, gram-positive bacteria, and fungi, respectively. Antifungals were routinely administered to certain patients as a prophylaxis.[14]

To decide whether microorganisms reported by mNGS were of clinical relevance, we evaluated the results according to the following criteria: mNGS was relevant if (a) it detected the same pathogens

as reported by microbial culture/PCR; (b) the patient improved within 3 days upon adjusting antibiotics based on mNGS; (c) it reported pathogens that have already been covered by prior antibiotics and the patient improved within 3 days; (d) results were negative and the final diagnosis indicated diseases not associated with microbial infection (*ie*, drug fever, tumor, autoimmune diseases *etc*). In contrast, we considered mNGS to be irrelevant if (a) it reported bacterial or fungal species and the patient recovered by antifungal or antibacterial treatment, respectively; (b) it reported microorganisms, but symptoms did not improve after adjusting antibiotics. In cases where multiple samples were analyzed, results from all samples were taken into consideration.

3 | RESULTS

3.1 | Clinical characteristics

In this study, 51/70 (72.9%) participants were under 10 years old. All patients were previously diagnosed with hematological disorders. These include 46 acute lymphoblastic leukemia (ALL), eight acute myeloid leukemia (AML), 13 non-Hodgkin lymphoma (NHL), one aplastic anemia (AA), one blastic plasmacytoid dendritic cell neoplasm (BPDCN) and one immunodeficiency disease (IDD). Samples were collected for mNGS at day 1-28 (6.9 ± 4.9) following symptom onset (Table 1 and Table S1). Results of traditional examinations were shown in Table 2. Notably, 36/70 (51.43%) had neutropenia, which was typical in hematological patients.[15]

TABLE 1 Clinical characteristics of study participants

	Count	Ratio
Gender		
Male	43	61.40%
Female	27	38.60%
Age (years)		
≥10	19	27.10%
<10	51	72.90%
Sample type		
Blood	62	59.62%
Nasopharyngeal swab	34	32.69%
Bronchoalveolar lavage	4	3.85%
Bone marrow	4	3.85%
Underlying disease		
ALL	46	65.71%
NHL	13	18.57%
AML	8	11.43%
AA	1	1.43%
BPDCN	1	1.43%
IDD	1	1.43%
Neutropenia		
Agranulocytosis	36	51.43%
Normal	34	48.57%
Chest CT scan		
Abnormal	30	42.86%
No abnormalities	40	57.14%
Clinical outcome		
Recovered	69	98.57%
Deceased	1	1.43%

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; NHL, non-Hodgkin lymphoma; AA, aplastic anemia; BPDCN, blastic plasmacytoid dendritic cell neoplasm;IDD, immunodeficiency disease.

3.2 | Microbiological testing and clinical significance

Two sets of blood culture for each patient (20 mL blood was drawn from each arm and incubated for detection of aerobic and anaerobic organisms) and MP RNA test reported positive findings in 5/70 (7.14%) patients. Particularly, blood culture identified one case of *Pseudomonas aeruginosa*, one case of *Klebsiella pneumoniae* and one case of *Staphylococcus epidermidis*. MP RNA test reported two positive cases (one throat swab and one BALF). These findings were also reported by mNGS (Table S1). Serology tests identified three case of EBV (1/3 reported by mNGS), two case of CMV (1/2 reported by mNGS), one case of *Aspergillus fumigatus* (not reported by mNGS), one case of HPIV (not reported by mNGS since RNA sequencing was not performed for plasma).

In total, 104 samples (62 plasma, 34 throat swabs, 4 bone marrow, 4 BALF) were tested. mNGS on 47/62 plasma, 34/34 swab, 3/4 bone marrow, 4/4 BALF reported positive microbial findings (normal flora detected from throat swabs was not counted as positive), respectively (Figure 1 and Table S1). For 34 patients, mNGS on blood and swab detected overlapping organisms in 14/34 (41.18%) cases, including human herpesviruses (five EBV, one HSV-1, and one HHV-7), human parvovirus B19 (three cases), *Pseudomonas aeruginosa* (two cases), *Acinetobacter baumannii* (one case), *Staphylococcus aureus* (one case), *Haemophilus parainfluenzae* (one case), and *Candida albicans* (one case). For four patients, mNGS on blood and BALF reported overlapping organisms in 2/4 (50%) (one *Mycoplasma pneumoniae* and one human parvovirus B19) (Table S1).

For 55/70 (78.57%) individuals, mNGS findings led to positive impact on patient outcome via adjustment of prior antibiotics. Notably, in two patients with osteomyelitis, all microbial tests were negative except that plasma mNGS reported *Staphylococcus aureus*. Both patients recovered after anti-Gram-positive bacteria treatment (Vancomycin and Linezolid). In one febrile patient, plasma mNGS reported *Staphylococcus aureus* when traditional tests were inconclusive. We adjusted antibiotics accordingly and the patient's fever subsided. However, the patient experienced recurrence of fever following drug withdrawal and a second set of blood culture identified *Staphylococcus aureus*, which was consistent with mNGS. Moreover, in two cases where mNGS was negative, one patient was diagnosed with hemophagocytic histiocytosis and the other with

myelodysplastic syndrome, both of which were not associated with microbial infection. Antibiotics were withdrawn in both cases.

For 15/70 (21.43%) patients, mNGS either reported organisms that were deemed irrelevant (one case of neoplastic fever, two cases of graft rejection after hematopoietic stem cell transplantation, three cases of bacterial enteritis) or failed to identify the causal pathogens when other tests and clinical evidence strongly suggested infectious diseases (five cases of pneumocystis pneumonia and two cases of pulmonary aspergillosis) (Table S1).

4 | DISCUSSION

4.1 | Clinical value of mNGS in diagnosis of infectious disease

Failure or delay in identifying the microorganisms responsible for critical infection could lead to prolonged hospitalization and elevated death rate.[16] Hematological patients are usually immunodeficient due to chemotherapy, hematopoietic cell transplantation and therefore are prone to opportunistic infections. The causal pathogens may consist of a wide range of microbes, including bacteria, fungi, and viruses. Due to the use of broad-spectrum antibiotics and prevalence of fastidious microorganisms, culture often fails to detect the culprit. Typically, the positive rate of blood culture is less than 10%.[17] In this study, culture was positive in 5.71% (4/70) of patients. In contrast, mNGS is culture-independent that can theoretically detect all pathogens of known genomic sequence. The detection rate of mNGS in our study was 88/104 (84.62%), making it a valuable diagnostic tool for polymicrobial and rare infections, especially in immunocompromised cohort.

In addition to bacterial and fungal species, mNGS detected a variety of DNA and RNA viruses from all sample types, including adenovirus, rhinovirus, parainfluenza virus, human parvovirus B19, polyomaviruses (Trichodysplasia spinulosa polyomavirus, JC virus, BK virus) and human herpesviruses (HSV-1, HSV-2, EBV, CMV, HHV-6, and HHV-7), which were of clinical value since we normally lacked diagnostic tests for these viruses (Figure 1). Prior to mNGS, antivirals were not as much considered as compared to antibacterial and antifungal treatment. mNGS enabled the clinicians to consider the possibility of viral infections and decide early on whether antivirals were necessary. In addition, the high incidence of herpesviruses as shown in our cohort was consistent with previous findings in which these viruses are common even in healthy individuals. Previous studies indicated a relationship between host immunity and herpesviruses that may influence the outcome of concurrent infections, cancers and grafts.[18] The clinical implications of herpesviruses in immunodeficient patients need further explorations.

TABLE 2 Routine laboratory test results

Test	Count
WBC	0.01-19.14 (3.38) $\times 10^9$/L
Neutrophill	0-10.9 (1.63) $\times 10^9$/L
hs-CRP	0.5-177.88 (43.42) mg/L
PCT	0.065-2.43 (0.36) ng/mL
IL-6	4-397.1 (73.17) pg/mL
IL-10	2.2-266.2 (18.74) pg/mL
γ-INF	1-116.3 (10.28) pg/mL
TNF	1-24.6 (2.53) pg/mL

Abbreviations: WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; PCT, procalcitonin; IL-6, interleukin 6; IL-10, interleukin 10; γ-INF, interferon gamma; TNF, tumor necrosis factor.

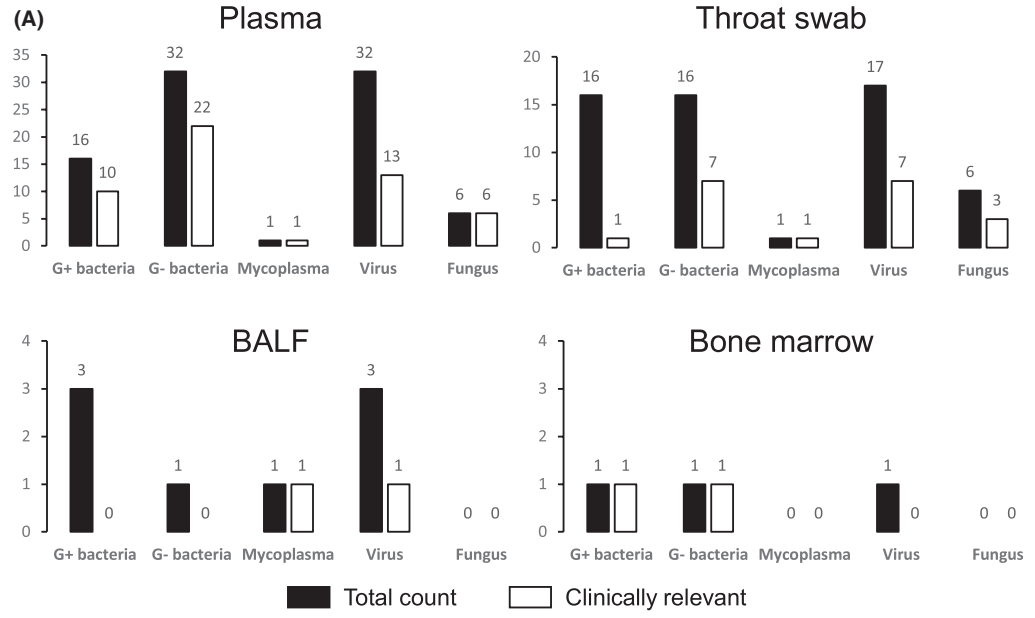
4.2 | Sampling is critical for the utility of mNGS

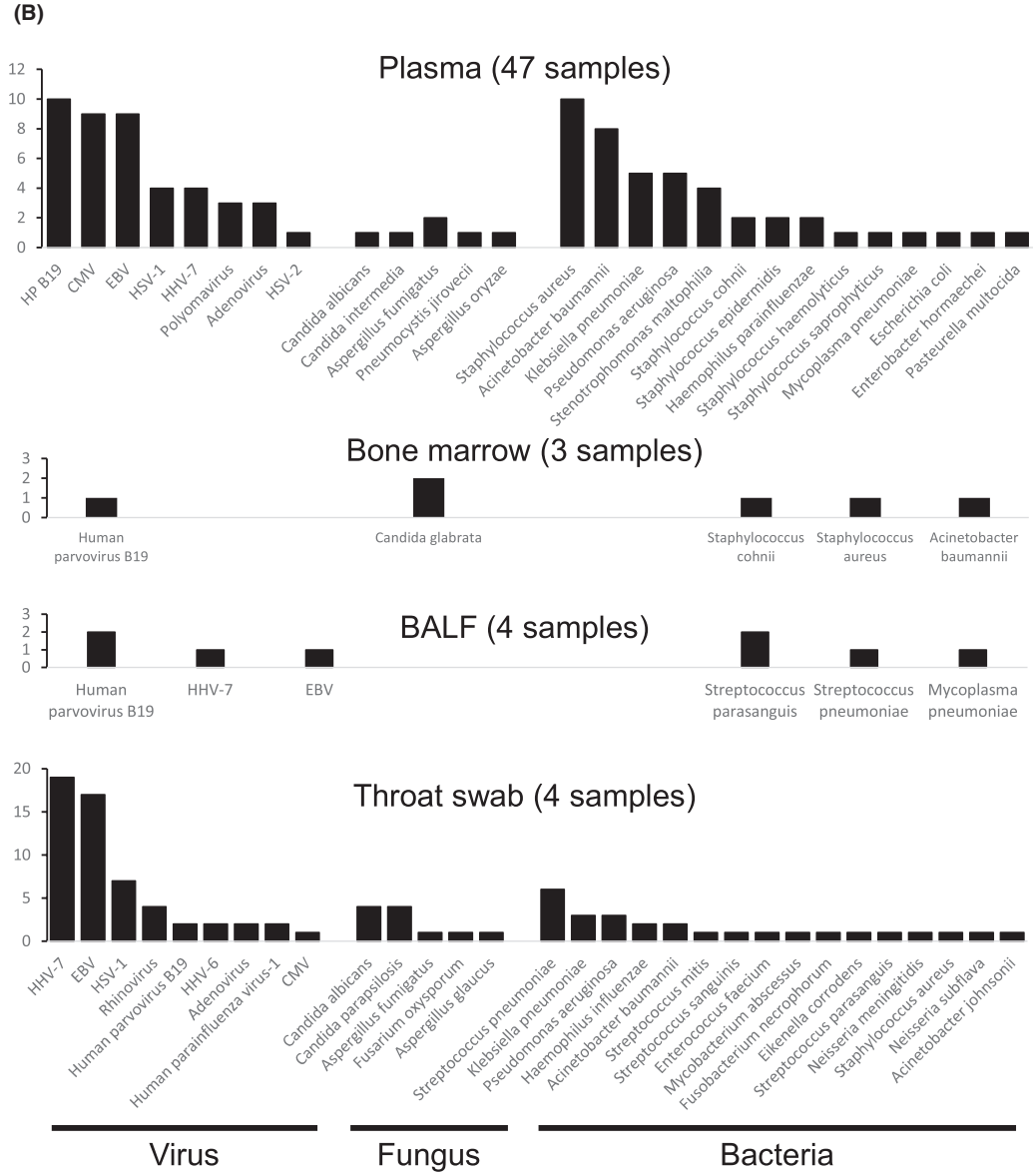
Plasma mNGS was of greater significance in helping clinicians determine the causal pathogen(s) as compared with throat swab, in which commensal microbiota from upper respiratory tract were present. Cell-free nucleic acid in plasma is thought to originate from apoptotic human cells and shedding of microbial nucleic acid from site of infection through interactions between the host immune system and invading pathogens.[19] In our study, 38/70 (54.29%) patients were suspected of respiratory infections. Indeed, previous studies also suggest that respiratory tract infection (RTI) is the most common type of infection in hematological patients.[20] While BALF was of great value in diagnosing pulmonary infections, performing bronchoscopy on pediatric patients is usually difficult. Hematological patients often have low platelet count, further restricting the application of invasive procedures. Moreover, plasma mNGS could yield false-negative results due to the high abundance of host DNA. Taken together, when bronchoscopy was not an option, collecting both throat swab and peripheral blood appeared to be a working strategy. As shown in our study, matching organism(s) from throat swab and plasma were identified in 14/34 (41.18%) patients (highlighted in red, Table S1).

4.3 | When to perform mNGS

The turnaround time (TAT), cost and interpretation of results are important factors to consider before using mNGS in a clinical setting. Furthermore, nucleic acid extraction seemed to be another key element to ensure sensitivity toward pathogens with thick cell walls or capsules that may prevent release of nucleic acid for sequencing. This is especially evident when it comes to fungi as mNGS appeared to have missed 5 cases of pneumocystis pneumonia and 2 cases of pulmonary aspergillosis. Fungal cell walls comprise of

FIGURE 1 mNGS results and clinical relevance. A total of 104 samples (62 plasma, 34 throat swabs, 4 bone marrow, 4 BALF) were collected for mNGS testing. 47/62 plasma, 34/34 swab, 3/4 bone marrow, 4/4 BALF reported positive findings, respectively. The count of total reported microorganisms and the count of clinically relevant microorganisms were shown (A). The species and the count of viruses, fungi and bacteria detected from 4 different sample types were graphed (B)


(A)
Plasma
Throat swab
BALF
Bone marrow
G+ bacteria
G- bacteria
Mycoplasma
Virus
Fungus
Total count
Clinically relevant


(B)
Plasma (47 samples)
HP B19
CMV
EBV
HSV-1
HHV-7
Polyomavirus
Adenovirus
HSV-2
Candida albicans
Candida intermedia
Aspergillus fumigatus
Pneumocystis jirovecii
Aspergillus oryzae
Staphylococcus aureus
Acinetobacter baumannii
Klebsiella pneumoniae
Pseudomonas aeruginosa
Stenotrophomonas maltophilia
Staphylococcus cohnii
Staphylococcus epidermidis
Haemophilus parainfluenzae
Staphylococcus haemolyticus
Staphylococcus saprophyticus
Mycoplasma pneumoniae
Escherichia coli
Enterobacter hormaechei
Pasteurella multocida
Bone marrow (3 samples)
Human parvovirus B19
Candida glabrata
Staphylococcus cohnii
Staphylococcus aureus
Acinetobacter baumannii
BALF (4 samples)
Human parvovirus B19
HHV-7
EBV
Streptococcus parasanguis
Streptococcus pneumoniae
Mycoplasma pneumoniae
Throat swab (4 samples)
HHV-7
EBV
HSV-1
Rhinovirus
Human parvovirus B19
HHV-6
Adenovirus
Human parainfluenza virus-1
CMV
Candida albicans
Candida parapsilosis
Aspergillus fumigatus
Fusarium oxysporum
Aspergillus glaucus
Streptococcus pneumoniae
Klebsiella pneumoniae
Pseudomonas aeruginosa
Haemophilus influenzae
Acinetobacter baumannii
Streptococcus mitis
Streptococcus sanguinis
Enterococcus faecium
Mycobacterium abscessus
Fusobacterium necrophorum
Eikenella corrodens
Streptococcus parasanguis
Neisseria meningitidis
Staphylococcus aureus
Neisseria subflava
Acinetobacter johnsonii
Virus
Fungus
Bacteria

N-acetylglucosamine polymer chitin. Therefore, experimental techniques such as bead-beating and sonication might be desirable for effective detection of these pathogens.

5 | CONCLUSION

We found mNGS to be of clinical value that can benefit pediatric hematological patients in the following scenarios: (a) patients with suspected infection are in critical condition and effective treatment is urgent; (b) immunocompromised patients who are more prone to polymicrobial infections; (c) routine microbiological tests are negative or inconclusive while empirical treatment is unsuccessful; (d) fever of unknown origin in which differential diagnosis is needed to confirm or rule out infectious diseases.

ACKNOWLEDGEMENT

The authors received no financial support for the research, authorship, and publication of this article.

CONFLICT OF INTEREST

The authors claim no conflict of interest.

AUTHOR CONTRIBUTIONS

Chao Liu and Jingying Zhang conceived and designed the research. Heping Shen collected and performed clinical data analysis. Diying Shen and Hua Song contributed clinical data and analysis. Xueqin Wu, Cong Xu and Guangyu Su performed the experiments and mNGS analysis. Heping Shen and Chao Liu wrote the manuscript.

DATA AVAILABILITY STATEMENT

All data generated and analyzed for this study are included in this published article and the supplemental files.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Shen H, Shen D, Song H, et al. Clinical assessment of the utility of metagenomic next-generation sequencing in pediatric patients of hematology department. *Int J Lab Hematol*. 2020;00:1–6. https://doi.org/10.1111/ijlh.13370