Primary exploring the value of metagenomic next-generation sequencing in detecting pathogenic bacteria of cholangitis with biliary atresia after Kasai operation

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Research Article

Keywords: Biliary atresia, Cholangitis, Blood culture, Metagenomic next-generation sequencing, Pathogenic bacteria

Posted Date: August 11th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1938055/v1

Abstract

Purpose

To evaluate the value of metagenomic next-generation sequencing (mNGS) in detecting pathogenic bacteria of cholangitis for patients with biliary atresia after Kasai operation.

Methods

Patients of biliary atresia with cholangitis after Kasai operation who were admitted to Xi'an Children's Hospital from July 2019 to December 2021 were retrospectively analyzed. Both blood culture and mNGS were carried out in all of these patients. The detection rate of pathogenic bacteria, pathogenic bacteria spectrum, test time, inflammatory indicators and liver function were compared. The correlation between drug resistance gene and drug resistance phenotype was analyzed. All the patients were followed up for 0.5-3 years to evaluate the onset of cholangitis and the survival status of autologous liver.

Results

a total of 30 episodes of cholangitis in 25 patients were included in this study. There were significant differences in the detection rate of pathogenic bacteria [23.3 vs.73.3%, $P < 0.05$] and the test time [120 (114.5–120) vs.16 (16–21) h, $P < 0.001$] between the blood culture and mNGS. Inflammatory indicators (CRP, PCT) and liver function (TB, DB, GGT) were compared before and after anti-infection, and there was significant statistical difference with two methods. Four kinds of bacteria were detected by blood cultures, and 10 kinds of bacteria were detected by mNGS. The drug-resistant phenotypes and drug-resistant genotypes of 3 Klebsiella pneumoniae strains were compared, h Cholangitis occurred 3 times in 1 case (4%) and twice in 3 cases (12%). Autologous liver survived in 17 cases (68%).

Conclusion

Compared with traditional blood culture, mNGS is more efficient, convenient and accurate in the detection of pathogens. It provides a new method for the accurate detection of pathogenic bacteria of cholangitis with biliary atresia after Kasai operation.

Introduction

Biliary atresia (BA) is an obstructive jaundice disease characterized by intrahepatic and extrahepatic bile duct occlusion, It often occurs in the perinatal period, and its etiology is still unclear [1, 2]. If untreated, it will eventually lead to death due to progressive aggravation of cirrhosis or liver failure. Kasai operation is the best way to restore bile flow and save autologous liver in biliary atresia [3]. Cholangitis is a serious complication after Kasai operation, with a morbidity of 40–93%, which has an important impact on the

long-term survival and life quality of patients, and is also a risk factor for poor prognosis of the disease. Therefore, the correct choice of antibiotics is the key to the treatment of cholangitis [4, 5]. Cholangitis is mainly caused by bacterial infection, and the detection of pathogenic bacteria is very important for the diagnosis and treatment of cholangitis. However, due to the results of traditional blood culture are affected by many factors, such as the timing of blood collection, the amount of blood collected, whether antibiotics are used before blood collection, the culture medium and the culture process, the probability of obtaining pathogenic bacteria is low, and the time required is long, thus it will affect the choice of antibiotics for the treatment of cholangitis. However, the birth of metagenomic sequencing technology has brought dawn to the efficient detection of pathogenic bacteria, which was first applied to the study of non-culturable microorganisms in various environments, latterly the workflow of the technology was optimized and verified by scholars, and the turnaround time (an average of 48 hours) has been shortened, sensitivity increased and bioinformatics pipelines customzied. Some scholars have promoted metagenomic sequencing technology into the field of clinical practice of pathogen identification [6]. In recent years, metagenomics next - generation sequencing (mNGS) has been proved to be a successful diagnostic tool, which can be used to detect pathogenic bacteria accurately in variety of infection sites, including the central nervous system, respiratory system, urinary system, etc. [7]. Therefore, the aim of this study was to investigate on the value of mNGS in detecting pathogenic bacteria of cholangitis with biliary atresia after Kasai operation.

Materials And Methods

Object and method

In this study, 25 biliary atresia patients with cholangitis after Kasai operation from July 2019 to December 2021 were collected, and all of them were compliant with the diagnostic criteria of cholangitis: 1) fever of unknown origin above 38 ℃, 2) recurrence or aggravation of clinical jaundice, accompanied by elevated bilirubin levels, or from yellow stool to acholic stool. 3) Elevated C-reactive protein (CRP). Cholangitis can be diagnosed with at least a combination of the above two clinical manifestations [8]. 30 episodes of cholangitis occurred in 25 patients. Blood culture and mNGS were performed in all patients during the attack of cholangitis, and the detection rate of pathogenic bacteria, pathogenic bacteria spectrum, detection time, inflammatory indicators and liver function before and after treatment, drug-resistant phenotypes and drug-resistant genotypes were compared and analyzed between the 2 methods. The patients were followed up for 0.5 to 3 years to assess the frequency of cholangitis and the survival status of the liver.

Data collection and analysis

The clinical data of 25 patients with cholangitis after Kasai operation for biliary atresia were analyzed retrospectively. Inclusion criteria: 1) All patients were diagnosed with biliary atresia and underwent Kasai operation. 2) compliant with cholangitis diagnostic criteria. Exclusion criteria: 1) combined with other parts of infection (such as: respiratory system, digestive system or urinary system, etc.), 2) combined with

other system diseases (such as: complex congenital heart disease, diabetes, nephropathy, etc.). 3) Parents refused to participate in the study.

The positive detection rates of pathogenic bacteria and detection time between blood culture and mNGS in 30 episodes of cholangitis were compared, and the pathogenic bacteria spectrum was drawn according to the types and quantities of pathogenic bacteria detected.

The antibiotic therapy scheme and treatment time were selected according to the results of pathogenic bacteria, and the results of inflammatory indicators (CRP, PCT) and liver function before and after treatment were compared.

Among the 25 patients, 4 patients had both the drug-resistant phenotypes and drug-resistant genotypes of pathogenic bacteria, and the correlation between the drug-resistant phenotypes and drug-resistant genotypes was compared.

25 patients were followed up for 0.5 to 3 years, and the frequency of cholangitis and the survival status of autologous liver were recorded.

Statistical analysis

Software SPSS 26.0 was used for data analysis. The data following normal distribution were expressed as mean ± standard deviation (SD), and the data following non-normal distribution were expressed as median (P25, P75). Non-parametric test and $\chi 2$ test were selected according to data distributions. $P < 0.05$ indicates statistical difference.

Result

Demographics characteristics of patients

In this study, the basic information of 25 patients were analyzed (Table 1), including age of operation, sex ratio, jaundice regression rate, jaundice regression time after operation, age of first cholangitis attack, time of cholangitis after operation, highest body temperature, stool color, etc.

Detection rate of pathogenic bacteria by two methods

According to the $\chi 2$ test of paired four-fold table data (Table 2), there were significant statistical difference in positive detection rates between the two methods ($\chi 2 = 11.53$, $P < 0.05$). In 30 episodes of cholangitis, the detection rate of pathogenic bacteria in blood cultures was 23.3%, which was 73.3% in mNGS (Figure 1). The detection rate of pathogenic bacteria in mNGS was significantly higher than that in blood culture.

Pathogenic spectrum

In 30 episodes of cholangitis， 11 types of pathogenic bacteria were detected in this study, including 4 types of pathogenic bacteria detected in blood culture and 10 types of pathogenic bacteria detected in mNGS. The pathogenic bacteria detected by blood culture was Klebsiella pneumoniae in 4 cases, Stenotrophomonas maltophilia, Klebsiella oxytoca and Enterococcus faecalis in 1 case respectively. Klebsiella pneumoniae was detected in 11 person-times by mNGS, Stenotrophomonas maltophilia, Escherichia coli were detected twice by mNGS, Klebsiella oxytoca, Acinetobacter baumannii, Enterococcus faecium, Enterobacter cloacae complex, Biliphilus wolfmanii, Candida tropicalis and Fusarium oxysporum were detected only once by mNGS. The number and types of pathogenic bacteria detected by mNGS were much more than those detected by blood culture, including fungi (Fig. 2).

Test time of pathogenic bacteria by two methods

In 30 episodes of cholangitis，blood culture and mNGS pathogenic bacteria test time [120 (114.5-120) vs. 16 (16-21) h, P < 0.001] were statistically different significantly. For patients with positive blood culture results, a total of 7 times, the test time of blood culture and mNGS in detecting pathogenic bacteria [94 (67-96) vs. 16 (16-20) H, P < 0.05] were still statistically different (Fig. 3). detection of pathogenic bacteria with method mNGS is superior to blood culture in timeliness.

Bacteria and treatment schemes

Pathogenic bacteria were detected in 23 of 30 episodes of cholangitis, including 21 cases of bacteria and 2 cases of fungi. For 21 cases with bacterial infections, antibiotics were selected according to the results of drug sensitivity of blood culture, and if the blood culture was negative, antibiotics were selected according to the results of mNGS and drug resistance genes. For carbapenem-resistant and multi-drug resistant bacteria, if the conventional treatment regimen is ineffective, with the discussion and agreement by the clinical expert group, approval by the ethics committee, and informed consent of the patient’s parents, the clinical pharmacist guided the use of tigecycline-based combined anti-infective treatment regimen according to the patient's condition, the results of drug sensitivity in blood culture or resistance genes in mNGS and reference[9,10] (Table3).

Inflammatory indicators

The inflammatory indicators (CRP and PCT) of 30 episodes of cholangitis were compared before and after anti-infection treatment, the results are: CRP [61.29 (24.43-119.27) vs.2.41 (1.13-4.34) mg/L, P < 0.001] and PCT [0.94 (0.34-7.41) vs. 0.16 (0.07-0.36) ng/dl, P < 0.001] (Table4). There were statistically significant differences in CRP and PCT. After treatment, the inflammatory indicators were significantly decreased compared with that before treatment.

Serum liver function

The liver function (ALT, AST, TB, DB, GGT) of 30 person-times (with 25 patients) were compared before and after anti-infection. ALT [125.5 (37.5-197.75) vs. 64.5（40.75-129.5）U/L, P>0.05], AST [125.5（72.25-182.25）vs. 108 (80.25-160.5) U/L, P > 0.05], ALT and AST had no significant changes before and after

treatment, TB [61.85 (36.55-118.03) vs. 50.75（25.93-102.68）μmol/L, P<0.05], DB[45.65（22.98-75.55）vs. 31.55 (13.48-66.9) μmol/L, P < 0.05], TB and DB decreased significantly after treatment compared with the data before treatment. GGT [531.10 (282.28-1024.13) vs. 718.65 (251.63-1723.45 μmol/L, P < 0.05), GGT after treatment was significantly higher than that before treatment (Table 5). The increase of GGT is considered to be related to the edema and obstruction of intrahepatic bile capillaries caused by cholangitis, and the decline in GGT lags behind TB and DB.

Drug-resistant phenotype and drug-resistant genotype

In this study, 4 patients had drug-resistant phenotype in blood culture drug and drug-resistant genotype in mNGS at the same time, and 2 types of pathogenic bacteria were detected, including 3 strains of Klebsiella pneumoniae, all of them were multi-resistant bacteria, and 1 strain of Stenotrophomonas maltophilia, no drug resistance was found (Table 6).

The resistance phenotypes of 3 strains of Klebsiella pneumoniae to antibacterial drugs are shown in Table 7, the resistance rates to ampicillin sulbactam, piperacillin tazobactam, cefoxitin, cefotetan, ceftriaxone, cefazolin, cefuroxime, cefoperazone sulbactam, ceftazidime, cefepime, meropenem, imipenem and trimethoprim-sulfamethoxazole were all 100%. The resistance rate to aztreonam and minocycline was 66.7%. The resistance rate to ciprofloxacin, levofloxacin and doxycycline was 33.3%. There was no resistance to amikacin, gentamicin, tobramycin and tigecycline.

The drug-resistant genotypes of 3 strains of Klebsiella pneumoniae are shown in Table 8. A total of 17 drug-resistant genes were detected, including 11 types of antibiotics. All of these three strains carried SHV beta-lactamase gene. sul1、AAC(3)-Ⅱc、FosA6、TEM beta-lactamase、NDM beta-lactamase、CTX-M beta-lactamase, Fosfomycin thiol transferase resistance genes were found in two strains, and the other nine resistance genes were found in one strain.

Compared the drug-resistant phenotypes and genotypes of 3 strains Klebsiella pneumoniae. The resistant phenotypes and genotypes of penicillins, cephalosporins, carbapenems, monobactams, fluoroquinolones, tetracyclines and sulfonamides were consistent. The phenotype and genotype of cephamycin-resistant and aminoglycoside-resistant bacteria were inconsistent (Table 9).

Follow-up

25 patients were followed up for 0.5-3 years, including the frequency of cholangitis and the survival of autologous liver.

1. Cholangitis attack frequency. Among the 25 cases, 1 case had 3 cholangitis attacks and 3 cases had 2 cholangitis attacks (Table 10). According to the results of pathogenic bacteria in different attack periods of cholangitis in these 4 patients, it indicated that each attack of cholangitis in the same patient was independent, and there is no connection between cholangitis (Table 11).

2. Survival status of autologous liver: 17 cases of autologous liver survived, 6 cases had liver transplantation, and 2 cases died (Table 12).

Discussion

Cholangitis is a common complication of biliary atresia after Kasai operation. The morbidity of bacterial cholangitis is 70% -90%, and most cases can recur [10, 11]. When cholangitis recurs, bacteria and inflammation in the bile canaliculi impair bile drainage, causing cholestasis leading to further liver injury and fibrosis, thus affecting the prognosis of the disease [13]. Routine use of antibiotics after Kasai surgery can effectively prevent the occurrence of cholangitis [14, 15]. In recent years, although people's understanding of BA has been improved, the morbidity of cholangitis is still high. Most cholangitis can be controlled by direct intravenous infusion of sufficient antibiotics, but some cholangitis does not respond to conventional treatment [16]. It is considered that it may be related to the diversity of pathogenic microorganisms and the gradual increase of drug-resistant pathogenic bacteria. Therefore, the acquisition of pathogenic bacteria plays a key role in the treatment of cholangitis. In this study, the inflammation was quickly and effectively controlled after choosing the treatment plan according to the pathogenic bacteria, which avoided the antibiotic resistance and uncontrolled infection that may be caused by empirical treatment.

Blood culture is widely used as an important means to obtain pathogenic bacteria, but there are still some shortcomings. The positive rate of blood culture is low, only 8.9–25.8% [12, 17], and the results are affected by many factors, such as the timing of blood collection and blood collection technology. Intravenous use of antibiotics before blood collection will lead to false negative blood culture results, and improper operation during blood collection will lead to specimen contamination, which may lead to false positive blood culture results. Antibiotic susceptibility test is the main method to detect the drug resistance of pathogenic bacteria in clinic, it is also the "gold standard" for the diagnosis of drug-resistant bacterial infections, but there are also shortcomings. Firstly, antibiotic susceptibility testing usually needs to be carried out on isolated pathogens, which is not only time-consuming, unable to obtain timely information on pathogens and drug resistance, but also further ignores unculturable bacteria. Secondly, the selection of antibiotics is limited by the list of antibiotic susceptibility tests, and there are biases and lags in the selection of antibiotics, and the drug susceptibility of some restricted antibiotics or new antibiotics can’t be obtained in time. Finally, there is a deviation between the drug resistance phenotype of some pathogens and the clinical reality.

In this study, the detection rate of pathogenic bacteria, test time, pathogenic bacteria spectrum, inflammatory indicators, drug resistance phenotype and drug resistance genotype were compared with the two methods, and it was found that the detection rate of pathogenic bacteria by mNGS was higher and the test time was shorter. In terms of pathogen detection, the number of pathogens detected by mNGS is not only large, but also more abundant. mNGS is a clinical laboratory diagnostic technology for

gene testing of pathogenic bacteria based on high-throughput sequencing technology and bioinformatics analysis technology [18, 19]. mNGS has both the ability to simultaneously detect DNA and RNA viruses, bacteria, fungi, and parasites present in a sample, and the ability to exclude infections [6]. This technology has gradually been widely used in the field of pediatric infections, including respiratory system, nervous system, blood system, bone and joint, and parasitic infections [20–24]. Therefore, in this study, mNGS was used to detect the pathogenic bacteria of cholangitis after Kasai operation in biliary atresia, and satisfactory results were obtained.

In recent years, mNGS is in the exploratory research stage of detecting drug resistance genes, and has clinical application potential and broad application prospects [25]. At the same time, there are also some problems to be solved, such as the inability to determine the source of drug resistance genes, the existence of incomplete gene-phenotype matching, and the qualitative but not quantitative bacterial resistance [26]. In this study, 4 patients had drug resistance phenotype in blood culture and drug resistance genotype in mNGS at the same time, and the drug resistance phenotype and drug resistance genotype were compared. One strain of Stenotrophomonas maltophilia was sensitive to levofloxacin, minocycline and trimethoprim-sulfamethoxazole, and no drug resistance gene was found in mNGS. Three strains of Klebsiella pneumoniae were all multidrug-resistant bacteria. The drug-resistant phenotypes and drug-resistant genotypes of the three strains of Klebsiella pneumoniae were compared, the drug-resistant phenotypes and drug-resistant genes of penicillins, cephalosporins, carbapenems, monobactams, fluoroquinolones, tetracyclines and sulfonamides were consistent, indicating that there was a close relationship between the drug-resistant phenotype and drug resistance genotypes. The phenotype and genotype of drug resistance were not consistent between cephamycin and aminoglycoside antibiotics. Three strains of Klebsiella pneumoniae were resistant to cephamycin antibiotics (cefoxitin and cefotetan), and the drug resistance rate was 100%, but only two strains of bacteria were detected to be resistant to cephamycin antibiotics. Firstly, this phenomenon may be related to the false negative of drug resistance genes caused by insufficient sequencing depth. Secondly, the formation of bacterial biofilm leads to the failure of antibiotics to enter bacteria to play a bactericidal role in antibiotic sensitivity tests. On the contrary, the three strains were sensitive to aminoglycoside antibiotics (amikacin, gentamicin, tobramycin), but the aminoglycoside antibiotic resistance genes were all positive. This phenomenon may be related to the expression of drug resistance gene. Because the drug resistance phenotype is related to many factors such as bacterial species and external environment, there are also cases where multiple genes co-express a certain drug resistance phenotype, so there may be a phenomenon that the sequencing drug resistance gene is positive but the phenotype is sensitive to the corresponding drug [27]. The mechanism of bacterial resistance to antibiotics is very complex. The location of resistance genes (plasmid or chromosome), genetic structure, the expression of resistance genes, the interaction between different resistance genes, and the formation of bacterial biofilm all affect the resistance of bacteria to antibiotics. The resistance of bacteria to one drug may be the result of the interaction of multiple resistance genes and resistance mechanisms. Bacterial resistance can be caused by epistatic relationships between multiple genes and can even occur through overexpression of normal genes. These complex mechanisms of resistance, coupled with the fact that known antimicrobial resistance genes may

not always be expressed, make it difficult to accurately predict phenotypic antimicrobial resistance from genotypic antimicrobial resistance data [28].

The mNGS can efficiently and quickly detect the pathogenic bacteria of cholangitis with biliary atresia after Kasai operation. However, this technology has limitations in the detection and interpretation of drug resistance genes of pathogenic bacteria, and the drug resistance genes of mNGS can't completely replace the traditional blood culture, thus, the two methods can complement each other and provide a basis for clinical precise treatment.

References

1. Sokoloff L. Metabolism of ketone bodies by the brain. Annu Rev Med. 1973,24:271–80.
2. Magistretti PJ, Allaman I. A cellular perspective on brain energy metabolism and functional imaging. Neuron. 2015 May 20,86(4):883–901.
3. Paoli A, Rubini A, Volek JS, Grimaldi KA. Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. Eur J Clin Nutr. 2013 Aug,67(8):789–96.
4. Suissa L, Kotchetkov P, Guigonis J-M, Doche E, Osman O, Pourcher T, et al. Ingested Ketone Ester Leads to a Rapid Rise of Acetyl-CoA and Competes with Glucose Metabolism in the Brain of Non Fasted Mice. Int J Mol Sci. 2021 Jan 7,22(2):E524.
5. Williams G, Kolodny GM. Suppression of myocardial 18F-FDG uptake by preparing patients with a high-fat, low-carbohydrate diet. AJR Am J Roentgenol. 2008 Feb,190(2):W151-156.
6. Selvaraj S, Margulies K, Dugyala S, Schubert E, Tierney A, Arany Z, et al. Comparison of Exogenous Ketone Administration versus Dietary Carbohydrate Restriction on Myocardial Glucose Suppression: A Crossover Clinical Trial. Journal of Nuclear Medicine. 2021 Oct 1 Jan 18, Available from: https://jnm.snmjournals.org/content/early/2021/10/21/jnumed.121.262734
7. Ułamek-Kozioł M, Czuczwar SJ, Januszewski S, Pluta R. Ketogenic Diet and Epilepsy. Nutrients. 2019 Oct 18,11(10):E2510.
8. Ye F, Li X-J, Jiang W-L, Sun H-B, Liu J. Efficacy of and patient compliance with a ketogenic diet in adults with intractable epilepsy: a meta-analysis. J Clin Neurol. 2015 Jan,11(1):26–31.
9. Rusek M, Pluta R, Ułamek-Kozioł M, Czuczwar SJ. Ketogenic Diet in Alzheimer's Disease. Int J Mol Sci. 2019 Aug 9,20(16):E3892.
10. Vanitallie TB, Nonas C, Di Rocco A, Boyar K, Hyams K, Heymsfield SB. Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. Neurology. 2005 Feb 22,64(4):728–30.
11. Stafstrom CE, Rho JM. The Ketogenic Diet as a Treatment Paradigm for Diverse Neurological Disorders. Front Pharmacol. 2012 Apr 9,3:59.
12. Siegmann MJ, Athinarayanan SJ, Hallberg SJ, McKenzie AL, Bhanpuri NH, Campbell WW, et al. Improvement in patient-reported sleep in type 2 diabetes and prediabetes participants receiving a continuous care intervention with nutritional ketosis. Sleep Med. 2019 Mar,55:92–9.

13. Kuehn BM. In Alzheimer Research, Glucose Metabolism Moves to Center Stage. JAMA. 2020 Jan 28,323(4):297–9.
14. Yang H, Shan W, Zhu F, Wu J, Wang Q. Ketone Bodies in Neurological Diseases: Focus on Neuroprotection and Underlying Mechanisms. Front Neurol. 2019 Jun 12,10:585.
15. Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nat Rev Neurosci. 2019 Mar,20(3):148–60.
16. Huffman J, Kossoff EH. State of the ketogenic diet(s) in epilepsy. Curr Neurol Neurosci Rep. 2006 Jul,6(4):332–40.
17. Owen OE, Morgan AP, Kemp HG, Sullivan JM, Herrera MG, Cahill GF. Brain Metabolism during Fasting. J Clin Invest. 1967 Oct 1,46(10):1589–95.
18. Zhang Y, Kuang Y, Xu K, Harris D, Lee Z, LaManna J, et al. Ketosis proportionately spares glucose utilization in brain. J Cereb Blood Flow Metab. 2013 Aug,33(8):1307–11.
19. Hasselbalch SG, Madsen PL, Hageman LP, Olsen KS, Justesen N, Holm S, et al. Changes in cerebral blood flow and carbohydrate metabolism during acute hyperketonemia. American Journal of Physiology-Endocrinology and Metabolism. 1996 May 1,270(5):E746–51.
20. Courchesne-Loyer A, Croteau E, Castellano C-A, St-Pierre V, Hennebelle M, Cunnane SC.Inverse relationship between brain glucose and ketone metabolism in adults during short-term moderate dietary ketosis: A dual tracer quantitative positron emission tomography study. J Cereb Blood Flow Metab. 2017 Jul,37(7):2485–93.
21. Liśkiewicz D, Liśkiewicz A, Nowacka-Chmielewska MM, Grabowski M, Pondel N, Grabowska K, et al. Differential Response of Hippocampal and Cerebrocortical Autophagy and Ketone Body Metabolism to the Ketogenic Diet. Front Cell Neurosci. 2021,15:733607.
22. Korsholm K, Law I. Effects of a ketogenic diet on brain metabolism in epilepsy. Clin Nucl Med. 2013 Jan,38(1):38–9.
23. Yakushev I, Landvogt C, Buchholz H-G, Fellgiebel A, Hammers A, Scheurich A, et al. Choice of reference area in studies of Alzheimer's disease using positron emission tomography with fluorodeoxyglucose-F18. Psychiatry Research: Neuroimaging. 2008 Nov 30,164(2):143–53.
24. Guedj E, Barbeau EJ, Didic M, Felician O, de Laforte C, Ranjeva J-P, et al. Effects of medial temporal lobe degeneration on brain perfusion in amnestic MCI of AD type: deafferentation and functional compensation? Eur J Nucl Med Mol Imaging. 2009 Jul,36(7):1101–12.
25. Arregle F, Martel H, Philip M, Gouriet F, Casalta JP, Riberi A, et al. Infective endocarditis with neurological complications: Delaying cardiac surgery is associated with worse outcome. Arch Cardiovasc Dis. 2021 Apr 29,S1875-2136(21)00068-1.
26. García-Cabrera E, Fernández-Hidalgo N, Almirante B, Ivanova-Georgieva R, Noureddine M,Plata A, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. Circulation. 2013 Jun 11,127(23):2272–84.

Tables

Table 1 to 12 are available in the Supplementary Files section.

Figures

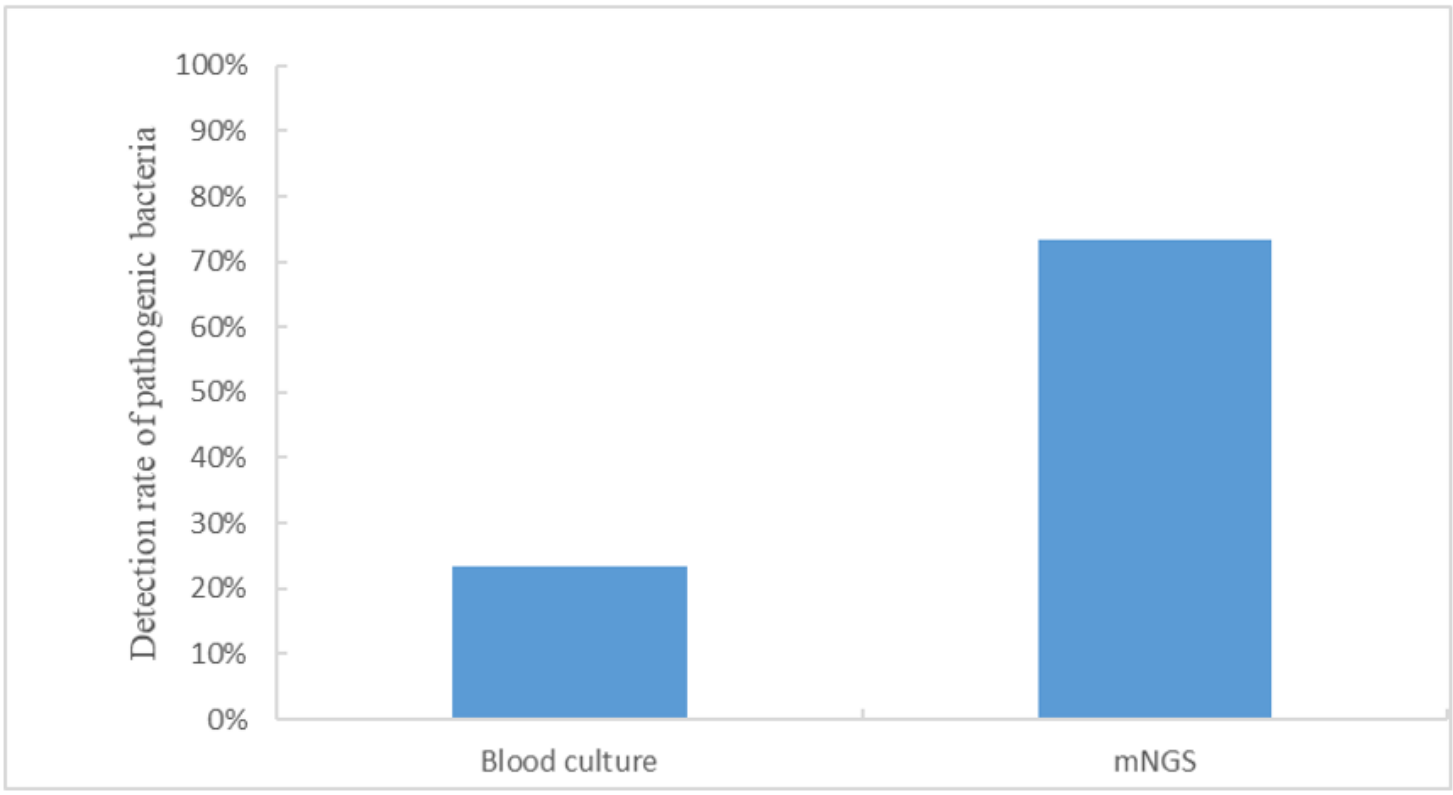

Figure 1

Detection rate of pathogenic bacteria detected by two methods

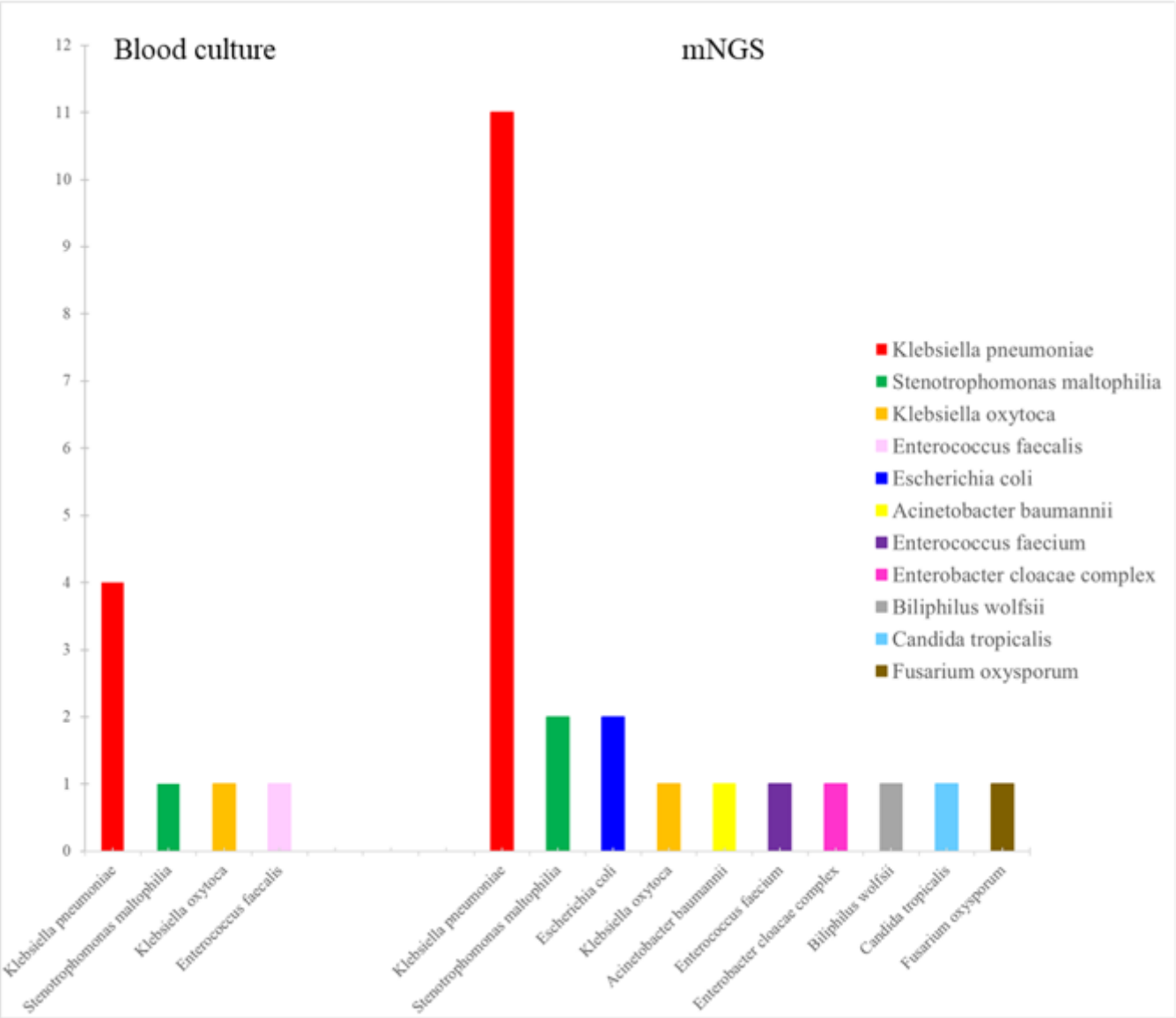

Figure 2

Pathogen spectrum

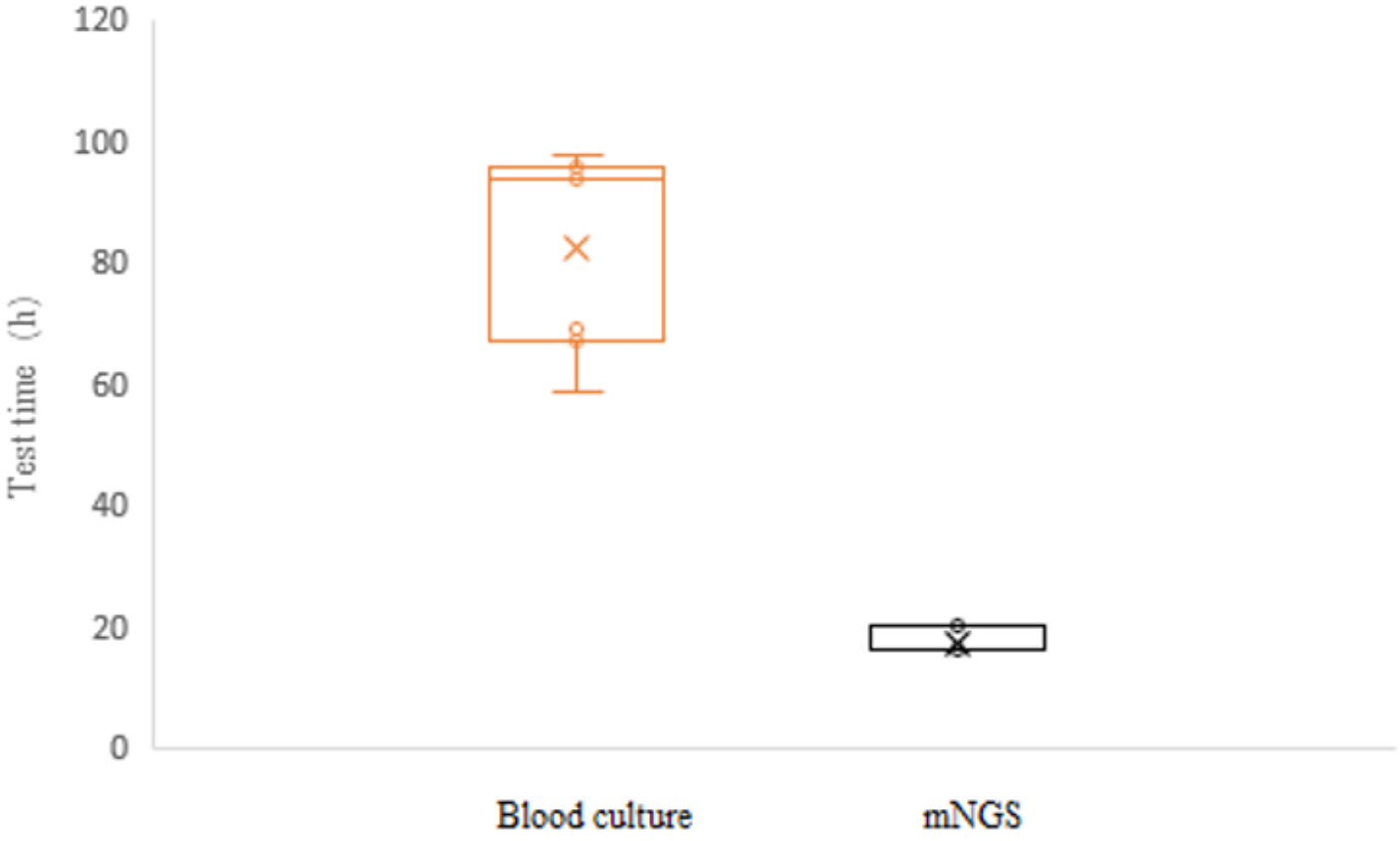

Figure 3

Test time of two methods for detection of pathogenic bacteria in patients with positive blood culture

Supplementary Files

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