Supplementary information for “**Understanding *K. pneumoniae* and phage game for optimal phage therapy: an evolving perspective**”

**The supplementary file contains two tables:**

**Supplementary Table 1**: Details of *Klebsiella pneumoniae* phage resistance mechanisms from PRISMA protocol.

**Supplementary Table 2**: which provides details of clinical cases involving phage therapy for *K. pneumoniae* infection.

**Supplementary Table 1**: Details of *Klebsiella pneumoniae* phage resistance mechanisms from PRISMA protocol.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Resistance category** | **Specific mechanism** | **Reported date** | **Sampling country (phage)** | **Strain source** | **DOI** | **Reference** |
| Putative Abi System | Putative Abi (*pdeC* mutation） | 2022 | China | Domestic wastewater | 10.1038/s42003-022-03001-y | 1 |
| Others | Kongming system | 2025 | China | / | 10.1126/science.ads6055 | 2 |
| Others | Bacterial biofilm resistance | 2024 | China | / | 10.1126/sciadv.adp5057 | 3 |
| Others | Undetermined system in KP PICI. | 2022 | United Kingdom | / | 10.1016/j.cell.2022.07.014 | 4 |
| Others | Sie | 2022 | France | *K. pneumoniae* patient | https://doi.org/10.1101/2022.07.11.499539 | 5 |
| Others | Mutations in *mnmE* and *rpoN* prolong the phage latency period | 2024 | Australia | Domestic wastewater | 10.1016/j.cmi.2024.03.015 | 6 |
| Others | Bsta defense proteins | 2021 | United States | / | 10.1016/j.chom.2021.09.002 | 7 |
| Nucleic acid interference | I-E type and Subtype I-E\* CRISPR-Cas system | 2023 | Egypt and globe | NCBI GenBank and *K. pneumoniae* patient | 10.3390/microorganisms11081948 | 8 |
| Nucleic acid interference | I-E type and Subtype I-E\* CRISPR-Cas system | 2023 | China | *K. pneumoniae* patient | 10.3389/fmicb.2023.1125531 | 9 |
| Nucleic acid interference | Subtype I-E\* CRISPR-Cas system | 2018 | China and globe | IMG and *K. pneumoniae* patient | 10.3389/fmicb.2018.01595 | 10 |
| Nucleic acid interference | IV-A3 type CRISPR-Cas system | 2024 | Switzerland | *K. pneumoniae* patient | 10.1016/j.chom.2024.04.016 | 11 |
| Nucleic acid interference | I-E type, Subtype I-E\* and I-F type CRISPR-Cas system | 2017 | Globe | NCBI GenBank | 10.1002/jobm.201600589 | 12 |
| Nucleic acid interference | CRISPR-Cas system | 2016 | China | *K. pneumoniae* patient | 10.1038/srep31644 | 13 |
| Nucleic acid interference | I-E type and Subtype I-E\*CRISPR-Cas system | 2022 | Globe | CRISPR Cas db | 10.3390/ijms232112766 | 14 |
| Nucleic acid interference | CRISPR-Cas system | 2023 | Iraq | *K. pneumoniae* patient | 10.3390/antibiotics12060980 | 15 |
| Nucleic acid interference | IV-3A type CRISPR-Cas system | 2021 | China | *K. pneumoniae* patient | 10.3389/fmicb.2021.762947 | 16 |
| Nucleic acid interference | IV-A3 type CRISPR-Cas system | 2020 | Egypt and United Kingdom | *K. pneumoniae* patient | 10.3389/fmicb.2020.01937 | 17 |
| Nucleic acid interference | IV type CRISPR-Cas system | 2020 | Globe | NCBI GenBank | 10.3389/fmicb.2019.02934 | 18 |
| Nucleic acid interference | CRISPR-Cas system | 2019 | United States | *K. pneumoniae* patient | 10.1371/journal.pone.0225131 | 19 |
| Nucleic acid interference | I-E type and IV-A3 type CRISPR‒Cas system | 2025 | Globe | NCBI GenBank and isolation | 10.1186/s13073-025-01428-6 | 20 |
| Nucleic acid interference | CRISPR-Cas system | 2024 | Iran | *K. pneumoniae* patient | 10.1186/s12879-024-10018-7 | 21 |
| Nucleic acid interference | Subtype I-E\* CRISPR-Cas system | 2024 | Iran | *K. pneumoniae* patient | 10.1186/s12879-024-09451-5 | 22 |
| Nucleic acid interference | CRISPR-Cas system and R-M system | 2024 | China | NCBI GenBank and *K. pneumoniae* patient | 10.1186/s12866-024-03381-7 | 23 |
| Nucleic acid interference | R-M system | 2024 | / | / | 10.1128/spectrum.03388-23 | 24 |
| Nucleic acid interference | I-E type, I-F type, IV-A, CRISPR‒Cas system and I type R-M system | 2024 | Globe | NCBI GenBank | 10.1128/spectrum.00009-24 | 25 |
| Nucleic acid interference | I-E type CRISPR-Cas system | 2020 | Globe and China | NCBI GenBank and *K. pneumoniae* patient | 10.1080/22221751.2020.1763209 | 26 |
| Nucleic acid interference | I-E type and Subtype I-E\*CRISPR-Cas system | 2024 | Iran | *K. pneumoniae* patient | 10.1016/j.micpath.2024.107151 | 27 |
| Adsorption inhibition | CPS | 2023 | China | Hospital wastewater | Preliminary application and resistance mechanism study of carbapenem-resistant lytic bacteriophage of Klebsiella pneumoniae (in Chinese) | 28 |
| Adsorption inhibition | LPS | 2024 | China | Hospital wastewater | Isolation and identification of bacteriophage vB\_KpnS\_SXK7 of Klebsiella pneumoniae and the resistance mechanism of resistant bacteria (in Chinese) | 29 |
| Adsorption inhibition | OMP | 2022 | China | Domestic wastewater and soil | Isolation and identification of Klebsiella pneumoniae and resistance mechanism of bacteriophage-resistant bacteria (in Chinese) | 30 |
| Adsorption inhibition | OMV | 2024 | China | Wastewater | The regulation of the synthesis and secretion of outer membrane vesicles by the luxS gene of Klebsiella pneumoniae affects phage sensitivity (in Chinese) | 31 |
| Adsorption inhibition | CPS | 2023 | Serbia | Wastewater | 10.3390/v15030628 | 32 |
| Adsorption inhibition | CPS | 2019 | China | Domestic wastewater | 10.3389/fmicb.2019.01189 | 33 |
| Adsorption inhibition | CPS and LPS | 2023 | France | Freshwater and wastewater | 10.1128/spectrum.04812-22 | 34 |
| Adsorption inhibition | CPS | 2022 | China | Freshwater | 10.1128/msphere.00518-22 | 35 |
| Adsorption inhibition | LPS | 2025 | China | Hospital wastewater | 10.1128/mbio.02957-24 | 36 |
| Adsorption inhibition | CPS, LPS, and OMP | 2020 | United States | / | 10.1128/mBio.02530-19 | 37 |
| Adsorption inhibition | OMP | 2022 | China | Domestic wastewater | 10.1128/AEM.01585-18 | 38 |
| Adsorption inhibition | CPS | 2025 | China | Wastewater | 10.1038/s42003-025-07687-8 | 39 |
| Adsorption inhibition | CPS | 2022 | China | Domestic wastewater | 10.1038/s42003-022-03001-y | 1 |
| Adsorption inhibition | CPS | 2022 | France | *K. pneumoniae* patient | https://doi.org/10.1101/2022.07.11.499539 | 5 |
| Adsorption inhibition | CPS | 2021 | Italy | / | 10.3390/microorganisms9040762 | 40 |
| Adsorption inhibition | CPS | 2020 | China | Domestic wastewater | 10.3390/microorganisms8030378 | 41 |
| Adsorption inhibition | CPS | 2021 | China | Hospital wastewater | 10.3390/antibiotics10080894 | 42 |
| Adsorption inhibition | CPS | 2023 | China | Hospital wastewater | 10.3389/fmicb.2023.1156292 | 43 |
| Adsorption inhibition | CPS and LPS | 2023 | China | Domestic wastewater | 10.1128/spectrum.04384-22 | 44 |
| Adsorption inhibition | CPS and LPS | 2024 | South Korea | Hospital wastewater | 10.1128/spectrum.01258-23 | 45 |
| Adsorption inhibition | CPS | 2022 | China | Hospital wastewater | 10.1128/msphere.00080-22 | 46 |
| Adsorption inhibition | LPS | 1985 | Spain | Freshwater | 10.1128/jb.162.3.1276-1279.1985 | 47 |
| Adsorption inhibition | CPS | 2020 | Australia | Wastewater | 10.1096/fj.201902735R | 48 |
| Adsorption inhibition | CPS | 2009 | India | Wastewater | 10.1093/jac/dkp360 | 49 |
| Adsorption inhibition | CPS | 2025 | China | Wastewater | 10.1080/22221751.2025.2455592 | 50 |
| Adsorption inhibition | CPS | 2016 | China | *K. pneumoniae* patient | 10.1038/srep31644 | 13 |
| Adsorption inhibition | CPS | 2022 | Russia | / | 10.1016/j.virusres.2022.198951 | 51 |
| Adsorption inhibition | LPS | 2024 | China | Hospital wastewater | 10.1016/j.ijantimicag.2024.107221 | 52 |
| Adsorption inhibition | OMP | 2024 | Australia | Domestic wastewater | 10.1016/j.cmi.2024.03.015 | 6 |
| Adsorption inhibition | LPS | 2023 | China | Livestock farm wastewater | 10.1016/j.cmi.2023.08.022 | 53 |
| Adsorption inhibition | CPS | 2023 | China | Hospital wastewater | A preliminary study of the phage resistance mechanism associated with Kl64 multidrug-resistant Klebsiella pneumoniae WzcT573R (in Chinese) | 54 |
| Abi system | TA | 2024 | United States | / | https://doi.org/10.1111/1751-7915.14543 | 55 |
| Abi system | DRT2 | 2024 | United States | / | 10.1126/science.adq3977 | 56 |
| Abi system | Retron system, Abi-C system, AbiJ-NTD4, and HEPN system | 2022 | United Kingdom | / | 10.1016/j.cell.2022.07.014 | 4 |
| Abi system | TA | 2023 | Spain | Wastewater | 10.1128/spectrum.03974-22 | 57 |
| Abi system | TA | 2022 | Spain | Wastewater | 10.1038/s41598-022-08111-5 | 58 |
| Abi system | Type 2 Avs proteins (Avs2) | 2024 | / | / | 10.1038/s41467-024-54214-0 | 59 |
| Abi system | TA | 2024 | / | / | 10.1128/spectrum.03388-23 | 24 |

**Table note**: For the five studies sourced from CNKI (originally published in Chinese), English-translated titles are provided in the **DOI** column, and their Chinese origin is referred in **Reference** column.

**Supplementary Table 2**: Clinical case studies of phage therapy targeting *K. pneumoniae* infection.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Symptom** | **Time** | **Pathogen serotype** | **Resistance** | **Combo** | **Dose** | **Engineering** | **Antibiotics** | **Route of administration** | **Course** | **Outcome** | **Resistance to phage** | **Reference** |
| Prosthetic joint infection (PJI) | 2020 | *K. pneumoniae* complex | NA | Single | 6.3 × 1010 PFU each weekday | No | Minocycline | Intravenous | 8 wks | Recovery without adverse effect | NA | 60 |
| Urinary tract infections (UTI) | 2021 | ST15 | MDR-KP | Serial phage therapy | 50 mL 5 × 108 PFU/mL per dose, every 48h, | No | Piperacillin/  tazobactam | Bladder irrigation (four courses) + kidney irrigation (final course) | Four courses (each ~ two wks) | The patient recovered his bladder healthy and no MDR *K. pneumoniae* was isolated in a follow-up of two months | NA | 61 |
| Obstructive nephrolithiasis and UTI | 2020 | ST307 | MDR-KP | Single | 10 mL 106 PFU/mL per dose twice daily; 1 million phages given daily intra-rectally | No | Ceftazidime-avibactam | Oral and intrarectal administration | 3 wks | Recovery without adverse effect | NA | 62 |
| UTI | 2020 | ST11 | XDR-KP | Five phages | 50 mL 5 × 10⁸ PFU/mL per dose daily | No | trimethoprim-sulfamethoxazole (SMZ-TMP) | Bladder irrigation | Three courses (each five days) | No recurrence | Repeated emergence of phage resistance | 63 |
| UTI | 2020 | NA | ESBL | Single | 10 mL twice daily, concentration undisclosed | No | Meropenem | Intrarectal administration | 29 days | No recurrence | NA | 64 |
| UTI | 2019 | NA | ESBL | Single | NA | No | Meropenem | Oral and intravesical administration | Three courses (2 wks+2 wks + 8 wks) | The urethral symptoms decreased from the beginning of phage therapy | NA | 65 |
| Pulmonary infection | 2020 | NA | PDR-KP | Two phages | 2 mL phages inhalation; 18 mL nasogastric administration twice a day | No | Meropenem | Inhaled and nasogastric administration | 4 days | No adverse event | NA | 66 |
| Tibial infection | 2019 | NA | MDR-KP | Two phages | 1 mL 5 × 107 PFU/mL per dose | No | Meropenem and colistin | Intravenous | 5 days | Wound has closed with no secretions and pain has disappeared | NA | 67 |
| Surgical wound infection of thigh | 2022 | ST893 | PDR-KP | Single | 2 × 108 PFU three times/day | No | Ceftazidime/avibactam, ciprofloxacin, moxifloxacin, tigecycline | Local administration through a catheter left in place | 3 days | Recovery from infection | NA | 68 |
| Pulmonary infection | 2023 | NA | MDR-KP | Serial phage therapy | 5 mL > 109 PFU/mL per dose | No | No | Inhaled administration | 16 hrs | Clinical symptoms improved, but *K. pneumoniae* had not been completely eliminated. | Phage-resistant  *K.pneumoniae* strains emerged | 69 |
| UTI | 2023 | *K. pneumoniae* complex | ESBL | Three phages | 5 × 109 PFU/dose, twice daily | No | NA | Intravenous administration | 4 wks | No recurrence in a year of follow-up | NA | 70 |
| PJI | 2022 | NA | ESBL | Serial phage therapy | 10 mL 1010 PFU/mL for first phage; 50 mL 1010 PFU/mL for second phage | No | Ertapenem, amoxicillin-clavulanate | Catheter and intravenous administration | 6 days | Without any adverse reactions and clinical symptoms | NA | 71 |

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