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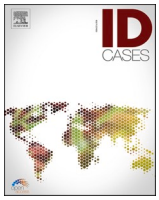

Case report

A unique case of hypervirulent *Klebsiella pneumoniae* acute cholecystitis complicated by portal vein thrombophlebitis: A case report and literature review

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ABSTRACT

Hypervirulent *Klebsiella pneumoniae* remains a significant global public health concern, characterized by a unique syndrome involving monomicrobial primary pyogenic liver abscesses, often leading to metastatic complications such as endophthalmitis, meningitis, and other infections. These infections are frequently observed in immunocompetent hosts or diabetic patients, particularly those of Asian ethnicity. In this report, we present the case of a 66-year-old Burmese female, currently residing in the United States, who presented with severe swelling, pain, discharge, and vision loss in her left eye, along with abdominal pain. Subsequent investigation revealed monomicrobial *Klebsiella pneumoniae* acute cholecystitis with an adjacent liver abscess, complicated by bacteremia, endogenous endophthalmitis, and portal vein thrombosis. Treatment with ceftriaxone proved successful in addressing her intra-abdominal infections, while anticoagulation therapy was initiated following multidisciplinary discussions among all involved subspecialties. Early diagnosis and the timely administration of appropriate treatment are crucial in reducing mortality and preventing further complications.

Introduction

Hypervirulent *Klebsiella pneumoniae* (hvKp) is a distinct and concerning subset of *Klebsiella pneumoniae* strains within bacterial epidemiology, characterized by its heightened virulence. Unlike classical *K. pneumoniae* (cKp), hvKp infections often result in severe, community-acquired illnesses even in individuals without underlying health conditions [1,2].

Since its initial documentation in the 1980s, the prevalence of hvKp has shown a concerning upward trend, particularly in regions such as Taiwan, Hong Kong, South Korea, and Singapore [1]. Notably, hvKp has emerged as the primary cause of pyogenic liver abscesses, posing significant challenges to public health systems. Despite its initial identification in the Asian Pacific rim, hvKp has demonstrated a remarkable ability to disseminate and establish itself globally.

Septic thrombophlebitis of the portal veins, known as pylephlebitis, represents a rare yet serious complication of hvKp infection. Although its true incidence remains unknown due to its rarity, its potential to contribute to increased morbidity and mortality underscores its significance [12,13]. The optimal management of pylephlebitis remains elusive, with the role of anticoagulation therapy remaining a subject of debate, highlighting the need for personalized treatment approaches [13,14].

In this paper, we present a case study involving an elderly Burmese patient who migrated to the United States. Notably, the patient had a history of diabetes mellitus and presented with invasive disease, including acute cholecystitis, liver abscess, endogenous endophthalmitis, and an uncommon manifestation of acute portal vein thrombosis attributed to hvKp.

Through this case, we aim to highlight the clinical challenges posed by hvKp infections and underscore the importance of tailored therapeutic strategies in managing such complex cases.

Case presentation

Our patient is a 66-year-old female with a significant medical history of diabetes mellitus, evidenced by a hemoglobin A1C (HbA1C) level of 7.9%. She presented to the emergency department reporting loss of vision, pain, and discharge from her left eye, which commenced five days prior to admission. Originally from Myanmar, she flew to the US in

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2021 to stay with her sister.

Ten days before admission, the patient experienced epigastric abdominal pain described as non-radiating and sharp. Initially attributing it to acid reflux, she self-treated with omeprazole for two days, resulting in the resolution of the abdominal pain. Subsequently, she developed fevers, chills, nausea, and vomiting lasting three days. She then noticed left orbital swelling accompanied by pain, loss of vision, lacrimation, and eventual purulent discharge.

The patient denied any history of previous eye issues, ocular surgery, or trauma. Prior to presenting to the emergency department, she sought care from an optometrist who prescribed oral ciprofloxacin, which failed to alleviate her visual symptoms. Due to concerns about acute panophthalmitis, she was referred to our emergency department for further management.

In the emergency department, the patient was afebrile and hemodynamically stable. Upon physical examination, notable findings included a proptosed left eye with complete ptosis. Restriction of extraocular muscle movement was observed. Additionally, the patient exhibited chemosis, purulent discharge, and diminished visual acuity in the left eye (Fig. 1). Examination of the right eye revealed no abnormalities.

Initial laboratory findings are described in Table 1. Inflammatory markers were elevated with CRP (C-reactive protein) 293 mg/L and ESR (erythrocyte Sedimentation ratio) 101. The rest of the laboratory findings were unremarkable.

A computed tomography (CT) scan of the orbit was conducted, revealing pre- and post-septal cellulitis affecting the left orbit, accompanied by panophthalmitis and thickening of the retrobulbar optic disc. Subsequently, a more extensive CT scan was performed, which did not reveal evidence of metastatic infection in the neck, brain, or chest.

Furthermore, magnetic resonance imaging (MRI) of the orbits demonstrated severe panophthalmitis localized to the left side, along with optic neuritis. Importantly, there was no evidence of thrombophlebitis in the superior thalamic veins bilaterally or retrograde extension to the cavernous sinus (Fig. 2).

A CT abdomen and pelvis scan was conducted, unveiling a distended gallbladder with circumferential thickening of the wall. Additionally, a hypodense lesion measuring 2.2 × 1.5 cm adjacent to segment 5 of the liver was identified, raising suspicion for an early liver abscess. However, the report noted difficulty in clearly visualizing the portal vein (Fig. 3).

An ultrasound of the right upper quadrant revealed cholelithiasis accompanied by mild gallbladder distention, gallbladder wall thickening, and trace pericholecystic fluid. Importantly, the sonographic Murphy sign was negative, and the portal vein appeared patent on imaging.

The patient received intravitreal ceftazidime and vancomycin. Additionally, intravenous treatment consisting of cefepime, vancomycin, and metronidazole was initiated. On hospital day 2, the patient underwent right CT-guided percutaneous cholecystostomy drain placement, during which 20 mL of purulent fluid was aspirated. Imaging conducted during the drain placement also revealed an enlarged irregular gallbladder wall with small liver abscesses (Fig. 4).

Meanwhile, blood cultures collected upon admission returned positive for *K. pneumoniae*, demonstrating resistance solely to ampicillin. Additionally, cultures obtained from the CT-guided aspiration yielded the same organism with an identical susceptibility profile. Furthermore, cultures from the corneal, conjunctival, and vitreous fluid of the left eye were positive for the same pathogen (Fig. 5).

Repeat blood cultures demonstrated no growth, prompting the de-escalation of the antibiotic regimen to ceftriaxone alone. However, the hospital course was complicated by the need for reinsertion of a larger

Table 1
Initial laboratory findings.

Laboratory parameters	Patient's Values	Reference Range
WBC	**19.4**	4.5–11.0 K/uL
HGB	**10.3**	11.7–15.0 g/dL
HCT	**31.1**	34.0–47.0%
MCV	90.5	79.0–98.0 fL
PLATELETS	342	150–450 K/uL
Differential Results		
NEUTROPHILS	**88.9**	40.0–78.0%
LYMPHOCYTES	**6.2**	15.0–50.0%
MONOCYTES	4.4	2.0–11.0%
EOSINOPHILS	0.3	0.0–5.0%
BASOPHILS	0.2	0.0–1.0%
BUN	**36**	6–23 mg/dL
CREATININE	**1.32**	0.50–1.10 mg/dL
SODIUM	**126**	135–145 mmol/L
POTASSIUM	4.7	3.5–5.2 mmol/L
CHLORIDE	**94**	96–108 mmol/L
GLUCOSE	**125**	60–100 mg/dL
EST GFR	**56**	> 59 mL/min/1.73 m2
ALBUMIN	**1.9**	3.5–5.0 g/dL
BILIRUBIN, TOTAL	0.9	0.1–1.2 mg/dL
ALK PHOS	**323**	38–126 U/L
AST	30	< 36 U/L
ALT	**60**	< 46 U/L
BILIRUBIN, DIRECT	0.7	< 0.9 mg/dL
LIPASE	218	8–78 U/L

WBC: white blood cells, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, BUN: blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, ALK PHOS: Alkaline Phosphatase, EST GFR: Estimated glomerular filtration rate.

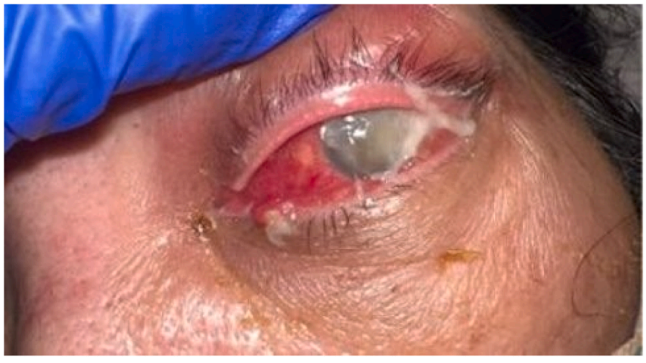

Fig. 1. Left eye proptosis, chemosis and discharge. Hypopyon noted on admission.

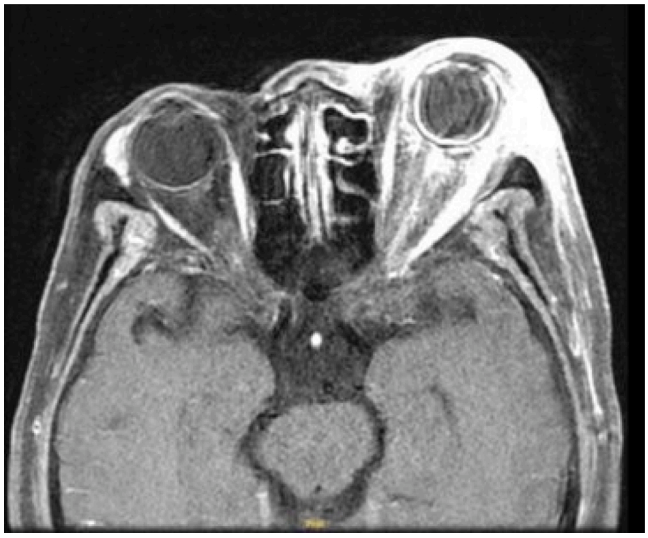

Fig. 2. Magnetic resonance imaging (MRI) of bilateral orbits showing severe left eye panopthalmitis and optic neuritis.

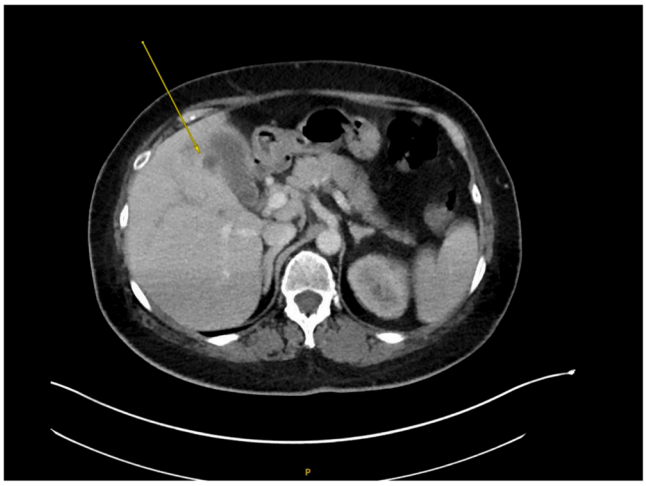

Fig. 3. Computed tomography (CT) of abdomen and pelvis showing distended gallbladder and adjacent 2.2 × 1.5 cm Liver abscess as indicated by the yellow arrow.

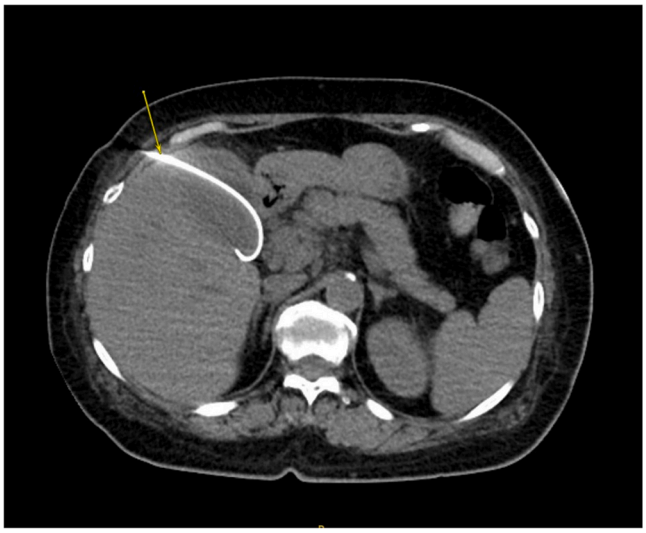

Fig. 4. Computed tomography (CT) guided percutaneous cholecystostomy drain placement as indicated by the yellow arrow.

catheter within the liver abscess, as the original catheter became obstructed. Despite these challenges, the patient exhibited clinical improvement, with resolving leukocytosis to 8.9 K/uL and remained afebrile until hospital day 20 when she developed a fever of 101.3°F accompanied by severe abdominal pain. Subsequent blood cultures obtained as part of the diagnostic workup revealed no growth.

A repeat CT scan of the abdomen was conducted, revealing thromboses in the left portal vein and the anterior segment 5 of the right portal vein. Consequently, the patient commenced anticoagulation therapy with apixaban. Upon discharge, the patient received nine intravitreal doses of ceftazidime. Due to the grim prognosis for the restoration of her vision, a plan was devised for pars plana vitrectomy to be performed in the outpatient setting.

Following discharge, the patient continued to receive at least 4 more weeks of ceftriaxone in the outpatient setting. The percutaneous drain from the liver abscess was removed after two months. A subsequent CT scan of the abdomen, performed after completion of antibiotic therapy and removal of the drain, revealed resolution of the liver abscess and decompression of the gall bladder. However, the thrombus within the portal vein remained unchanged. Upon recommendation from the hematology-oncology team, the patient underwent anticoagulation therapy for at least three months. After two months following drain removal, she underwent an open cholecystectomy, which was followed by an uncomplicated post-operative course. The final pathology report indicated findings consistent with active chronic cholecystitis.

Clinically, the patient is currently recovering well post-surgery and is scheduled for pars plana vitrectomy.

Discussion

We presented a case that displayed several characteristics consistent with hypervirulent *Klebsiella pneumoniae* (hvKp) invasive infection. Firstly, the patient experienced a community-acquired disseminated infection. Secondly, the infection originated as acute cholecystitis, subsequently spreading to the liver, resulting in liver abscess, pylephlebitis, and ultimately, endogenous endophthalmitis [1,2]. Thirdly, the patient did not exhibit evidence of underlying abdominal pathology or biliary disease. Lastly, the fluid aspirated was monomicrobial, which differs from other cases of liver abscesses where the infection is typically polymicrobial. Additionally, the patient, of Asian descent, had a medical history significant for diabetes mellitus, two risk factors commonly associated with hvKp infections.

hvKp was first described in Southeast Asian countries as part of a distinct syndrome involving community-acquired liver abscesses in patients without any history of biliary disease. Although initially linked to specific geographical regions in Asia, hvKp has now been reported worldwide, highlighting its global dissemination [1,3].

While there is no single factor that definitively characterizes hvKp, a combination of phenotypic features and multiple virulence factors act as markers for virulence in this pathogen [4].

Hypermucoviscosity serves as a distinctive feature of hvKp and significantly contributes to its heightened virulence. This characteristic phenotype is commonly evaluated in clinical laboratories using the "string test." During this test, a bacterial colony is stretched with a loop or bacteriological stick, and the length of the resulting mucoid string is measured. A positive string test result indicates hypermucoviscosity, thereby serving as a key diagnostic criterion for identifying hvKp strains.

However, it's important to recognize that not all hypervirulent strains exhibit a positive string test, and classical strains may occasionally demonstrate this phenomenon as well. Furthermore, it's essential to understand that hypermucoviscosity alone does not necessarily lead to invasive disease in immunocompetent individuals [5].

Key virulence factors associated with hvKp include hypermucoviscosity, which aids in evading the host's immune defenses and facilitating colonization. Additionally, hvKp possesses various iron acquisition systems, enabling it to thrive in the iron-rich environment of the host. Moreover, hvKp often harbors genes encoding for a highly efficient capsular polysaccharide (K antigen) that provides protection against phagocytosis. These virulence attributes underscore the formidable pathogenic potential of hvKp and its capacity to cause invasive and life-threatening infections [6].

While diabetes mellitus has been suggested as a significant risk factor in numerous reports, it's worth noting that hvKp infections have been documented across all age groups, irrespective of the presence of diabetes or any other comorbid conditions [7].

Endogenous or septic endophthalmitis, initially described in 1986, represents a rare yet devastating complication and serves as a distinguishing feature from cKp infections [1,8]. This condition tends to manifest as unilateral disease, consistent with our patient's presentation. Clinical indicators such as the presence of hypopyon and poor visual acuity upon presentation are recognized as poor prognostic indicators, both of which were evident in our patient [9].

We hypothesize that the requirement for a larger drainage catheter in our patient was likely attributed to the mucoviscosity of the abscess. Previous reports have documented instances of clogging of percutaneous drainage catheters in similar cases [10]. Therefore, clinicians should

Susceptibility

	Klebsiella pneumoniae MINIMUM INHIBITORY CONCENTRATION	
Amikacin	<=16	Susceptible
Ampicillin	>16	Resistant
Ampicillin-S	<=4	Susceptible
Aztreonam	<=4	Susceptible
Cefazolin-Urine	<=2	Susceptible
Cefepime	<=2	Susceptible
Ceftazidime-Avibactam	<=4	Susceptible
Ceftolozane-Tazobactam	<=2	Susceptible
Ceftriaxone	<=1	Susceptible
Ciprofloxacin	<=0.25	Susceptible
Ertapenem	<=0.5	Susceptible
Gentamicin	<=2	Susceptible
Levofloxacin	<=0.5	Susceptible
Meropenem	<=1	Susceptible
Piperacillin/Tazo	<=8	Susceptible
Tetracyclines	<=4	Susceptible
Tobramycin	<=2	Susceptible
Trimethoprim/Sulfa	<=0.5	Susceptible

Fig. 5. Antibiotic Sensitivity test of blood cultures from admission.

contemplate employing larger bore catheters for the drainage of liver abscesses caused by hvKp to circumvent this complication.

The emergence of portal vein thrombosis stood out as the most distinctive feature in our patient. Pylephlebitis, also known as septic thrombophlebitis of the portal venous system, represents a grave medical condition associated with significant morbidity and mortality risks [11]. Historically, prior to the antibiotic era, appendicitis served as the primary cause of pylephlebitis in the Western world. However, in contemporary times, diverticulitis has supplanted appendicitis as the leading cause. Notably, Klebsiella liver abscesses have emerged as a primary culprit for pylephlebitis, particularly in regions such as Taiwan, where prevalence rates for this invasive syndrome surpass those observed in Western nations [12].

The most frequent site of thrombus occurrence linked to liver abscesses is within the hepatic veins, with the portal venous system being less commonly affected. The primary treatment approach continues to entail drainage of the liver abscess, followed by the prompt administration of appropriate antibiotics. Presently, there exists a lack of definitive data regarding the role of anticoagulation therapy in the management of pylephlebitis. Typically, follow-up imaging scans indicate resolution of the thrombus without specific targeted treatment [12, 13]. However, in urgent cases, anticoagulation therapy may be warranted to prevent complications such as extension of the thrombus into mesenteric vessels, bowel ischemia, hepatic infarction, or even death, as was deemed necessary for our patient to receive anticoagulation [14, 15].

The optimal duration of treatment for pylephlebitis remains a subject of debate, with certain studies advocating for a minimum of three months of therapy for provoked cases [16]. In our patient's case, a regimen of apixaban 5 mg twice daily was prescribed for a duration of three months, in conjunction with concurrent intravenous antibiotics.

hvKp typically exhibits intrinsic resistance to ampicillin; however, it demonstrates surprising sensitivity to the most used antimicrobial agents, which generally results in a favorable outcome [6,17]. In our patient's case, the hvKp strain was sensitive to treatment, leading to a full recovery. Despite this positive outcome, the patient experienced poor visual acuity, limited to light perception only in the left eye.

Antimicrobial susceptibility patterns of hvKp have generally remained consistent since their initial reporting. However, there has been an alarming rise in the prevalence of antibiotic-resistant strains of hvKp in recent years. Furthermore, the virulent genes associated with hvKp have been identified in cKp, leading to the development of hypervirulent strains [17].

This convergence of hypervirulence and multi-drug resistance presents a significant challenge to public health. The resulting phenotype is highly transmissible and poses a grave risk, potentially leading to fatal infections [18]. Addressing this emerging threat requires urgent and comprehensive strategies to mitigate the spread of these resistant and virulent strains.

Conclusion

Diagnosing pylephlebitis can be challenging due to its rarity, necessitating clinicians to maintain a high level of suspicion. Regrettably, this condition is frequently misidentified or left untreated for extended periods, resulting in significant morbidity and mortality. Until recently, the susceptibility pattern of hvKp remained largely unchanged for three decades. However, recent reports of highly drug-resistant *K. pneumoniae* strains acquiring hypervirulent genes raise concerns about the emergence of difficult-to-treat, dangerous, and potentially life-threatening infections.

The string test is an unreliable method for determining the presence of hypervirulent genes, highlighting the importance of utilizing biomarkers to accurately detect hvKp infections. Additionally, precise definitions for hvKp need to be established to differentiate it from cKp. This is crucial for assessing the prevalence of the disease and understanding its clinical impact.

Ethical approval

NA.

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Institutional review board statement

Not applicable.

Consent

Informed consent was obtained from the patient involved in the study.

CRediT authorship contribution statement

Harika Kalangi: Conceptualization, Data curation, Writing – original draft. **Bernard Camins:** Supervision, Writing – review & editing. **Stanley R. Yancovitz:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no competing interests. This manuscript has not been published and is not under consideration for publication elsewhere. Additionally, all authors have approved this paper's contents and agreed to the journal's submission policies.

Data availability

Data is unavailable.

Acknowledgment

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References

[1] Lee CR, Lee JH, Park KS, et al. Antimicrobial resistance of hypervirulent Klebsiella pneumoniae: epidemiology, hypervirulence-associated determinants, and resistance mechanisms. Front Cell Infect Microbiol 2017;21:483. https://doi.org/10.3389/fcimb.2017.00483.

[2] Liu YC, Cheng DL, Lin CL. Klebsiella pneumoniae liver abscess associated with septic endophthalmitis. Arch Intern Med 1986;(146):1913–6. https://doi.org/10.3947/ic.2018.50.3.210.

[3] Saccente M. Klebsiella pneumoniae liver abscess, endophthalmitis, and meningitis in a man with newly recognized diabetes mellitus. Clin Infect Dis 1999;29:1570–1. https://doi.org/10.1086/313539.

[4] Harada S, Doi Y. Hypervirulent Klebsiella pneumoniae: a call for consensus definition and international collaboration. J Clin Microbiol 2018;9:6113475. 10.1128/JCM.00959-18.

[5] Catalán-Nájera JC, Garza-Ramos U, Barrios-Camacho H. Hypervirulence and hypermucoviscosity: two different but complementary Klebsiella spp. phenotypes? Virulence 2017;8:1111–23. https://doi.org/10.1080/21505594.2017.1317412.

[6] Russo TA, Marr CM. Hypervirulent Klebsiella pneumoniae. Clin Microbiol Rev 2019;15:00001–19. https://doi.org/10.1128/CMR.00001-19.

[7] Fang Chi-Tai, Lai Shau-Yan, Yi Wen-Ching, Hsueh Po-Ren, Liu Kao-Lang, Chang Shan-Chwen. Klebsiella pneumoniae genotype K1: an emerging pathogen that causes septic ocular or central nervous system complications from pyogenic liver abscess. Clin Infect Dis 2007;Volume 45(Issue 3):284–93. https://doi.org/10.1086/519262.

[8] Serban D, Popa Cherecheanu A, Dascalu AM, et al. Hypervirulent Klebsiella pneumoniae endogenous endophthalmitis-a global emerging disease. Life 2021;10:676. https://doi.org/10.3390/life11070676.

[9] Chen Yung-Jen, Kuo Hsi-Kung, Wu Pei-Chang, Kuo Min-Lun, Tsai Hsih-Hao, Liu Chi-Chang, Chen Chih-Hsin. A 10-year comparison of endogenous endophthalmitis outcomes: an East Asian experience with klebsiella pneumoniae infection. Retina June. 2004;24(3):383–90.

[10] Tan YM, Chung AY, Chow PK, et al. FACS. An appraisal of surgical and percutaneous drainage for pyogenic liver abscesses larger than 5 cm. Ann Surg March. 2005;241(3):485–90. https://doi.org/10.1097/01.sla.0000154265.14006.47.

[11] Choudhry AJ, Baghdadi YM, Amr MA, et al. Pylephlebitis: a review of 95 cases. J Gastrointest Surg 2016;20:656–61. https://doi.org/10.1007/s11605-015-2875-3.

[12] Wang YF, Chang CC, Lee TC, et al. Recent trend of pylephlebitis in Taiwan: Klebsiella pneumoniae liver abscess as an emerging etiology. Infection; 41: p. 1137–43.

[13] Molton JS, Chee YL, Hennedige TP, Venkatesh SK, Archuleta S. Impact of regional vein thrombosis in patients with Klebsiella pneumoniae liver abscess. PLoS One 2015;7:0140129. https://doi.org/10.1371/journal.pone.0140129.

[14] Baril N, Wren S, Radin R, Ralls P, Stain S. The role of anticoagulation in pylephlebitis. Am J Surg 1996;172:449–52. https://doi.org/10.1016/S0002-9610(96)00220-6.

[15] Duffy FJJr, Millan MT, Schoetz DJJr, Larsen CR. Suppurative pylephlebitis and pylethrombosis: the role of anticoagulation. Am Surg 1995;61:1041–4.

[16] Naymagon L, Tremblay D, Schiano T, Mascarenhas J. The role of anticoagulation in pylephlebitis: a retrospective examination of characteristics and outcomes. J Thromb Thrombolysis 2020;49:325–31. https://doi.org/10.1007/s11239-019-01949-z.

[17] Wu Y, Wu C, Bao D, Jia H, Draz MS, He F, Ruan Z. Global evolution and geographic diversity of hypervirulent carbapenem-resistant Klebsiella pneumoniae. Lancet Infect Dis 2022;22:761–2. https://doi.org/10.1016/S1473-309900275-4.

[18] Gu D, Dong N, Zheng Z, et al. A fatal outbreak of ST11 carbapenem-resistant hypervirulent Klebsiella pneumoniae in a Chinese hospital: a molecular epidemiological study. Lancet Infect Dis 2018;18:37–46. https://doi.org/10.1016/S1473-3099(17)30489-9.