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Reproducibility and Dynamics of Biochemical Phenotypic Shifts in Enterobacteriaceae Following Lisinopril Exposure: Implications for Diagnostic Bacteriology

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Abstract

Conventional biochemical profiling remains central to bacterial identification in diagnostic microbiology. However, non-antibiotic pharmaceuticals can exert metabolic stress on bacteria, potentially inducing phenotypic variation that complicates species identification. This study evaluated the biochemical fingerprints of paired wild-type and sub-inhibitory lisinopril-exposed (10 mg/mL) isolates of *Escherichia coli* (E1/E2), *Klebsiella pneumoniae* (K1/K2), and *Salmonella Typhi* (S1/S2) across three independent biological triplicates. Phenotypic characterization was performed using standardized commercial micro-substrate panels (0.5 McFarland, 37 °C, 18–24 h) alongside parallel 16S rRNA gene sequencing. Molecular analysis verified 100% species identity conservation post-exposure. However, lisinopril exposure triggered reproducible, species-specific phenotypic shifts across key metabolic pathways. In *E. coli*, exposure induced a complete loss of lysine decarboxylase activity (3/3 replicates) and gained novel carbohydrate fermentation capacity for inositol, sorbitol, saccharose, arabinose, and raffinose. In *K. pneumoniae*, exposure abolished citrate utilization and urease activity while inducing phenylalanine deaminase activity and inositol utilization. In *S. Typhi*, ONPG hydrolysis was completely suppressed, while arabinose and raffinose fermentation capacities were newly expressed; urease activity remained stably positive. These physiological alterations demonstrate that non-antibiotic drug exposure can epigenetically modify primary metabolic phenotypes without altering genotypic identity. Diagnostic laboratories relying exclusively on single-run biochemical panels risk misidentifying xenobiotic-stressed enteric pathogens. Implementation of orthogonal workflows combining phenotypic panels with MALDI-TOF MS or sequencing is essential when characterizing atypical enteric isolates recovered from patients undergoing non-antibiotic pharmacotherapy.

Keywords: Lisinopril; Enterobacteriaceae; Phenotypic variation; Biochemical profiling; Diagnostic bacteriology; non-antibiotic stress; 16S rRNA sequencing.

1. INTRODUCTION

1.1 Background of the Study

Accurate bacterial identification is a central activity in diagnostic microbiology. It supports clinical decision-making, infection surveillance and the selection of appropriate antimicrobial treatment. Members of the family Enterobacteriaceae include organisms of clinical importance, among them Escherichia coli, Klebsiella pneumoniae and Salmonella enterica serovar Typhi. Conventional identification continues to rely on combinations of phenotypic and biochemical characteristics, although mass spectrometry and molecular approaches increasingly complement these methods (Arbefeville et al., 2024; Calderaro & Chezzi, 2024; Dunn, 2023; Gant & Chamot-Rooke, 2024; Jover-García et al., 2023).

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Biochemical identification depends on recognising characteristic reaction patterns rather than interpreting a single test in isolation. Commercial systems use combinations of reactions to generate profiles that are compared with reference databases. The reliability of an identification therefore depends on the quality of the test procedure, the purity and physiological condition of the inoculum, and the scope and currency of the system's reference database (Arbefeville et al., 2024; Caliskan-Aydogan & Alocilja, 2023; Dunn, 2023).

Bacterial physiology is responsive to environmental conditions. Nutrient availability, pH, temperature and exposure to chemical compounds can influence growth and metabolic activity. Research on host–microbiome–drug interactions has demonstrated that some non-antibiotic medicines can interact directly with bacteria, be accumulated or transformed by them, or alter microbial community behaviour. The magnitude and biological relevance of these effects vary by compound, organism and experimental context (Heirali et al., 2023; Klünemann et al., 2021; Maier et al., 2018; Noto Guillen et al., 2024; Zimmermann et al., 2021).

Lisinopril is an angiotensin-converting enzyme inhibitor used in the management of hypertension and certain cardiovascular conditions. It is not prescribed as an antibacterial agent. Evidence that some non-antibiotic medicines interact with bacteria provides a rationale for investigating individual compounds, but it cannot be taken as proof of a specific lisinopril effect. Studies of drug–microbiome interactions have documented compound-specific effects, including drug accumulation, changes in microbial metabolism and community-level responses (de la Cuesta-Zuluaga et al., 2024; Garcia-Santamarina et al., 2024; Homolak et al., 2024; Maier et al., 2024; Verdegaal & Goodman, 2024).

1.2 Statement of the Research Problem

Diagnostic bacteriology relies heavily on the stability of phenotypic biochemical markers. When enteric pathogens isolated from patients undergoing complex pharmacotherapy produce aberrant biochemical profiles, standard diagnostic probability algorithms can fail (Dunn, 2023; Arbefeville, 2024). Preliminary observations indicated that exposure to lisinopril coincided with modified enzymatic and fermentation profiles in *E. coli*, *K. pneumoniae*, and *S. Typhi*. However, earlier reports lacked multi-replicate statistical validation, 16S rRNA identity verification, and modern mechanistic interpretation, leaving uncertainty as to whether these shifts represented experimental noise, transient adaptation, or true phenotypic plasticity (Gupta et al., 2025).

1.3 Objectives of the Study

i. Assess the phenotypic biochemical and carbohydrate fermentation profiles of wild-type and sub-inhibitory lisinopril-exposed *Escherichia coli*, *Klebsiella pneumoniae*, and *Salmonella Typhi* across independent biological triplicates using standardized micro-substrate panels.
ii. Verify the genotypic identity of wild-type and exposed isolates via 16S rRNA gene sequencing and determine the diagnostic implications of observed phenotypic shifts for conventional identification systems.

1.4 Research Questions

This study addressed the following core research questions:

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i. What reproducible shifts occur in the enzymatic activity and carbohydrate fermentation profiles of *Escherichia coli*, *Klebsiella pneumoniae*, and *Salmonella Typhi* following sub-inhibitory exposure to lisinopril across independent biological triplicates?
ii. Does lisinopril exposure alter the 16S rRNA genotypic identity of these isolates, and what are the clinical diagnostic implications of xenobiotic-induced biochemical variations for conventional bacterial identification?

2. LITERATURE REVIEW

2.1 Principles of Biochemical Identification in Diagnostic Bacteriology

Phenotypic characterization of Enterobacteriaceae relies on testing metabolic pathways, substrate utilization, and enzymatic cleavage. Standard biochemical batteries evaluate amino acid decarboxylases (lysine, ornithine, arginine), carbon source utilization (citrate, malonate), hydrolytic enzymes (urease, ONPG, phenylalanine deaminase), and specific carbohydrate fermentation profiles (Dunn, 2023; Arbefeville, 2024). These test results generate a composite numerical profile or code compared against reference probability databases to establish species identification (Dunn, 2023).

2.2 Mechanisms of Phenotypic Plasticity and Environmental Stress Responses

Bacterial phenotypes are highly dynamic, governed by complex regulatory networks that respond to environmental cues such as pH, osmotic stress, temperature, and chemical exposure (Arbefeville, 2024; Maier and Typas, 2024). Under sub-lethal stress, bacteria reallocate cellular resources via global stress regulators such as RpoS and MarA, resulting in transcriptional activation or silencing of metabolic operons (Noto Guillen et al., 2024; Gupta et al., 2025). Such phenotypic modulation allows survival without requiring structural genome mutations, yet it can substantially alter expressed enzymatic profiles measured in diagnostic panels.

2.3 Non-Antibiotic Pharmaceuticals as Microbial Modulators

Beyond traditional antibiotics, a broad range of human pharmaceuticals exert direct bioactivity on microbial cells (Heirali et al., 2023; Verdegaal and Goodman, 2024). Large-scale drug screening initiatives have demonstrated that over 24% of human-targeted non-antibiotic medicines inhibit bacterial growth or perturb metabolic pathways in commensal and pathogenic bacteria (Heirali et al., 2023; Maier and Typas, 2024). Cardiovascular agents, including ACE inhibitors like lisinopril, interact with bacterial membrane transporters and ion channels, triggering physiological adaptive responses that influence carbohydrate transport systems and amino acid catabolism (Verdegaal and Goodman, 2024; Noto Guillen et al., 2024).

2.4 Diagnostic Limitations of Conventional Biochemical Kits

Commercial micro-substrate systems operate on standardized probability matrices built upon wild-type reference strains grown under stress-free conditions (Dunn, 2023). When environmental or xenobiotic stress alters metabolic expression, test profiles can deviate from baseline, generating atypical codes that produce low-confidence scores or erroneous species assignments (Arbefeville, 2024; Gupta et al., 2025). Recognizing these diagnostic vulnerabilities reinforces the imperative for orthogonal testing platforms, such as matrix-assisted laser

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desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) and 16S rRNA gene sequencing (Arbefeville, 2024).

3. MATERIALS AND METHODS

3.1 Bacterial Strains and Growth Conditions

Three standardized reference strains of *Enterobacteriaceae* were evaluated: *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC BAA-1705), and *Salmonella Typhi* (ATCC 6539). Wild-type parent strains were designated E1, K1, and S1, respectively. Stock cultures were maintained at −80 °C in Luria-Bertani (LB) broth supplemented with 20% glycerol and revived on Nutrient Agar (Oxoid, UK) at 37 °C for 18–24 h prior to experimental assays.

3.2 Sub-Inhibitory Lisinopril Exposure Protocol

Pharmaceutical-grade lisinopril (Sigma-Aldrich, USA) was dissolved in sterile distilled water to produce a 100 mg/mL stock solution and filter-sterilized (0.22 µm PTFE). Minimum inhibitory concentration (MIC) testing was performed via broth microdilution to confirm that 10 mg/mL represented a non-lethal, sub-inhibitory concentration (Maier and Typas, 2024). Wild-type isolates were inoculated into LB broth containing 10 mg/mL lisinopril and incubated at 37 °C for 24 h. Sub-cultures were sequentially passaged three times under continuous lisinopril exposure to generate stably adapted exposed lineages designated E2, K2, and S2 (Noto Guillen et al., 2024).

3.3 Biochemical Fingerprint Assays and Biological Replicates

Phenotypic biochemical profiles were determined using standardized commercial micro-substrate identification panels (Microbact 24E, Oxoid, UK; Dunn, 2023). Bacterial suspensions from overnight pure cultures were prepared in 0.85% physiological saline and turbidity-adjusted to exactly 0.5 McFarland standard (~1.5×10^8 CFU/mL). Inoculation, mineral oil overlay for anaerobic wells, and 37 °C incubation (18–24 h) were executed strictly according to manufacturer instructions (Dunn, 2023). Reagent additions (Kovac's reagent for indole, ferric chloride for phenylalanine deaminase, VP1/VP2 for Voges-Proskauer) were performed systematically. To ensure statistical rigor, all assays were performed in triplicate across three independent biological replicates (n = 3) on separate days.

3.4 Molecular Confirmation via 16S rRNA Gene Sequencing

To verify that lisinopril exposure did not introduce cross-contamination or genetic divergence, genomic DNA was extracted from wild-type (E1, K1, S1) and exposed (E2, K2, S2) isolates using a QIAamp DNA Mini Kit (Qiagen, Germany; Arbefeville, 2024). The 16S rRNA gene was amplified using universal primers 27F (5'-AGAGTTTGATCMTGGCTCAG-3') and 1492R (5'-TACGGYTACCTTGTTACGACTT-3'). Sanger sequencing was conducted, and refined contigs were aligned against the NCBI GenBank database using BLASTn to confirm species identity.

3.5 Justification of the Study

Elucidating how non-antibiotic pharmaceuticals alter bacterial phenotype is vital for maintaining diagnostic accuracy in clinical settings. By systematically evaluating the biochemical responses of *Enterobacteriaceae* to sub-inhibitory lisinopril exposure across independent biological

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triplicates and confirming species identity via 16S rRNA gene sequencing, this study establishes the physiological boundaries of phenotypic identification systems under pharmaceutical stress (Dunn, 2023; Noto Guillen et al., 2024). The findings provide actionable guidance for diagnostic microbiologists, highlighting when phenotypic profiles should be validated through orthogonal platforms such as MALDI-TOF MS or molecular sequencing (Arbefeville, 2024).

4. RESULTS

4.1 Molecular Species Verification

BLASTn sequence analysis of the amplified 16S rRNA genes confirmed 100% identity between wild-type and lisinopril-exposed pairs (E1/E2 = *Escherichia coli*, K1/K2 = *Klebsiella pneumoniae*, S1/S2 = *Salmonella Typhi*). Genotypic identity remained entirely conserved post-exposure, demonstrating that observed biochemical modifications arose from phenotypic plasticity rather than taxonomic divergence or contamination.

Table 1. Biochemical and carbohydrate fermentation profiles of wild-type and lisinopril-exposed Enterobacteriaceae across biological triplicates (n = 3)

Biochemical Test	E1 (WT)	E2 (Exp)	K1 (WT)	K2 (Exp)	S1 (WT)	S2 (Exp)
ONPG hydrolysis	+ (3/3)	+ (3/3)	+ (3/3)	+ (3/3)	+ (3/3)	− (0/3)
Lysine decarboxylase	+ (3/3)	− (0/3)	+ (3/3)	+ (3/3)	+ (3/3)	+ (3/3)
Ornithine decarboxylase	+ (3/3)	+ (3/3)	− (0/3)	− (0/3)	− (0/3)	− (0/3)
Arginine decarboxylase	+ (3/3)	+ (3/3)	− (0/3)	− (0/3)	+ (3/3)	+ (3/3)
Phenylalanine deaminase	− (0/3)	− (0/3)	− (0/3)	+ (3/3)	− (0/3)	− (0/3)
Citrate utilization	− (0/3)	− (0/3)	+ (3/3)	− (0/3)	− (0/3)	− (0/3)
Urease activity	− (0/3)	− (0/3)	+ (3/3)	− (0/3)	+ (3/3)	+ (3/3)
Hydrogen sulphide (H_2S)	− (0/3)	− (0/3)	− (0/3)	− (0/3)	− (0/3)	− (0/3)
Malonate utilization	− (0/3)	− (0/3)	− (0/3)	− (0/3)	− (0/3)	− (0/3)
Voges–Proskauer (VP)	− (0/3)	− (0/3)	− (0/3)	− (0/3)	− (0/3)	− (0/3)
Indole production	+ (3/3)	+ (3/3)	− (0/3)	− (0/3)	− (0/3)	− (0/3)
Glucose fermentation	+ (3/3)	+ (3/3)	+ (3/3)	+ (3/3)	+ (3/3)	+ (3/3)
Mannitol fermentation	+ (3/3)	+ (3/3)	+ (3/3)	+ (3/3)	+ (3/3)	+ (3/3)
Inositol fermentation	− (0/3)	+ (3/3)	− (0/3)	+ (3/3)	− (0/3)	− (0/3)
Sorbitol fermentation	− (0/3)	+ (3/3)	+ (3/3)	+ (3/3)	+ (3/3)	+ (3/3)
Saccharose fermentation	− (0/3)	+ (3/3)	+ (3/3)	+ (3/3)	+ (3/3)	+ (3/3)
Arabinose fermentation	− (0/3)	+ (3/3)	+ (3/3)	+ (3/3)	− (0/3)	+ (3/3)
Raffinose fermentation	− (0/3)	+ (3/3)	+ (3/3)	+ (3/3)	− (0/3)	+ (3/3)

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Table illustrate that the phenotypic testing across three independent biological triplicates reveals that sub-inhibitory lisinopril exposure induces reproducible, species-specific biochemical shifts in Escherichia coli, Klebsiella pneumoniae, and Salmonella Typhi while maintaining complete consensus stability (3/3 positive or 0/3 positive) across all replicates. In E. coli, exposure results in the complete loss of lysine decarboxylase activity alongside the novel acquisition of carbohydrate fermentation capacity for inositol, sorbitol, saccharose, arabinose, and raffinose. For K. pneumoniae, lisinopril stress represses both citrate utilization and urease activity to negative, while simultaneously inducing phenylalanine deaminase expression and enabling inositol fermentation. In S. Typhi, exposure completely silences ONPG hydrolysis while derepressing arabinose and raffinose fermentation pathways, though urease activity remains stably positive in both wild-type and exposed strains. Conversely, core reactions such as glucose and mannitol fermentation remain positive, and hydrogen sulphide, malonate, and Voges–Proskauer tests remain negative across all tested isolates. These highly consistent profile shifts demonstrate that non-antibiotic drug exposure can significantly alter diagnostic biochemical fingerprints through phenotypic plasticity without compromising intra-assay reproducibility or biological stability across independent trials.

4.3 Species-Specific Phenotypic Modulation

In *Escherichia coli* (E2), lisinopril exposure resulted in a complete loss of lysine decarboxylase activity, while inducing carbohydrate fermentation for inositol, sorbitol, saccharose, arabinose, and raffinose. In *Klebsiella pneumoniae* (K2), lisinopril exposure abolished citrate utilization and urease activity, induced phenylalanine deaminase activity, and gained inositol fermentation capacity. In *Salmonella Typhi* (S2), ONPG hydrolysis was silenced, while arabinose and raffinose fermentation were derepressed; urease activity remained consistently positive in both S1 and S2.

5. DISCUSSION

This study provides robust, multi-replicate empirical evidence that sub-inhibitory exposure to the non-antibiotic drug lisinopril induces substantial biochemical phenotypic variation across key enteric pathogens. Importantly, 16S rRNA sequencing confirmed 100% genotypic conservation between wild-type and exposed isolates, ruling out genetic divergence or contamination and proving that these shifts reflect genuine phenotypic plasticity under pharmaceutical stress (Noto Guillen et al., 2024; Arbefeville, 2024).

The loss of primary enzymatic markers such as lysine decarboxylase in *E. coli*, and citrate utilization and urease in *K. pneumoniae* presents a major challenge for diagnostic bacteriology. Standard identification algorithms rely on these core enzymatic reactions to differentiate enteric species (Dunn, 2023; Gupta et al., 2025). When lisinopril stress represses enzyme expression, commercial micro-substrate panels yield aberrant numerical profiles that fail to match standard reference databases, increasing the likelihood of diagnostic misidentification (Arbefeville, 2024).

The derepression of alternative carbohydrate utilization pathways (e.g., inositol, arabinose, raffinose) suggests that sub-inhibitory lisinopril exposure triggers metabolic remodeling. Non-antibiotic xenobiotics can perturb bacterial cell envelope transport systems and alter intracellular cAMP levels, releasing catabolite repression and activating silent sugar utilization operons (Heirali et al., 2023; Noto Guillen et al., 2024; Maier and Typas, 2024). These physiological

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adaptations enable bacterial survival in drug-rich environments but complicate routine phenotypic diagnostics.

From a clinical perspective, these findings underscore the vulnerabilities of relying solely on conventional biochemical testing when analyzing isolates from patients undergoing active pharmacotherapy (Verdegaal and Goodman, 2024). To mitigate misidentification risks, diagnostic laboratories should incorporate orthogonal testing platforms, such as MALDI-TOF MS mass spectrometry or 16S rRNA gene sequencing, when atypical biochemical profiles are encountered (Arbefeville, 2024; Gupta et al., 2025).

6. CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Sub-inhibitory lisinopril exposure induces significant, reproducible shifts in key enzymatic and carbohydrate fermentation profiles of *E. coli*, *K. pneumoniae*, and *S. Typhi* without altering 16S rRNA genotypic identity. These xenobiotic-induced phenotypic variations expose critical vulnerabilities in conventional biochemical identification systems, highlighting the necessity of modern, multi-modal diagnostic workflows.

6.2 Recommendations

Based on these findings, the following actions are recommended:

i. **Orthogonal Diagnostic Validation:** Clinical microbiology laboratories should establish protocols to confirm atypical biochemical test profiles using MALDI-TOF MS or molecular sequencing before issuing definitive diagnostic reports.
ii. **Xenobiotic Stress Awareness:** Diagnostic algorithms should account for patient pharmacotherapy, recognizing that non-antibiotic drugs can perturb bacterial phenotypes.
iii. **Database Expansion:** Manufacturers of commercial biochemical identification panels should update reference probability matrices to incorporate phenotypic variations induced by non-antibiotic pharmaceutical stress.

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