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Report

A retrospective analysis of pyogenic liver abscess and antibiotic resistivity of common pathogens in Peshawar

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ABSTRACT

Background: Pyogenic liver abscess (PLA) is a rare but life-threatening disease, with a frequency ranging from 10.83 to 17.45 per 100,000 persons. The major cause of PLA is bacterial infection of liver parenchyma. The present research study was designed to investigate the common microbes causing PLA in Peshawar (Pakistan) and to evaluate a variety of the most capable and efficient antibiotics for treatment of PLA. **Methods:** A 7-year (2012 – 2018) retrospective demographic study of medical records of all PLA patients (n = 379) admitted to the Hayatabad Medical Complex (HMC) and Khyber Teaching Hospital (KTH) was initially performed. The demographic study was followed by biochemical tests and antibiotic resistivity tests of microorganisms, isolated from available samples and selected from literature using web services. **Results & Conclusion:** The demographic data revealed that 70% of the PLA patients were under the age of 50, with male predominance (male to female ratio of 3:1). It was concluded that *K. pneumonia*, poly-microbes (*K. pneumonia* and *Citrobacter*), and *E. coli* are the most common microbes involved in causing PLA in the population of Peshawar. *E. coli*, *Citrobacter* and *K. pneumonia* were sensitive to Cefixime and Ciprofloxacin (100% sensitivity rate), but showed significant resistance against Amoxycillin, Oxacillin and Fusidic Acid. It is, therefore, prudent to practice susceptibility-directed antibiotic therapy.

Key words: Pyogenic liver abscess (PLA), E.coli, K pneumonia, Citrobacter, Antibiotic resistance

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BACKGROUND

Liver is the most vital metabolic core and the largest organ of the human body. Hepatocytes are the main functional unit of the liver and perform many crucial roles which include bile production, lipid metabolism and protein synthesis [1]. Pyogenic liver abscess (PLA) is a rare but potentially serious hepatic disease with pathophysiological characteristics that fluctuate over time. The morbidity of PLA patients is significantly amplified in Asia, where the yearly occurrence has gradually increased from 10.83 to 17.45 per 100,000 persons, with a mortality rate of 3 - 19% [2,3]. According to recent reports, PLA has become an emerging public health problem worldwide, even affecting the European and American populations [4–11]. The diagnosis and therapeutic strategies of PLA are medical challenges due to the wide (non-specific) and numerous symptoms, which include fever, nausea, vomiting, abdominal pain and asthenia [12,13]. The pathogenic spectra of hepatic abscess may vary across different regions and areas. For successful treatment of PLA patients, it is necessary to understand the entire etiology. The common microbes responsible for causing hepatic abscess are *K. pneumonia*, *E. coli*, *Citrobacter*, *Staphylococcus aureus*, *Proteus*, and anaerobic organisms [12,14–17]. PLA diagnosis has increased due to advances in medical science, including ultrasonography and computed tomography scans [18]. Since the use of antibiotics, including irrelevant ones, was first initiated in clinical medicine, antibiotic-resistant bacteria strains have gradually developed over time [19].

The purpose of the present study was to inspect the pathogenic and clinical features of PLA in Peshawar. A retrospective demographic study was conducted on medical records for all PLA patients (n = 379) admitted to the Hayatabad Medical Complex (HMC) and Khyber Teaching Hospital (KTH) during 2012 - 2018 (7-year review). The aim was to investigate the common pathogens and discern the clinical features and microbiological characteristics of PLA more broadly, as well as to identify the most suitable antibiotics for the prevention and treatment of PLA.

METHODS

Initially, a retrospective study was conducted on PLA patients admitted to the Hayatabad Medical Complex (HMC) and Khyber Teaching Hospital (KTH) in Peshawar, Pakistan, during a 7-year period (January 2012 – December 2018). The study also evaluated the microbiological and clinical attributions of hepatic abscess. The medical and microbiological records

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of all the PLA patients who were hospitalized and treated at the KTH and HMC were retrospectively reviewed. Demographic data and medical information were also retrospectively collected. Patients with the typical clinical symptoms of liver abscess, imaging evidence, laboratory examination samples (blood or pus), and/or surgical findings were included in the present study. Patients with incomplete medical treatment data were not included in the present study.

All the samples, including blood and pus, were processed for bacterial culture in the Department of Microbiology at Khyber Medical University (KMU); our research collaborators were from the Department of Microbiology, College of Life Sciences, Wuhan University, China. To identify the bacterial isolates, VITEK 2 Compact (bioMérieux, Marcy l'Etoile, France) was used. The pathogens causing PLA, as discussed in previous literature, were also exposed to antibiotic sensitivity testing. The antibiotic susceptibility testing was performed by agar disk diffusion method using antibiotic disks. The antibiotics used for susceptibility test included: Amoxycillin, Cefotaxime, Cefixime, Oxacillin, Marinum, Norfloxacin, Ciprofloxacin, Enoxacin, Gentamicin, Amikacin, Clindamycin, Erythrocin and Fusidic Acid.

RESULTS

Demographic data

For demographic data of PLA patients, the database of the KTH and HMC was accessed. Initially, the database showed 431 PLA patients, among which 52 patients were eliminated due to lack of data, and results of pus and blood culture. The demographic data of patients is shown in **Table 1**. An early recognition and appropriate treatment strategy of PLA patients is required due to its severe complications [12,20]. Underlying diseases, such as diabetes and other biliary system complications, can play a key role in the development and progression of PLA. To diagnose PLA, ultrasonography and other imaging assessments are useful, while microbiological techniques are essential to identify the key pathogens and understand the etiology of the disease prior to any therapeutic procedure [17,20,21].

The present findings are in correlation with previous studies which reported on the male predominance in PLA [3,15,22–24]. Indeed, in our review, it was noted that 70% of the PLA patients were under the age of 50 years. The predominant sex was males (n = 264, 69.66%), with the mean age of 47.7 ± 10.4 years. The most effective treatment of hepatic abscess is likely percutaneous drainage and supplement of a broad spectrum of antibiotics [7,12].

The common microbes causing PLA are *Bacteroides, E. coli, Citrobacter, K. pneumoniae, Enterococci, Streptococci,* and *Staphylococci* [12,14,15,25]. It can be observed from previous reports that during the past few decades, *K. pneumonia* has surpassed *E coli* in becoming the leading cause of PLA [12,26–29]. Similar results were also observed in our current study; *K. pneumoniae* and *E. coli* were the most ubiquitous pathogens involve in causing PLA, affecting 143 and 63 patients, respectively. However, *Citrobacter*, in the presence of *K. pneumoniae* (*i.e. Citrobacter* + *K. pneumonia*) also infected many patients with PLA (n = 98). In a few patients, other pathogens were also detected, such as *Marginella* + *E. Coli* (n = 24), and *Pseudomonas* + *E. Coli* (n = 18) (**Figure 1**). Among the microbes detected in PLA patients, *Staphylococcus aureus* was the only gram-positive bacteria, as seen by the arrangement of cocci in cluster form (**Table 2**).

Biochemical tests and antibiotic resistivity

The biochemical tests on microbes revealed that the E. *coli*, *E. aerogenes*, *Staphylococcus aureus*, *K. pneumoniae* and *Citrobacter* are lactose fermenters by chemical nature. The indole test is usually used to determine the aptitude of an organism to split amino acid tryptophan to form indole compound. Results are shown by either a red or yellow color appearing on the surface layer of the broth. E. *coli*, *Marginella* and *Citrobacter* were found to be positive by indole test, while the rest of the microbes were found to be negative. The methyl red test showed that *Pseudomonas*, *Enterobacter*, *Staphylococcus aureus* and *K. pneumoniae* were negative for methyl red, as shown in the color change from orange to yellow, while *Marginella* and *Citrobacter* were positive for methyl red, as shown by the red color (**Table 3**).

The oxidase test is used to verify the potential of the bacteria to produce cytochrome c oxidases. The fluctuation in color from violet to purple indicates a positive test, while production of a light-pink or no color indicates a negative test. Among the microbes subjected to the oxidase test, only *Pseudomonas* and *K. pneumoniae* were oxidase-positive. The Voges-Proskauer (VP) test was conducted to investigate the bacterial broth culture for acetoin production. Among the microbes, only *E.coli*, *E. aerogenes* and *K. pneumoniae* have the ability to produce acetoin (**Table 3**).

K. pneumonia can easily penetrate into the liver through portal circulation, direct spreading or cross

Table 1: Details of PLA patients admitted for treatment in KTH and HMC, Peshawar

Age in years	No of cases	Males	Females	Male (%)	Female (%)
1 to 10	13	10	3	76.92	20.08
11 to 20	37	21	16	56.75	43.25
21 to 30	67	46	21	68.65	31.35
31 to 40	74	56	18	75.67	24.33
41 to 50	89	68	21	76.40	23.60
51 to 60	32	20	12	62.50	37.50
60 to 70	37	22	15	59.46	40.54
70 to 80	27	19	8	70.37	29.63
85 to 90	3	2	1	66.67	33.33
Total	379	264	115	69.66	30.34

Table 2: Morphological characteristics of microbes causing PLA

Name of micro-organism	Arrangement	Shape	Gram reaction	Motility	Aerobic/anaerobic
E. Coli	Scattered	Rod	Gram Negative	Motile	Anaerobic
K. pneumoniae	Scattered	Rod	Gram Negative	Non-Motile	Facultative anaerobic
Staphylococcus aureus	Clusters	Cocci	Gram Positive	Non-Motile	Facultative anaerobic
E. aerogenus	Single	Bacillus	Gram Negative	Motile	Facultative anaerobes
Marginella	Single	Rod	Gram Negative	Motile	Facultative anaerobes
Citrobacter	Clusters	Bacillus	Gram Negative	Motile	Aerobic
Pseudomonas	Single	Bacillus	Gram Negative	Motile	Aerobic

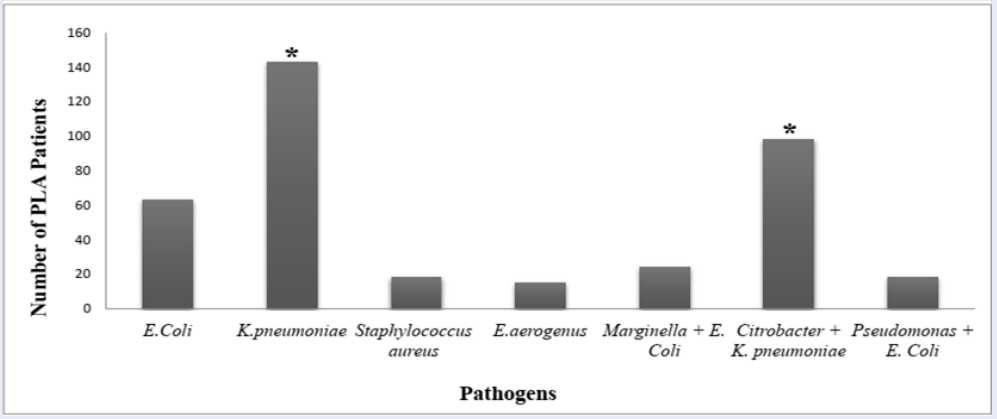

Figure 1: The number of PLA patients infected by various types of pathogens.

Table 3: Biochemical tests on microbes causing PLA

Name of microbes	Chemical nature	Motility test	Catalase test	Indole test	Methyl red test	Oxidase test	Vogas-Prosakuer test
E. coli	Lactose fermenter	Motile	Positive	Positive	Not done	Negative	Positive
Pseudomona	Doesnot ferment lactose	non-Motile	Positive	Negative	Negative	Positive	Negative
E. aerogenus	Lactose fermenter	non-Motile	Positive	Negative	Negative	Negative	Positive
Staphlococcu aureus	Lactose fermenter	Motile	Positive	Negative	Negative	Negative	Negative
Marginella	Doesnot ferment lactose	Motile	Positive	Positive	Positive	Negative	Negative
K. pneumoniae	Lactose fermenter	Motile	Positive	Negative	Negative	Positive	Positive
Citrobacter	Lactose fermenter	Motile	Not done	Positive	Positive	Negative	Negative

the intestinal barrier to cause *K. pneumonia*-induced hepatic abscess [12,24,30,31]. Patients should be regularly monitored in order to identify and treat *K. pneumonia*-induced PLA in a timely manner. Pathogens isolated from PLA patients are highly sensitive to almost every kind of antibiotic, such as β-lactamases, third generation cephalosporins and carbapenems [7,28,32]. The use of amoxicillin or ampicillin may predispose patients to develop *K. pneumonia*-induced PLA. It has been clinically confirmed that ampicillin or amoxicillin therapy is correlated with *K. pneumonia*-induced PLA risk [22,33,34]. In a recent animal study, when *K. pneumonia*-colonized mice were treated with oral ampicillin, *K. pneumonia* was found to be resistant to ampicillin and induced KP-PLA in the mice; moreover, ampicillin disrupted the intestinal microflora of the mice [33]. According to the antibiotic susceptibility tests in the present study, the microbes showed a significant rate of resistance against Amoxycillin, Oxacillin and Fusidic Acid. Since the microbes can build resistance to the antibiotics, it is essential before any sort treatment is initiated, to examine the patient's blood or pus samples in order to accurately identify the key pathogen(s) involved in causing PLA. β-lactams are broad spectrum antibiotics which include penicillin derivatives, carbapenems and monobactams. These antibiotics inhibit bacterial growth and progression by inhibiting cell wall synthesis of the target bacteria. Among the β-lactam antibiotics applied, Cefixime was found to be the most efficient antibiotic. *E. coli, K. pneumoniae, Citrobacter* and *E. aerogenes* were 100% sensitive to Cefixime, followed by Cefotaxime (70%, 58.3%, 67.8% and 52% susceptibility rate, respectively) (**Table 4**).

Quinolones are a vital group of antibiotics that are responsible for inhibiting DNA synthesis by limiting DNA gyrase activity. Among the quinolones antibiotics used, Ciprofloxacin exhibited the greatest harmful effects on the various bacteria. Indeed, *E. coli, E. aerogenes, K. pneumoniae* and *Citrobacter* were 100% sensitive when exposed to Ciprofloxacin (**Table 5**).

Besides β-lactam and quinolone antibiotics, there are many different antibiotics that are responsible for inhibiting protein synthesis by interacting with the bacterial 70S ribosome. Among the protein-inhibiting antibiotics used, Erythrocin and Gentamicin significantly limited bacterial progression by inhibiting protein synthesis. *E. coli, K. pneumoniae* and *Citrobacter* were noted as being susceptible to Erythrocin (78%, 82.7% and 100% susceptibility rate, respectively) (**Table 6**).

CONCLUSION & FUTURE PERSPECTIVES

In conclusion, hepatic abscess is a hazardous health problem common in Asia and rapidly spreading around the world, and one that requires immediate hospitalization. *K. pneumonia* and *E. coli* are the leading microbes causing PLA with male predominance.

Table 4: Susceptibility test of PLA causing microbes against β-Lactam antibiotics (inhibit cell wall synthesis)

Name of microbes	Amoxycillin	Cofoxitin	Cefotaxime	Cefixime	Oxacillin	Maronum
E. coli	0	0	70	100	0	17.1
Pseudomonas	10	0	27.4	80	22.1	0
E. aerogenus	0	0	52	100	0	0
Staphylococcus aureus	8.33	3.84	11	58.3	3.84	0
Marginella	20	0	19.4	60	2.31	0
K. pneumoniae	0	47.4	58.3	100	3.84	11.3
Citrobacter	9.63	0	67.8	100	0	10.1

Table 5: Susceptibility test of PLA causing microbes against Quinolones antibiotics (inhibit DNA synthesis)

Name of microbes	Norfloxacin	Ciprofloxacin	Enoxacin
E. coli	16.66	100	0
Pseudomonas	0	40	0
E. aerogenus	100	100	0
Staphylococcus aureus	16.6	50	0
Marginella	0	40	60
K. pneumoniae	41.6	100	19.3
Citrobacter	34	100	0

Table 6: Susceptibility test of PLA causing microbes against protein synthesis inhibiting antibiotics

Name of microbes	Gentamycin	Amikicin	Clindamycin	Erythrocin	Fusidic acid
E. coli	51.2	50	33.2	78	0
Pseudomonas	40	10	17.2	30	0
E. aerogenus	100	0	20	55.3	12
Staphylococcus aureus	33.3	0	76.9	58	0
Marginella	20	53.7	20.4	43	0
K. pneumoniae	71.1	33.8	35.6	82.7	19.4
Citrobacter	50	0	25	100	0

In the present study, a clear profile of the antibiotics with potential against the pathogenic microbes is indicated. Analysis of the microbes demonstrate that they are significantly resistant against Amoxycillin, Oxacillin and Fusidic Acid. As the microbes advance and develop greater resistance to drugs, it is crucial to perform prompt identification of the disease-inducing pathogens, followed by empiric antimicrobial and other effective therapeutic strategies.

A population-based or large-scale study is required to clarify the association between genotypes, resistance spectrum, phenotypes and clones of microbes isolated from patients with PLA. Further studies should be conducted to better understand *K. pneumonia*-induced PLA and increase awareness, and to develop and deliver more effective treatments for PLA patients.

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AUTHOR'S CONTRIBUTION

All the authors equally contributed in the study concept and design, laboratory procedures, data and statistical analysis, initial draft preparation and the revision of the manuscript.

DATA AVAILABILITY

The manuscript contains all the analyzed data and make material.

ETHICAL APPROVAL AND CONSENT

The Bio-ethics committee of Khyber medical university approved all the study and procedure, while the data of patients accessed was unspecified therefore the ethics committee of both the hospitals approved the retrospective analysis.

CONFLICT OF INTEREST

All the authors declared that they have no conflict of interest.

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