Advances in Clinical Medicine 临床医学进展, 2024, 14(5), 2479-2488
Published Online May 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.1451709

Hans汉斯

高毒力肺炎克雷伯菌侵袭性感染研究进展

张怀东，周　智*

重庆医科大学附属第二医院感染科，重庆

收稿日期：2024年4月29日；录用日期：2024年5月24日；发布日期：2024年5月31日

摘　要

高毒力肺炎克雷伯菌(hypervirulent Klebsiella pneumoniae, hvKP)作为一种侵袭性肺炎克雷伯菌(*Klebsiella pneumoniae*, KP)菌株，目前已在全球范围内广泛传播。该菌株的高毒力使其可生存于免疫功能正常的人群中，且容易引起严重的侵袭性感染，包括化脓性肝脓肿、内源性眼内炎、脑膜炎、坏死性筋膜炎等，许多患者经积极治疗后仍出现不可逆的灾难性残疾，整体预后差。本综述就hvKP引起的各类侵袭性感染的临床表现、感染机制、危险因素、临床诊疗及预后等多方面进行论述，总结经验，为临床提供诊疗思路，以期改善相关患者的预后。

关键词

高毒力肺炎克雷伯菌，侵袭性感染，临床表现

Research Progress on Invasive Infections of *Hypervirulent klebsiella* Pneumoniae

Huaidong Zhang, Zhi Zhou*

Department of Infectious Diseases, Second Affiliated Hospital, Chongqing Medical University, Chongqing

Received: Apr. 29th, 2024; accepted: May 24th, 2024; published: May 31st, 2024

Abstract

The global prevalence of hypervirulent Klebsiella pneumoniae (hvKP), a highly invasive strain of *Klebsiella pneumoniae* (KP), has led to its widespread distribution. The heightened virulence of hvKP enables it to persist in immunocompetent populations, resulting in severe invasive infections such as liver abscess, endogenous endophthalmitis, meningitis, and necrotising fasciitis. Despite aggressive treatment, many patients experience irreversible catastrophic disability, leading to a poor overall prognosis. This review discusses the clinical manifestations, infection mechanisms, risk factors, clinical diagnosis and treatment, and prognosis of various types of invasive infections

文章引用: 张怀东, 周智. 高毒力肺炎克雷伯菌侵袭性感染研究进展[J]. 临床医学进展, 2024, 14(5): 2479-2488.
DOI: 10.12677/acm.2024.1451709

caused by hvKP, summarising the experience and providing ideas for clinical diagnosis and treatment, with a view to improving the prognosis of patients with hvKP.

Keywords

Hypervirulent Klebsiella Pneumoniae, Invasive Infection, Clinical Manifestation

1. hvKP 的流行病学

肺炎克雷伯菌(*Klebsiella pneumoniae*, KP)是一种革兰氏阴性机会致病菌，于 1882 年被首次报道，被归类为肠杆菌科。这类病原体可定殖于人类、动物的胃肠道及口咽部黏膜处，同时在土壤、植被、水、医疗设备中广泛存在[1]。可引起各种类型的感染，如血流感染、化脓性感染、肺部感染、尿路感染、手术部位感染等[2]，死亡率风险较高。既往研究指出，根据其对抗生素的敏感性，KP 感染患者的死亡率在 21%~42%之间[3]。目前，经典肺炎克雷伯菌(cKP)和高毒力肺炎克雷伯菌(hypervirulent Klebsiella pneumoniae, hvKP)是 KP 在全球传播的两种主要病理类型，cKP 通常发生于医疗机构中，免疫功能低下的老年住院患者为主要的易感人群[4]，而 hvKP 的感染通常发生于社区中，覆盖了所有年龄段，包括免疫功能正常或低下的患者[5]。1986 年，台湾地区报道了一例肺炎克雷伯菌肝脓肿(*Klebsiella pneumoniae* Liver abscess, KLA)患者，伴有化脓性脑膜炎、前列腺脓肿、化脓性眼炎等肝外并发症，虽然经过积极的抗菌治疗，但患者最终仍然出现了失明[6]，这引起了当时对一种新的侵袭性菌株的关注，并首次被认为是一种独特的临床病原体，其高毒力性通过动物致死试验、中性粒细胞测定等确定[7] [8] [9]。在过去的三十余年中，世界各地报道越来越多的 hvKP，最开始主要集中于亚太地区，由于人口流动性的增加，hvKP 感染已蔓延到全世界[10]。它能够引起健康人群中的严重侵袭性感染，包括肝脓肿、肺脓肿、脾脓肿、眼内炎、脑膜炎、菌血症、尿路感染等[11] [12] [13]，且可引起多部位的同时感染，临床上称为肺炎克雷伯菌侵袭综合征(*Klebsiella pneumoniae* invasion syndrome, KPIS)，死亡率显著增加[14]。在早期关于 hvKP 的研究中，明显增强的毒力为其主要的特点，对常见的抗生素存在较高的敏感性，然而近年来报道了越来越多对碳青霉烯类抗生素耐药的 hvKP，带来了令人担忧的挑战[15]。本综述就 hvKP 侵袭性感染相关研究进展进行总结，为临床早期诊断与治疗提供思路。

2. hvKP 的毒力因素

KP 表现四大类毒力因子，包括荚膜、脂多糖、铁载体和菌毛，这些毒力因子在不同类型的菌株中起着不同的作用[16]。

2.1. 荚膜

荚膜是 KP 表面的多糖基质，由菌株特异性荚膜多糖组成，称为 K 抗原，是 KP 的毒力决定因素，至今为止，至少有 79 种 KP 荚膜血清型的报道[17]。hvKP 菌株通常为 K1 型与 K2 型，它们也是 KP 中最普遍的荚膜抗原，可作为细菌外部的保护层，对宿主免疫反应与吞噬功能等具有更强的抵抗力[18]；其次是 K5、K20、K54 和 K57。与 cKP 相比，大多数 hvKP 表现出高黏液表型，由 c-rmpA、c-rmpA2、p-rmpA、

p-rmpA2 和 wzy-K1 等多个毒力基因调控，同样与 hvKP 的高致病性相关[17]。目前只有少部分 KP 谱系表现出高毒力，CG23 是最常见的谱系，包括 ST23、26、57 和 1633 等序列类型[19]，其中，ST23 菌株是肝脓肿的主要原因，且与 K1 荚膜型及侵袭性感染密切相关[20]，是目前占主导地位的 hvKP 菌株[21]。

2.2. 脂多糖

脂多糖由脂质 A、寡糖核心和 O 抗原组成，被称为所有革兰氏阴性菌(包括 cKP 和 hvKP)的内毒素，O 抗原是宿主固有免疫遇到的第一个分子，可结合补体成分 C3b，保护病原体免受补体介导的杀伤，同时也是炎症反应的强激活剂。O 血清型有至少 8 种，其中 O1 抗原在 KP 中最为常见[1]。Lugo JZ 等人的研究指出，O1 抗原阳性的 K2 型 KP 中，O 抗原可通过削弱巨噬细胞活化和促进菌血症的形成来增强细菌毒力和致死性[22]，但目前，尚不能证明 hvKP 菌株产生的脂多糖是否在其高毒力的形成中具有明确的作用。

2.3. 铁载体

铁元素是 KP 生存和繁殖所需要的必须元素，是其毒力的影响因素，KP 可分泌铁载体，与细胞外的铁相结合，并重新进入细菌[23]。肠杆菌素是 KP 的核心铁载体，在 KP 中几乎无处不在。其次分别为沙门菌素、耶尔森杆菌素、气杆菌素。研究表明，与 cKP 相比，hvKP 的铁载体活性增强了 6~10 倍[24]，大幅度提高了细菌的生长能力，是 hvKP 高毒力的重要影响因素[10]。

2.4. 菌毛

KP 的菌毛类型为 1 型和 3 型菌毛，可帮助细菌粘附在宿主表面。现有研究证明，3 型菌毛可介导生物膜的形成，有助于提升细菌的耐药性和毒力。同时，生物膜的活性也受到铁元素的影响[1]。在 hvKP NTUH-2044 的基因组中，鉴定了 7 个新的菌毛基因簇，即 kpa、kpb、kpc、kpd、kpe、kpf 和 kfg，并且 Kpc 菌毛与 K1 血清型 hvKP 高度相关[10]。

3. hvKP 感染的危险因素

hvKP 可发生于免疫功能正常的健康人群，但在酗酒、糖尿病、恶性肿瘤、肝胆系统疾病、慢性阻塞性肺病、肾功能衰竭以及接受皮质醇治疗的免疫功能受损的患者，hvKP 感染风险增加，伴随着多部位的侵袭性感染率上升，且 98%的侵袭菌株表现出与 hvKP 高度相关的高黏液表型[25]。hvKP 引起的 KPIS 通常表现为伴有迁徙性感染的肝脓肿，往往难以诊断，近年来一项研究表明，其死亡率高高 14% [26]。糖尿病是其中最重要的危险因素，主要的原因包括：(1) 长期高血糖水平导致的免疫功能障碍；(2) 高血糖会抑制中性粒细胞的粘附、趋化和吞噬功能，使感染难以控制；(3) 高血糖状态致周围血管病变，导致周围组织缺氧，为细菌的生长和增殖提供了有利条件[27] [28] [29]。而在健康人群中，hvKP 的感染主要与其各种毒力因子的活性相关[30]。

4. hvKP 侵袭性感染的临床特性

hvKP 易引起侵袭性感染，其症状是非特异性的，主要包括发热、寒战、腹痛、恶心和呕吐等，但也可能是由迁徙性感染的位置引起的[31]。目前常见的感染类型包括化脓性肝脓肿、内源性眼内炎、脑膜炎、坏死性筋膜炎等。

4.1. 化脓性肝脓肿

肝脓肿是最常见的内脏脓肿之一，危险因素包括糖尿病、肝胆疾病、恶性疾病等[32]。自 1986 年报

告了第一例由 hvKP 引起的肝脓肿病例以来，hvKP 已成为其主要的致病菌。与传统的多种微生物感染的化脓性肝脓肿不同，hvKP 化脓性肝脓肿几乎都是单微生物感染[33]。hvKP 化脓性肝脓肿很少出现胆源性感染或门静脉来源性感染，邻近部位的直接蔓延以及来自肝动脉的血流感染是其常见的感染途径[34]。另外，一项使用小鼠模型的动物研究证明，hvKP 可直接穿过肠道屏障引起肝脓肿[35]。韩国的一项研究显示，在 1175 份粪便样本中，有 248 份(21.1%)分离出 KP，其中 23%为 K1 血清型[36]，hvKP 很可能通过环境暴露或粪口传播在胃肠道定植后，穿过肠道屏障侵入肝脏。hvKP 化脓性肝脓肿常见的临床表现为高热、寒战与腹痛，白细胞增多、血小板减少、C 反应蛋白和葡萄糖浓度升高以及肝功能不全较为常见[37]；影像学中多累及单叶，表现为单发、多房、实性外观[38]。糖尿病是 hvKP 化脓性肝脓肿明确的危险因素，同时与迁徙性感染的发生率相关[39]，5~6 cm 大小的脓肿也被证明是转移性感染患者的重要独立预测因素[40]。据报道，hvKP 化脓性肝脓肿迁徙性感染的发生率为 28% [41]，常见的迁徙部位包括眼(眼内炎、葡萄膜炎)、肺(肺炎、脓胸)、中枢神经系统(包括脑膜炎、脑脓肿和硬膜外脓肿)，也有患者表现为严重的皮肤软组织感染、骨髓炎，坏死性筋膜炎等[42]。此外，近年来一项 77 例的临床研究也指出了 hvKP 化脓性肝脓肿并发严重横纹肌溶解的可能性[42]。第三代头孢菌素类药物是 hvKP 化脓性肝脓肿抗生素治疗的传统推荐药物，但由于产 ESBL (Extended-spectrum β-lactamase)菌株的逐年增加，β-内酰胺类/β-内酰胺酶抑制剂联合用药已取代超广谱头孢菌素，以控制产 ESBL 菌株的流行[43]。而对于有产 ESBL 菌株感染高危因素的人群，在获取明确的病原学及药敏试验结果前，更推荐使用碳青霉烯类抗生素，以降低其死亡率[44]。经皮肝脓肿穿刺引流是目前被广泛应用的局部干预治疗方式，相较于传统手术引流，其具有相同的疗效，且住院时间更短，并发症发生率及治疗成本更低[45]。近年来，法国的一项大型回顾性研究表明，化脓性肝脓肿引流干预是与其死亡率降低相关的重要因素[46]，但对于多发性脓肿，穿刺引流的失败率较高[47]。对于多发性脓肿、无法穿刺的脓肿、经抗生素治疗和经皮引流后仍存在脓毒症的患者、破裂性脓肿，仍推荐手术干预[48]。

4.2. 内源性眼内炎

目前，hvKP 被认为是内源性眼内炎的主要原因，多继发于化脓性肝脓肿的迁徙性感染，hvKP 化脓性肝脓肿中内源性眼内炎的发病率在 3.4%和 12.6%之间，多数患者最后出现了不可逆转的视力丧失[49] [50]。同时，肝外其他部位的感染，包括尿路感染、肺部感染等也是其常见的病因[51] [52]。各种报道发现，水肿、红肿、疼痛、视力下降、视物模糊等眼部表现多先于原发感染灶相关症状出现[53]，其发生与转移性脓毒性栓子相关。随着疾病进展，可出现视网膜下脓肿、眼眶蜂窝组织炎、巩膜穿孔等临床表现[51]。糖尿病、高血压、脂肪肝等代谢紊乱性疾病与内源性眼内炎的发病率增加相关，但目前相关机制尚不明确[54] [55]。眼部超声、CT 和 MRI 检查有助于内源性眼内炎的诊断，房水和玻璃体穿刺有机会获取病原学证据。当患者合并内源性眼内炎时，应考虑可用抗生素在眼内的渗透性，第三代头孢菌素类药物可作为治疗的首选[56]。玻璃体内注射抗生素可增加患眼保留视力的机会，目前推荐的使用药物包括头孢他啶、阿米卡星、万古霉素等[57]。另外，玻璃体切除术是一种可供选择的治疗方案，但目前对于选择其的时机及适应症尚存在争议。内源性眼内炎患者的预后极差，Ang 等人的研究中，尽管进行了充分的治疗，但仍有 76%的患者出现了严重的视力丧失，甚至需要行眼球摘除术[58]。

4.3. 脑膜炎

社区获得性脑膜炎是 hvKP 的少见并发症，但在 hvKP 化脓性肝脓肿患者中，脑膜炎是最常见的并发症之一，尤其是当患者合并糖尿病时[59]。据报道，hvKP 感染是台湾社区获得性脑膜炎的主要病因，死亡率达 30%~40% [31] [38]。当 hvKP 患者并发脑膜炎时，患者的预后极差，往往引起偏瘫、听力损失、

癫痫发作等后遗症[60] [61]。除化脓性肝脓肿之外，糖尿病、酒精性肝硬化也是 hvKP 脑膜炎的危险因素[14]。发热、颈强直和精神状态的改变是常见的临床表现，但并非所有患者均会同时出现三类典型症状[62]。脑膜炎的诊断目前仍存在挑战性，延误诊断和治疗会明显增加死亡率，未经治疗的死亡率可达 70%[63]，当具有糖尿病、酒精性肝硬化等高危因素的脑膜炎患者就诊时，应高度怀疑潜在的 hvKP 感染及 KPIS 并发脑膜炎。既往的病例报道指出，hvKP 脑膜炎患者表现出极高的脑脊液蛋白水平[61]，及时腰椎穿刺有助于诊断。严格的血糖控制及合理抗生素应用是必需的治疗方案，但目前尚无明确的管理指南。

4.4. 坏死性筋膜炎

坏死性筋膜炎是一种软组织感染性疾病，可导致脓毒血症、全身多器官功能衰竭和潜在的致命结局[64]。有研究指出，相较于化脓性链球菌，hvKP 引起的坏死性筋膜炎具有更高的死亡率，超过 27%的 hvKP 坏死性筋膜炎病例伴有远处的脓肿形成，并与 K1 型菌株高度相关[65]。坏死性筋膜炎的危险因素包括糖尿病、慢性疾病、免疫抑制、营养不良、高龄、使用非甾体抗炎药、病态肥胖、肝硬化、酗酒、外周血管疾病、慢性肾功能衰竭、免疫系统疾病、艾滋病等[64]。坏死性筋膜炎的初始症状多为局部红肿与发热，病情迅速进展，进一步出现局部压痛与水肿、感觉异常，并很快出现脓毒血症相关体征，如全身发热、心动过速等[66] [67]。坏死性筋膜炎的早期诊断较为困难，通常通过临床诊断或手术探查诊断[68]。当患者高度怀疑坏死性筋膜炎，且影像学结果为阴性时，可行手指检查进一步明确诊断，在局部麻醉的条件下，在皮肤上做一个 2 到 3 厘米的切口到深筋膜，若伤口中没有出血及灰色脓液，则高度提示坏死性筋膜炎，而一旦患者确诊，早期经验性的抗生素治疗以及坏死组织的手术清创有助于改善患者预后，降低截肢的风险与死亡率[64]。

4.5. 化脓性肺栓塞

化脓性肺栓塞是 hvKP 化脓性肝脓肿的罕见并发症，是一种含病原微生物的栓子所导致的疾病，通常由原发感染灶通过静脉循环进入肺动脉系统引起细菌性栓塞[69]，糖尿病是其重要的危险因素[70]。化脓性肺栓塞最常见的临床表现为发热与呼吸急促，与常见的呼吸道感染性疾病相似，缺乏特异性[69]，因此其早期诊断存在困难。化脓性肺栓塞在胸部 CT 最常见的影像学表现包括：(1) 双肺多发外周结节；(2) 空洞形成；(3) 局灶性或楔形浸润；(4) 胸腔积液[71]，当患者高度怀疑化脓性肺栓塞时，常规推荐完善胸部 CT 检查明确诊断。据报道，当 hvKP 化脓性肺栓塞合并化脓性肝脓肿时，其死亡率达 12%，死亡的原因主要为呼吸衰竭与感染性休克[37]。化脓性肺栓塞的治疗以及时控制感染为主，在经验性使用抗生素的同时，积极寻找阳性血培养结果有可能改善患者的预后[72]。

5. 耐碳青霉烯 hvKP 的流行

多重耐药肺炎克雷伯菌(Multidrug-Resistant *Klebsiella pneumoniae*, MDR-KP)与 hvKP 以往被认为是两种不同的病理类型，前者在西方世界流行，以 ST258、ST147、ST101 等序列类型为主，后者在东方世界，尤其是亚太地区流行，以 ST23、ST65、ST86 等序列类型为主[73]。然而，近年来出现了一些多重耐药高毒力肺炎克雷伯菌(Multidrug-Resistant hypervirulent *Klebsiella pneumoniae*, MDR-hvKP)的报道[74]，两种病理类型的 KP 菌株之间的界限正在逐渐消失，MDR-hvKP 同时表现出高毒力和碳青霉烯类耐药表型，容易导致当前抗生素难以治疗的严重感染，目前，MDR-hvKP 已在全球范围内流行，对人类公共卫生造成了巨大的威胁[75]。MDR-hvKP 的耐药机制包括：(1) 由质粒介导的碳青霉烯酶的产生；(2) 外排泵系统的激活；(3) 外膜孔蛋白表达的改变或缺失[76]。MDR-hvKP 通常引起严重的医院获得性感染，能够在多种抗生素的抑制下定殖于胃肠道及呼吸道，其高水平的毒力与耐药性常常导致了较差的临床结局，替

加环素、粘菌素是目前为数不多的可选择治疗方案，β-内酰胺/β-内酰胺酶组合抑制剂(头孢他啶/阿维巴坦)也是一种有希望的替代方案[77]。令人担忧的是，最新研究指出，替加环素的临床使用有可能促成MDR-hvKP的广泛传播[78]，目前临床可供选择的抗生素越来越少，且存在不可确定的风险，MDR-hvKP的流行及匮乏的治疗方式为临床工作带来了巨大难题。

6. 小结

hvKP目前已在世界范围内广泛传播，容易引起严重的侵袭性感染，包括化脓性肝脓肿、坏死性筋膜炎、内源性眼内炎、脑膜炎等，通常为多个部位的同时感染，糖尿病是目前最常见的危险因素，且往往导致不良的临床结局。hvKP引起的严重侵袭性感染以及MDR-hvKP的流行为目前临床感染的诊治带来了巨大威胁。对于具有高危因素、伴有全身多部位感染的患者，因考虑hvKP侵袭性感染可能，而在诊治此类患者时，早期诊断与及时正确的治疗显得尤为重要，对于病原菌未明的经验治疗，选择碳青霉烯类抗生素治疗成功率更高，可以降低其死亡率。尽管近些年来关于hvKP有大量相关研究，但目前临床上仍缺乏快速简便的检测方法，hvKP侵袭性感染的早期识别困难是目前相关研究的局限性。而准确、快速的识别方法，新型抗菌药物的研发，以及寻找影响hvKP耐药性的可控制因素，是目前关于hvKP的临床研究所面临的巨大挑战。

参考文献

[1] Mendes, G., Santos, M.L., Ramalho, J.F., *et al*. (2023) Virulence Factors in Carbapenem-Resistant Hypervirulent *Klebsiella pneumoniae*. *Frontiers in Microbiology*, **14**, Article ID: 1325077. https://doi.org/10.3389/fmicb.2023.1325077

[2] Liang, Z., Wang, Y., Lai, Y., *et al*. (2022) Host Defense against the Infection of *Klebsiella pneumoniae*: New Strategy to Kill the Bacterium in the Era of Antibiotics? *Frontiers in Cellular and Infection Microbiology*, **12**, Article ID: 1050396. https://doi.org/10.3389/fcimb.2022.1050396

[3] Xu, L., Sun, X. and Ma, X. (2017) Systematic Review and Meta-Analysis of Mortality of Patients Infected with Carbapenem-Resistant *Klebsiella pneumoniae*. *Annals of Clinical Microbiology and Antimicrobials*, **16**, Article No. 18. https://doi.org/10.1186/s12941-017-0191-3

[4] Martin, R.M. and Bachman, M.A. (2018) Colonization, Infection, and the Accessory Genome of *Klebsiella pneumoniae*. *Frontiers in Cellular and Infection Microbiology*, **8**, Article No. 4. https://doi.org/10.3389/fcimb.2018.00004

[5] Chen, J., Zhang, H. and Liao, X. (2023) Hypervirulent *Klebsiella pneumoniae*. *Infection and Drug Resistance*, **16**, 5243-5249. https://doi.org/10.2147/IDR.S418523

[6] Liu, Y.C., Cheng, D.L. and Lin, C.L. (1986) *Klebsiella pneumoniae* Liver Abscess Associated with Septic Endophthalmitis. *Archives of Internal Medicine*, **146**, 1913-1916. https://doi.org/10.1001/archinte.1986.00360220057011

[7] McLaughlin, M.M., Advincula, M.R., Malczynski, M., *et al*. (2014) Quantifying the Clinical Virulence of *Klebsiella pneumoniae* Producing Carbapenemase *Klebsiella pneumoniae* with a Galleria Mellonella Model and a Pilot Study to Translate to Patient Outcomes. *BMC Infectious Diseases*, **14**, Article No. 31. https://doi.org/10.1186/1471-2334-14-31

[8] Diago-Navarro, E., Chen, L., Passet, V., *et al*. (2014) Carbapenem-Resistant *Klebsiella pneumoniae* Exhibit Variability in Capsular Polysaccharide and Capsule Associated Virulence Traits. *The Journal of Infectious Diseases*, **210**, 803-813. https://doi.org/10.1093/infdis/jiu157

[9] Deleo, F.R., Chen, L., Porcella, S.F., *et al*. (2014) Molecular Dissection of the Evolution of Carbapenem-Resistant Multilocus Sequence Type 258 *Klebsiella pneumoniae*. *Proceedings of the National Academy of Sciences of the United States of America*, **111**, 4988-4993. https://doi.org/10.1073/pnas.1321364111

[10] Zhu, J., Wang, T., Chen, L., *et al*. (2021) Virulence Factors in Hypervirulent *Klebsiella pneumoniae*. *Frontiers in Microbiology*, **12**, Article ID: 642484. https://doi.org/10.3389/fmicb.2021.642484

[11] Lee, C.R., Lee, J.H., Park, K.S., *et al*. (2017) Antimicrobial Resistance of Hypervirulent *Klebsiella pneumoniae*: Epidemiology, Hypervirulence-Associated Determinants, and Resistance Mechanisms. *Frontiers in Cellular and Infection Microbiology*, **7**, Article No. 483. https://doi.org/10.3389/fcimb.2017.00483

[12] Lim, H.W., Shin, J.W., Cho, H.Y., *et al*. (2014) Endogenous Endophthalmitis in the Korean Population: A Six-Year Retrospective Study. *Retina*, **34**, 592-602. https://doi.org/10.1097/IAE.0b013e3182a2e705

[13] Lye, W.C., Chan, R.K., Lee, E.J., *et al*. (1992) Urinary Tract Infections in Patients with Diabetes Mellitus. *Journal of Infection*, **24**, 169-174. https://doi.org/10.1016/0163-4453(92)92876-K

[14] Sun, R., Zhang, H., Xu, Y., *et al*. (2021) *Klebsiella pneumoniae*-Related Invasive Liver Abscess Syndrome Complicated by Purulent Meningitis: A Review of the Literature and Description of Three Cases. *BMC Infectious Diseases*, **21**, Article No. 15. https://doi.org/10.1186/s12879-020-05702-3

[15] Kocsis, B. (2023) Hypervirulent *Klebsiella pneumoniae*: An Update on Epidemiology, Detection and Antibiotic Resistance. *Acta Microbiologica et Immunologica Hungarica*, **70**, 278-287. https://doi.org/10.1556/030.2023.02186

[16] Wang, G., Zhao, G., Chao, X., *et al*. (2020) The Characteristic of Virulence, Biofilm and Antibiotic Resistance of *Klebsiella pneumoniae*. *International Journal of Environmental Research and Public Health*, **17**, Article No. 6278. https://doi.org/10.3390/ijerph17176278

[17] Dai, P. and Hu, D. (2022) The Making of Hypervirulent *Klebsiella pneumoniae*. *Journal of Clinical Laboratory Analysis*, **36**, e24743. https://doi.org/10.1002/jcla.24743

[18] Paczosa, M.K. and Mecsas, J. (2016) *Klebsiella pneumoniae*: Going on the Offense with a Strong Defense. *Microbiology and Molecular Biology Reviews*, **80**, 629-661. https://doi.org/10.1128/MMBR.00078-15

[19] Sanikhani, R., Moeinirad, M., Shahcheraghi, F., *et al*. (2021) Molecular Epidemiology of Hypervirulent *Klebsiella pneumoniae*: A Systematic Review and Meta-Analysis. *Iranian Journal of Microbiology*, **13**, 257-265. https://doi.org/10.18502/ijm.v13i3.6384

[20] Chen, Y.T., Lai, Y.C., Tan, M.C., *et al*. (2017) Prevalence and Characteristics of Pks Genotoxin Gene Cluster-Positive Clinical *Klebsiella pneumoniae* Isolates in Taiwan. *Scientific Reports*, **7**, Article No. 43120. https://doi.org/10.1038/srep43120

[21] Choby, J.E., Howard-Anderson, J. and Weiss, D.S. (2020) Hypervirulent *Klebsiella pneumoniae*—Clinical and Molecular Perspectives. *Journal of Internal Medicine*, **287**, 283-300. https://doi.org/10.1111/joim.13007

[22] Lugo, J.Z., Price, S., Miller, J.E., *et al*. (2007) Lipopolysaccharide O-Antigen Promotes Persistent Murine Bacteremia. *Shock*, **27**, 186-191. https://doi.org/10.1097/01.shk.0000238058.23837.21

[23] Gonzalez-Ferrer, S., Peñaloza, H.F., Budnick, J.A., *et al*. (2021) Finding Order in the Chaos: Outstanding Questions in *Klebsiella pneumoniae* Pathogenesis. *Infection and Immunity*, **89**, e00693. https://doi.org/10.1128/IAI.00693-20

[24] Russo, T.A., Olson, R., Macdonald, U., *et al*. (2014) Aerobactin Mediates Virulence and Accounts for Increased Siderophore Production under Iron-Limiting Conditions by Hypervirulent (Hypermucoviscous) *Klebsiella pneumoniae*. *Infection and Immunity*, **82**, 2356-2367. https://doi.org/10.1128/IAI.01667-13

[25] Luo, Y., Hu, W., Wu, L., *et al*. (2023) *Klebsiella pneumoniae* Invasive Syndrome with Liver, Lung, and Brain Abscesses Complicated with Pulmonary Fungal Infection: A Case Report and Review of the Literature. *International Journal of Emergency Medicine*, **16**, Article No. 92. https://doi.org/10.1186/s12245-023-00574-1

[26] Bhide, P.P., Ketkar, A.A., Almeligy, A., *et al*. (2022) Klebsiella Invasive Syndrome: A Challenging Diagnosis. *BMJ Case Reports*, **15**, e251977. https://doi.org/10.1136/bcr-2022-251977

[27] Zhang, C.G., Duan, M., Zhang, X.Y., *et al*. (2021) *Klebsiella pneumoniae* Infection Secondary to Spontaneous Renal Rupture That Presents Only as Fever: A Case Report. *World Journal of Clinical Cases*, **9**, 2602-2610. https://doi.org/10.12998/wjcc.v9.i11.2602

[28] Turk Wensveen, T., Gašparini, D., Rahelić, D., *et al*. (2021) Type 2 Diabetes and Viral Infection; Cause and Effect of Disease. *Diabetes Research and Clinical Practice*, **172**, Article ID: 108637. https://doi.org/10.1016/j.diabres.2020.108637

[29] Llorente, L., De La Fuente, H., Richaud-Patin, Y., *et al*. (2000) Innate Immune Response Mechanisms in Non-Insulin Dependent Diabetes Mellitus Patients Assessed by Flow Cytoenzymology. *Immunology Letters*, **74**, 239-244. https://doi.org/10.1016/S0165-2478(00)00255-8

[30] Chang, D., Sharma, L., Dela Cruz, C.S., *et al*. (2021) Clinical Epidemiology, Risk Factors, and Control Strategies of *Klebsiella pneumoniae* Infection. *Frontiers in Microbiology*, **12**, Article ID: 750662. https://doi.org/10.3389/fmicb.2021.750662

[31] Siu, L.K., Yeh, K.M., Lin, J.C., *et al*. (2012) *Klebsiella pneumoniae* Liver Abscess: A New Invasive Syndrome. *The Lancet Infectious Diseases*, **12**, 881-887. https://doi.org/10.1016/S1473-3099(12)70205-0

[32] Webb, G.J., Chapman, T.P., Cadman, P.J., *et al*. (2014) Pyogenic Liver Abscess. *Frontline Gastroenterology*, **5**, 60-67. https://doi.org/10.1136/flgastro-2013-100371

[33] Oikonomou, K, G., Aye, M. (2017) *Klebsiella pneumoniae* Liver Abscess: A Case Series of Six Asian Patients. *American Journal of Case Reports*, **18**, 1028-1033. https://doi.org/10.12659/AJCR.905191

[34] Qian, Y., Wong, C.C., Lai, S., *et al*. (2016) A Retrospective Study of Pyogenic Liver Abscess Focusing on *Klebsiella pneumoniae* as a Primary Pathogen in China from 1994 to 2015. *Scientific Reports*, **6**, Article No. 38587.

https://doi.org/10.1038/srep38587

[35] Tu, Y.C., Lu, M.C., Chiang, M.K., *et al*. (2009) Genetic Requirements for *Klebsiella pneumoniae*-Induced Liver Abscess in an Oral Infection Model. *Infection and Immunity*, **77**, 2657-2671. https://doi.org/10.1128/IAI.01523-08

[36] Chung, D.R., Lee, H., Park, M.H., *et al*. (2012) Fecal Carriage of Serotype K1 *Klebsiella pneumoniae* ST23 Strains Closely Related to Liver Abscess Isolates in Koreans Living in Korea. *European Journal of Clinical Microbiology & Infectious Diseases*, **31**, 481-486. https://doi.org/10.1007/s10096-011-1334-7

[37] Lee, S.S., Chen, Y.S., Tsai, H.C., *et al*. (2008) Predictors of Septic Metastatic Infection and Mortality among Patients with *Klebsiella pneumoniae* Liver Abscess. *Clinical Infectious Diseases*, **47**, 642-650. https://doi.org/10.1086/590932

[38] Alsaif, H.S., Venkatesh, S.K., Chan, D.S., *et al*. (2011) CT Appearance of Pyogenic Liver Abscesses Caused by *Klebsiella pneumoniae*. *Radiology*, **260**, 129-138. https://doi.org/10.1148/radiol.11101876

[39] Fazili, T., Sharngoe, C., Endy, T., *et al*. (2016) *Klebsiella pneumoniae* Liver Abscess: An Emerging Disease. *The American Journal of the Medical Sciences*, **351**, 297-304. https://doi.org/10.1016/j.amjms.2015.12.018

[40] Law, S.T., Kong and Li, M.K. (2013) Is There Any Difference in Pyogenic Liver Abscess Caused by *Streptococcus milleri* and Klebsiella spp? Retrospective Analysis over a 10-Year Period in a Regional Hospital. *Journal of Microbiology, Immunology and Infection*, **46**, 11-18. https://doi.org/10.1016/j.jmii.2011.12.028

[41] Lederman, E.R. and Crum, N.F. (2005) Pyogenic Liver Abscess with a Focus on *Klebsiella pneumoniae* as a Primary Pathogen: An Emerging Disease with Unique Clinical Characteristics. *American Journal of Gastroenterology*, **100**, 322-331. https://doi.org/10.1111/j.1572-0241.2005.40310.x

[42] Deng, L., Jia, R., Li, W., *et al*. (2017) A *Klebsiella pneumoniae* Liver Abscess Presenting with Myasthenia and Tea-Colored Urine: A Case Report and Review of 77 Cases of Bacterial Rhabdomyolysis. *Medicine* (*Baltimore*), **96**, E9458. https://doi.org/10.1097/MD.0000000000009458

[43] Lee, J., Pai, H., Kim, Y.K., *et al*. (2007) Control of Extended-Spectrum Beta-Lactamase-Producing *Escherichia coli* and *Klebsiella pneumoniae* in a Children's Hospital by Changing Antimicrobial Agent Usage Policy. *Journal of Antimicrobial Chemotherapy*, **60**, 629-637. https://doi.org/10.1093/jac/dkm225

[44] Paterson, D.L., Ko, W.C., Von Gottberg, A., *et al*. (2004) Antibiotic Therapy for *Klebsiella pneumoniae* Bacteremia: Implications of Production of Extended-Spectrum Beta-Lactamases. *Clinical Infectious Diseases*, **39**, 31-37. https://doi.org/10.1086/420816

[45] Ferraioli, G., Garlaschelli, A., Zanaboni, D., *et al*. (2008) Percutaneous and Surgical Treatment of Pyogenic Liver Abscesses: Observation over a 21-Year Period in 148 Patients. *Digestive and Liver Disease*, **40**, 690-696. https://doi.org/10.1016/j.dld.2008.01.016

[46] Rossi, G., Nguyen, Y., Lafont, E., *et al*. (2022) Large Retrospective Study Analysing Predictive Factors of Primary Treatment Failure, Recurrence and Death in Pyogenic Liver Abscesses. *Infection*, **50**, 1205-1215. https://doi.org/10.1007/s15010-022-01793-z

[47] Malik, A.A., Bari, S.U., Rouf, K.A., *et al*. (2010) Pyogenic Liver Abscess: Changing Patterns in Approach. *World Journal of Gastrointestinal Surgery*, **2**, 395-401. https://doi.org/10.4240/wjgs.v2.i12.395

[48] Liu, Y., Wang, J.Y. and Jiang, W. (2013) An Increasing Prominent Disease of *Klebsiella pneumoniae* Liver Abscess: Etiology, Diagnosis, and Treatment. *Gastroenterology Research and Practice*, **2013**, Article ID: 258514. https://doi.org/10.1155/2013/258514

[49] Yang, C.S., Tsai, H.Y., Sung, C.S., *et al*. (2007) Endogenous Klebsiella Endophthalmitis Associated with Pyogenic Liver Abscess. *Ophthalmology*, **114**, 876-880. https://doi.org/10.1016/j.ophtha.2006.12.035

[50] Tan, Y.M., Chee, S.P., Soo, K.C., *et al*. (2004) Ocular Manifestations and Complications of Pyogenic Liver Abscess. *World Journal of Surgery*, **28**, 38-42. https://doi.org/10.1007/s00268-003-6963-2

[51] Dubey, D., Raza, F.S., Sawhney, A., *et al*. (2013) *Klebsiella pneumoniae* Renal Abscess Syndrome: A Rare Case with Metastatic Involvement of Lungs, Eye, and Brain. *Case Reports in Infectious Diseases*, **2013**, Article ID: 685346. https://doi.org/10.1155/2013/685346

[52] Wong, J.S., Chan, T.K., Lee, H.M., *et al*. (2000) Endogenous Bacterial Endophthalmitis: An East Asian Experience and a Reappraisal of a Severe Ocular Affliction. *Ophthalmology*, **107**, 1483-1491. https://doi.org/10.1016/S0161-6420(00)00216-5

[53] Chung, C.Y., Wong, E.S., Liu, C.C.H., *et al*. (2017) Clinical Features and Prognostic Factors of *Klebsiella endophthalmitis*—10-Year Experience in an Endemic Region. *Eye* (*London*), **31**, 1569-1575. https://doi.org/10.1038/eye.2017.92

[54] Serban, D., Popa Cherecheanu, A., Dascalu, A.M., *et al*. (2021) Hypervirulent *Klebsiella pneumoniae* Endogenous Endophthalmitis—A Global Emerging Disease. *Life* (*Basel*), **11**, Article No. 676. https://doi.org/10.3390/life11070676

[55] Coburn, P.S., Wiskur, B.J., Christy, E., *et al*. (2012) The Diabetic Ocular Environment Facilitates the Development of

Endogenous Bacterial Endophthalmitis. *Investigative Ophthalmology & Visual Science*, **53**, 7426-7431. https://doi.org/10.1167/iovs.12-10661

[56] Fang, C.T., Lai, S.Y., Yi, W.C., *et al*. (2007) *Klebsiella pneumoniae* Genotype K1, an Emerging Pathogen That Causes Septic Ocular or Central Nervous System Complications from Pyogenic Liver Abscess. *Clinical Infectious Diseases*, **45**, 284-293. https://doi.org/10.1086/519262

[57] Callegan, M.C., Engelbert, M., Parke, D.W., *et al*. (2002) Bacterial Endophthalmitis: Epidemiology, Therapeutics, and Bacterium-Host Interactions. *Clinical Microbiology Reviews*, **15**, 111-124. https://doi.org/10.1128/CMR.15.1.111-124.2002

[58] Ang, M., Jap, A. and Chee, S.P. (2011) Prognostic Factors and Outcomes in Endogenous *Klebsiella pneumoniae* Endophthalmitis. *American Journal of Ophthalmology*, **151**, 338-344.E2. https://doi.org/10.1016/j.ajo.2010.08.036

[59] Cheng, D.L., Liu, Y.C., Yen, M.Y., *et al*. (1991) Septic Metastatic Lesions of Pyogenic Liver Abscess. Their Association with *Klebsiella pneumoniae* Bacteremia in Diabetic Patients. *Archives of Internal Medicine*, **151**, 1557-1559. https://doi.org/10.1001/archinte.1991.00400080059010

[60] Lin, Y.T., Liu, C.J., Chen, T.J., *et al*. (2012) Long-Term Mortality of Patients with Septic Ocular or Central Nervous System Complications from Pyogenic Liver Abscess: A Population-Based Study. *PLOS ONE*, **7**, e33978. https://doi.org/10.1371/journal.pone.0033978

[61] Chang, Y., Chen, J.H., Chen, W.L., *et al*. (2023) *Klebsiella pneumoniae* Invasive Syndrome with Liver Abscess and Purulent Meningitis Presenting as Acute Hemiplegia: A Case Report. *BMC Infectious Diseases*, **23**, Article No. 397. https://doi.org/10.1186/s12879-023-08383-w

[62] Durand, M.L., Calderwood, S.B., Weber, D.J., *et al*. (1993) Acute Bacterial Meningitis in Adults. A Review of 493 Episodes. *The New England Journal of Medicine*, **328**, 21-28. https://doi.org/10.1056/NEJM199301073280104

[63] Rosenstein, N.E., Perkins, B.A., Stephens, D.S., *et al*. (2001) Meningococcal Disease. *The New England Journal of Medicine*, **344**, 1378-1388. https://doi.org/10.1056/NEJM200105033441807

[64] Salati, S.A. (2022) Necrotizing Fasciitis: A Review. *Polski Przeglad Chirurgiczny*, **95**, 1-8. https://doi.org/10.5604/01.3001.0015.7676

[65] Cheng, N.C., Yu, Y.C., Tai, H.C., *et al*. (2012) Recent Trend of Necrotizing Fasciitis in Taiwan: Focus on Monomicrobial *Klebsiella pneumoniae* Necrotizing Fasciitis. *Clinical Infectious Diseases*, **55**, 930-939. https://doi.org/10.1093/cid/cis565

[66] Goh, T., Goh, L.G., Ang, C.H., *et al*. (2014) Early Diagnosis of Necrotizing Fasciitis. *British Journal of Surgery*, **101**, E119-E125. https://doi.org/10.1002/bjs.9371

[67] Fustes-Morales, A., Gutierrez-Castrellon, P., Duran-Mckinster, C., *et al*. (2002) Necrotizing Fasciitis: Report of 39 Pediatric Cases. *Archives of Dermatology*, **138**, 893-899. https://doi.org/10.1001/archderm.138.7.893

[68] Fedder, A.M., Hvas, A.M., Wang, M., *et al*. (2022) Necrotizing Fasciitis. *Ugeskrift for Læger*, **184**, V11210825.

[69] Wang, Y., Wang, H., Liu, Z., *et al*. (2022) The Incidence of Septic Pulmonary Embolism in Patients with *Klebsiella pneumoniae* Liver Abscess: A Systematic Review and Meta-Analysis. *Gastroenterology Research and Practice*, **2022**, Article ID: 3777122. https://doi.org/10.1155/2022/3777122

[70] Chou, D.W., Wu, S.L., Chung, K.M., *et al*. (2015) Septic Pulmonary Embolism Caused by a *Klebsiella pneumoniae* Liver Abscess: Clinical Characteristics, Imaging Findings, and Clinical Courses. *Clinics* (*Sao Paulo*), **70**, 400-407. https://doi.org/10.6061/clinics/2015(06)03

[71] Chang, Z., Gong, Z., Zheng, J., *et al*. (2016) Computed Tomography Features of Septic Pulmonary Embolism Caused by *Klebsiella pneumoniae* Liver Abscess Associated with Extrapulmonary Metastatic Infection. *Journal of Computer Assisted Tomography*, **40**, 364-369. https://doi.org/10.1097/RCT.0000000000000383

[72] Nishimura, Y., Hagiya, H., Obika, M., *et al*. (2020) Comparison of the Clinico-Microbiological Characteristics of Culture-Positive and Culture-Negative Septic Pulmonary Embolism: A 10-Year Retrospective Study. *Pathogens*, **9**, Article No. 995. https://doi.org/10.3390/pathogens9120995

[73] Arcari, G. and Carattoli, A. (2023) Global Spread and Evolutionary Convergence of Multidrug-Resistant and Hypervirulent *Klebsiella pneumoniae* High-Risk Clones. *Pathogens and Global Health*, **117**, 328-341. https://doi.org/10.1080/20477724.2022.2121362

[74] Tang, M., Kong, X., Hao, J., *et al*. (2020) Epidemiological Characteristics and Formation Mechanisms of Multidrug-Resistant Hypervirulent *Klebsiella pneumoniae*. *Frontiers in Microbiology*, **11**, Article ID: 581543. https://doi.org/10.3389/fmicb.2020.581543

[75] Gu, D., Dong, N., Zheng, Z., *et al*. (2018) A Fatal Outbreak of ST11 Carbapenem-Resistant Hypervirulent *Klebsiella pneumoniae* in a Chinese Hospital: A Molecular Epidemiological Study. *The Lancet Infectious Diseases*, **18**, 37-46. https://doi.org/10.1016/S1473-3099(17)30489-9

[76] Bonomo, R.A., Burd, E.M., Conly, J., *et al*. (2018) Carbapenemase-Producing Organisms: A Global Scourge. *Clinical Infectious Diseases*, **66**, 1290-1297. https://doi.org/10.1093/cid/cix893

[77] Pu, D., Zhao, J., Chang, K., *et al*. (2023) “Superbugs” with Hypervirulence and Carbapenem Resistance in *Klebsiella pneumoniae*: The Rise of Such Emerging Nosocomial Pathogens in China. *Science Bulletin* (*Beijing*), **68**, 2658-2670. https://doi.org/10.1016/j.scib.2023.09.040

[78] Xie, M., Ye, L., Chen, K., *et al*. (2024) Clinical Use of Tigecycline May Contribute to the Widespread Dissemination of Carbapenem-Resistant Hypervirulent *Klebsiella pneumoniae* Strains. *Emerging Microbes & Infections*, **13**, Article ID: 2306957. https://doi.org/10.1080/22221751.2024.2306957