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THE RELEVANCE OF MICROBIOLOGICAL METHODS FOR THE DETECTION AND EARLY DIAGNOSIS OF CLIBSIELLA

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Abstract: The most frequent pathogen responsible for hospital respiratory tract infections and epidemics is Klebsiella pneumoniae (K. pneumoniae). Clinical diagnosis frequently uses the gold standard methods of microscopic inspection and biochemical identification, which have the drawbacks of low sensitivity, time commitment, and the need for complex equipment. To support clinical medicine and disease control, a sensitive, specific, and effective on-site identification of K. pneumoniae based on nucleic acid amplification is required. In order to specifically detect Klebsiella pneumoniae in fecal samples, this study set out to create a quick and sensitive droplet digital PCR (ddPCR) technique. Its clinical applicability was assessed by contrasting it with real-time PCR assays and traditional microbiological culture. A probe and particular primers were created to target the K. pneumoniae hemolysin (khe) gene. The specificity of the primers and probe was assessed using thirteen additional diseases. To evaluate the sensitivity, repeatability, and reproducibility of the ddPCR, a recombinant plasmid carrying the khe gene was created and examined using real-time PCR, ddPCR, and traditional microbial culture techniques. In comparison to real-time PCR, ddPCR demonstrated reduced inhibitory inhibition in the fecal sample. Thus, we developed a ddPCR-based assay technique for K. pneumoniae that is both sensitive and efficient. It might be a helpful technique for detecting K. pneumoniae in feces, and it might be a trustworthy way to find the bacteria that are causing the illness and assist direct treatment choices.This thorough investigation offers important insights into the region's K. pneumoniae epidemiological patterns and antibiotic susceptibility profile. The study's conclusions emphasize how urgently antimicrobial stewardship initiatives are needed to address the growing problem of antibiotic resistance. Healthcare providers can choose the right medications and enhance patient outcomes by having a better understanding of the K. pneumoniae resistance landscape. These statistics can help physicians make informed decisions about antibiotic treatment and aid in the creation of regional antibiotic policies.

Keyword: Klebsiella pneumonia, K. pneumoniae hemolysin, digital PCR, extended-spectrum β-lactamase, Solid-surface-grown K. pneumoniae, hypervirulence, hypermucoviscosity.

Introduction. When body resistance is decreased, *Klebsiella pneumoniae* (*K. pneumoniae*), a significant opportunistic pathogen, can easily cause pneumonia and pleural effusion. However, the positive detection rate of *K. pneumoniae* from clinical pleural effusion using conventional methods, such as bacterial culture,

is low; therefore, new detection techniques are desperately needed to increase the positive detection rate of *K. pneumoniae* and other bacteria in pleural effusion.In patients connected to medical devices including artificial implants, endotracheal tubes, and catheters, *K. pneumoniae* is a clinically significant nosocomial pathogen that has the ability to produce biofilms both *in vitro* and *in vivo*. Solid-surface-grown *K. pneumoniae* biofilms encourage cell adhesion, microcolony formation, maturity, and ultimately, dispersal as free-living cells. Fimbriae (type 3) and capsular polysaccharides are essential for the formation of biofilm formations. While capsular polysaccharides affect cell-to-cell communication and the formation of the biofilm, fimbriae preserve persistent adhesion. Drug resistance is a result of *K. pneumoniae's* biofilm formation, which shields it from antibiotic penetration and the host immune response [1-5]. Human septicemia, bloodstream infections, pneumonia, and urinary tract infections can all be brought on by the capsulated Gram-negative bacterium *Klebsiella pneumoniae*. *K. pneumoniae*, which is second only to *Escherichia coli* as a major opportunistic pathogen, has recently acquired attention. In order to become hypervirulent, *K. pneumoniae* might acquire genetic characteristics. Furthermore, *K. pneumoniae* has a high level of antibiotic resistance due to its high output of carbapenems and extended-spectrum β-lactamase. The World Health Organization classified it as a "critical threat" bacterium in 2017. In addition to being widely dispersed on human mucosal surfaces, such as those of the nasopharynx, respiratory tract, and gastrointestinal tract, *K. pneumoniae* can also be found in external environments, such as soil and surface waters [6-11]. A recombinase-aided amplification (RAA) assay was recently used to detect *K. pneumoniae* in milk samples by adding an expensive enzyme mixture. Loop-mediated isothermal amplification (LAMP)-based *K. pneumoniae* assays were developed by selecting sophisticated four- to six-oligonucleotide primers to amplify eight distinct regions. Therefore, given that complex primer design and expensive recombinase might lead to inefficient application, an effective, straightforward, and on-site detection assay of *K. pneumoniae* in clinical settings is required for direct and accurate treatment [12,13,14,15]. The use of third-generation cephalosporins, such as ceftriaxone, cefotaxime, and ceftazidime, has been limited for the treatment of *K. pneumoniae* infections because effective control measures against the rapid dissemination of drug resistance depend on a thorough understanding of the antimicrobial susceptibility patterns of *Klebsiella*, which can vary across different geographic settings. These bacteria, known as *K. pneumoniae carbapenemases* (KPCs), are highly resistant to carbapenems, aminoglycosides, cephalosporins, and fluoroquinolones, but typically retain susceptibility to colistin, making a combination of three different antibiotics necessary for effective treatment. Unfortunately, the indiscriminate use of colistin has resulted in several cases of *K. pneumoniae* resistance [16-24]. Although it takes a long time and has poor specificity, the conventional bacterial culture approach was once extensively used as the gold standard for identifying *K. pneumoniae*. PCR demonstrated better sensitivity, specificity, and timeliness than microbial culture. Real-time PCR is a quick and commercially available molecular diagnostic technique used to identify a variety of microorganisms, including *K. pneumoniae*. However, its clinical applicability is limited by its low sensitivity and reproducibility, and its accuracy is largely dependent on a standard curve of known concentrations [25,26,27,28].

The main purpose of the presented analytical work is to conduct a brief review of the literature on the relevance of early detection of klebsiella, methods of microbiological detection and diagnosis.

Circumstance at a look. In early 2024, the Worldwide Antimicrobial Resistance and Observation Framework on Developing Antimicrobial Resistance Announcing (GLASS-EAR) issued a ask for data to survey the current worldwide circumstance given the expanded distinguishing proof of separates of hypervirulent *Klebsiella pneumoniae* (hvKp) grouping sort (ST) 23 carrying safe qualities to the carbapenem anti-microbials a carbapenemase qualities. *K. pneumoniae* strains that can cause serious diseases in solid people and have been distinguished with expanding recurrence in later a long time are considered hypervirulent compared to classical strains since of their capacity to contaminate both healthy and immunocompromised people as a result of their expanded propensity to create intrusive infections.The

nearness of hvKp ST23 was detailed in at slightest one nation in all six WHO Districts [11,12,13,14,19]. The rise of these confines with resistance to last-line anti-microbials like carbapenems requires the organization of elective antimicrobial treatment, which may not be accessible in numerous settings. WHO prescribes that Part States continuously increment their research facility demonstrative capacity to permit for the early and solid recognizable proof of hvKp, as well as fortify research facility capacities in atomic testing, location, and investigations of pertinent destructiveness qualities in expansion to resistance qualities. The appraisal of chance at the worldwide level is direct given the challenges with observation, need of information on research facility testing rates, track and scale of community transmission, the crevice within the accessible information on contaminations, hospitalization, and the generally burden of the infection [21,24,25,26,28].

Depiction of the circumstance. In early 2024, the Worldwide Antimicrobial Resistance and Observation Framework on Developing Antimicrobial Resistance Announcing (GLASS-EAR) issued a ask for data to the Worldwide Antimicrobial Resistance and Reconnaissance Framework (GLASS) Antimicrobial Resistance (AMR) National Central focuses enlisted in GLASS-AMR. The point was to quickly evaluate the current worldwide circumstance given the expanded distinguishing proof of segregates of hypervirulent *Klebsiella pneumoniae* (hvKp) arrangement sort (ST) 23 carrying safe qualities to the carbapenem anti-microbials a carbapenemase qualities a detailed in a few nations. The archived maintained transmission of this ancestry has been watched over a few a long time and the qualities related with the antimicrobial resistance were identified in hvKp strains in later a long time in numerous nations [12,13,14,15]. A add up to of 43 out of 124 nations, regions, and regions over the six WHO Districts given reactions: Africa (10); Europe (10); East Mediterranean (10); Western Pacific (6); America (4); South-East Asia (3). From these, a add up to of 16 nations and domains (Algeria, Argentina, Australia, Canada, Cambodia, Hong Kong Extraordinary Regulatory Locale (China), India, Iran, Japan, Oman, Papua Unused Guinea, Philippines, Switzerland, Thailand, the Joined together Kingdom of Awesome Britain and Northern Ireland (the Joined together Kingdom), and the Joined together States of America) detailed the nearness of hvKp and 12 detailed particularly the nearness of the strain ST23-K1 (Algeria, Argentina, Australia, Canada, India, Iran, Japan, Oman, Philippines, Switzerland, Thailand and the Joined together Kingdom) [31,32,33,34]. The data and information on the instruments that improve the capacity of the microscopic organisms to cause the malady are still inadequate. More inquire about is required to create demonstrative instruments that are accessible in nations with restricted research facility capacity, permitting fast recognizable proof of diseases caused by hvKp strains. There's a ought to find unused helpful options pointed not as it were at the treatment of multi-resistant contaminations, but moreover at diseases caused by hypervirulent variations [15,16,17,18,19].

Development of *Klebsiella pneumonia* detection using PCR-LbCas12a. Researchers used blast to search the most pertinent gene as a target for nucleic acid detection in order to identify a viable target. Since 5.2 M is the full genomic DNA size for *K. pneumonia*, we extracted the 14,288 genomic sequences that we downloaded from NCBI. Consequently, 2,024 sequences were preserved for additional examination. They are therefore appropriate targets for the detection of nucleic acids [29-35]. Authors created five 36-nt long crRNAs with 17 nt unique sequences and 19 nt shared standard nucleotides to base-pair various K. pneumoniae DNA targets, taking into account the TTTV PAM sequences needed for LbCas12a targeting. The targets of K.P.-crRNA-1,2, K.P.-crRNA-3,4, and K.P.-crRNA-5 are 16S RNA, YP_005224572.1, and IF-2, respectively. These five crRNA targets were identified independently in 98.86% (2001/2024), 98.67% (1997/2024), 95.90% (1941/2024), 98.81% (2000/2024), and 99.90% (2022/2024) of the genomes of K. pneumonia that we screened [45-50].

In *Klebsiella pneumonia*, PCR-LbCas12a exhibits both sensitivity and specificity. PCR, qPCR, and PCR-LbCas12a procedures were tested on serially diluted standard DNA samples in order to determine the

smallest quantity of DNA sample needed for nucleic acid detection. As few as 10 copies of the target DNA were detected by basic PCR. The LbCas12a system with qPCR, on the other hand, can show a signal in 40 minutes when the copy number is as low as one copy. The authors then used PCR-LbCas12a detection in 10 frequently encountered pathogens in the laboratory department, including *Escherichia coli (E. coli), Staphylococcus aureus (S. aureus), Shigella dysenteriae, Salmonella enterica, Pseudomonas aeruginosa, Proteus mirabilis, Stenotrophomonas maltophilia, Acinetobacter baumannii, Corynebacterium striatum,* and *Candida albicans* (fungi), in order to verify whether the detection system's specificity only targets *K. pneumoniae* [38-44].

Discussion. Through the use of molecular confirmation assays and string testing, the epidemiology of hvKp in clinical routine diagnostics was examined. In order to evaluate a fast and accurate technique for detecting potential hvKp among mucoid isolates, comparisons of string testing on common commercial solid media under various growth conditions were conducted. Additionally, the study sought to use phenotypic and WGS analyses to describe potential hvKp isolates. *K. pneumoniae* can cause different maladies and effectively creates resistance to most antibacterial drugs. Hence, curing *K. pneumoniae*-caused diseases is getting to be progressively troublesome. Early location is in this way basic for convenient clinical conclusion and successful treatment. The routine location strategy, bacterial culture, is moderate and has moo discovery affectability for *K. pneumoniae*. Improvement of atomic demonstrative strategies has considerably improved the proficiency of pathogen location. Real-time PCR is utilized as a day by day demonstrative instrument to check for pathogens due to its great affectability and specificity. Be that as it may, there are a few restrictions to its utilize; when the concentration of the test being tried is exceptionally moo, real-time PCR may appear destitute exactness [1-7]. Furthermore, a standard bend is required for the measurement of *K. pneumoniae* in each real-time try, coming about in a more complex and time-consuming test prepare. Moreover, the choice of reference guidelines plays a conclusive part in real-time PCR comes about; an improper reference standard may influence their exactness, and thus the precision of conclusion. Through the use of molecular confirmation assays and string testing, the epidemiology of hvKp in clinical routine diagnostics was examined. In order to evaluate a fast and accurate technique for detecting potential hvKp among mucoid isolates, comparisons of string testing on common commercial solid media under various growth conditions were conducted. Additionally, the study sought to use phenotypic and WGS analyses to describe potential hvKp isolates [8-14]. Since K. pneumoniae frequently colonizes the intestinal tract, the amount of the bacteria in feces somewhat mirrors the conditions in the gut. We measured the K. pneumoniae bacterial burden in fecal samples for the first time. Using microbial culture, real-time PCR, and ddPCR techniques, 103 fecal samples were obtained and examined in order to assess the application of ddPCR detection to fecal samples from the clinic. Compared to fecal culture and real-time PCR, ddPCR had a greater positive detection rate. Additionally, correlation analysis revealed a strong relationship between the K. pneumoniae detection outcomes from ddPCR and real-time PCR. ddPCR was found to be less affected by residual matrix in fecal samples, whereas the presence of residual matrix in fecal extract can significantly reduce the amplification effectiveness in PCR, potentially leading to a false-negative result or an underestimation of the pathogen titer in clinical samples [15,16,21,24, 27]. The closed dumbbell-mediated isothermal amplification (CDA) test is a revolutionary nucleic acid detection tool that was developed to address the shortcomings of PCR and LAMP techniques. Because the CDA assay didn't require a lengthy primer sequence, a costly recombinase, or a heat cycler, it was easier to use than other molecular diagnostic technologies. The development of the CDA test necessitated a short and straightforward primer design in order to achieve a cost-effective reaction as compared to other isothermal amplification technologies. In this work, we effectively developed and assessed on-site visual-based molecular diagnostics of K. pneumoniae utilizing the CDA approach, as well as real-time fluorescence [28, 29, 30, 31,33].

Conclusion. It is still challenging to link hypervirulence, hypermucoviscosity, and string-test positive. Depending on the culture settings, we saw some significant changes in the string-test findings. According to our findings, hypervirulence genes under anaerobe development on MH-agar are correlated with longer string length. We also advise emphasizing on string-length measurement, incorporating culture parameters, and abandoning the binary definition of string-test positive or negative with the declared threshold of 5 mm. These results need to be examined and assessed further. In conclusion, we support routine diagnostics that include a prospective screening for hypervirulence features in *K. pneumoniae*, particularly when isolated from respiratory materials and blood cultures.

The disk diffusion antibiotic susceptibility test is the most widely utilized detection technique. But the accuracy and sensitivity are only roughly 65% and 56%, respectively. Additionally, it takes more time to identify particular antibiotic information because two rounds of testing are needed. In contrast, the stability and precision of nucleic acid detection are better. Using its antibiotic-resistant gene, qPCR distinguishes *K. pneumonia* from bacteria such as *E. coli* and *S. aureus* with high specificity and accuracy. But qPCR requires specialized personnel and costly equipment.

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