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REVIEW ARTICLE

Clinical Applications of Metabolomics: Advancing Insights into Bacterial Infections

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ABSTRACT

Metabolomics, the comprehensive analysis of small-molecule metabolites within biological systems, has emerged as a powerful analytical platform for advancing the diagnosis, prognosis, and management of infectious diseases. Leveraging high-throughput technologies such as mass spectrometry (MS) and nuclear magnetic resonance (NMR), metabolomics enables the identification of distinct metabolic fingerprints associated with infections, offering novel metabolomic insights host-pathogen interactions and disease pathophysiology. MS-based platforms, coupled with chromatographic techniques like gas chromatography (GC-MS) and liquid chromatography (LC-MS), provide exceptional sensitivity and specificity for metabolite detection in biofluids such as blood, urine, and cerebrospinal fluid (CSF). NMR spectroscopy complements these approaches by enabling non-destructive, reproducible analyses ideal for longitudinal studies and treatment monitoring. In infectious disease diagnostics, metabolomics has demonstrated the ability to differentiate bacterial, viral, and fungal infections through unique metabolic signatures. For example, bacterial sepsis is characterized by significant perturbations in lipid metabolism, including alterations in phospholipids and sphingolipids, which correlate with systemic inflammation and immune activation. Beyond diagnostics, metabolomics contributes to understanding antimicrobial resistance (AMR) by profiling metabolic reprogramming in resistant strains, revealing mechanisms such as increased efflux pump activity, biofilm formation, and membrane remodeling. These insights present potential therapeutic targets and inform personalized treatment strategies. The integration of metabolomics with genomics and proteomics further enhances diagnostic and prognostic accuracy. This review details metabolomics applications in sepsis, meningitis, tuberculosis (TB), respiratory tract infections (RTIs), UTIs, and *Helicobacter pylori (H. pylori)* infections, emphasizing its potential to revolutionize infection management while discussing current challenges and future directions.

Keywords: Metabolomic, Infectious, Antimicrobial resistance, Gas chromatography, Nuclear magnetic resonance.

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Introduction

Metabolomics, the comprehensive profiling of metabolites within biological systems, has emerged as a pivotal tool in clinical research, offering detailed insights into disease mechanisms, diagnosis, and therapeutic monitoring (1). By capturing dynamic metabolic shifts during infections, metabolomics provides a systems-level understanding of host-pathogen interactions and enables the identification of biomarkers critical for early diagnosis, prognosis, and treatment optimization (2).

Recent technological advancements in mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy, coupled with chromatographic methods such as gas chromatography (GC-MS) and liquid chromatography (LC-MS), have significantly enhanced analytical sensitivity and resolution, facilitating clinical application. These techniques enable precise quantification of metabolites in biofluids, including blood, urine, and cerebrospinal fluid (CSF)(3).

Infectious diseases ranging from urinary tract infections (UTIs) to life-threatening sepsis and meningitis pose significant diagnostic and therapeutic challenges. Conventional methods often lack the sensitivity, specificity, or rapid turnaround required for effective management (3, 4). Metabolomics addresses these limitations by identifying pathogen-specific metabolic fingerprints and host metabolic alterations. For instance, metabolic shifts in energy metabolism, amino acid pathways, and lipid profiles enable differentiation between bacterial, viral, and fungal infections, supporting more accurate diagnosis and pathogen identification. Furthermore, metabolomics plays a crucial role in detecting antimicrobial resistance (AMR), monitoring treatment response, and guiding personalized therapy (2, 3, 5).

Metabolomics also elucidates infection pathophysiology. In sepsis, for example, early metabolic disturbances in lactate levels, tricarboxylic acid (TCA) cycle intermediates, and lipid metabolism have been quantitatively linked to disease severity and progression. In meningitis, CSF metabolomics reveals elevated lactate and reduced glucose levels reflective of bacterial metabolism and immune response. Metabolomic signatures distinguish active tuberculosis (TB) from latent infection and predict therapeutic outcomes (6, 7). Additionally, metabolomics informs understanding of non-tuberculous mycobacterial (NTM) infections, respiratory tract infections (RTIs), and *Helicobacter pylori (H. pylori)*–associated gastric disease (8). Integration with other omics approaches, including genomics, proteomics, and transcriptomics, enhances diagnostic and prognostic utility (9). This review synthesizes current metabolomic applications in infectious disease diagnosis, highlighting sepsis, meningitis, and TB, RTI, UTI, and *H. pylori* infection. It also addresses implementation challenges, advocating for standardized protocols, cost-effective platforms, and collaborative research to fully realize metabolomics' clinical potential.

Metabolomic Profiling in Infection Diagnosis

Metabolomics enables biomarker discovery for infection diagnosis, prognosis, and treatment monitoring by comprehensive metabolite analysis (1, 10). Metabolomic studies have revealed candidate biomarkers with potential utility in the early diagnosis and prognosis of bacterial infections (Table 1).

Advances in high-throughput technologies, particularly MS and NMR, have improved the resolution, sensitivity, and clinical applicability of metabolomic profiling (11). MS, often coupled with GC-MS or LC-MS, offers high sensitivity and specificity for metabolite detection in biofluids such as CSF, blood, and urine (12). NMR spectroscopy provides non-destructive, reproducible metabolite profiling with minimal sample preparation, ideal for longitudinal monitoring of disease progression and therapeutic response (13) (Figure 1).

Metabolomic studies employ targeted and untargeted approaches to maximize biomarker discovery and clinical translation. Targeted metabolomics quantifies predefined metabolites (e.g., glucose, lactate) and facilitates clinical validation. Untargeted metabolomics surveys the metabolome broadly, uncovering novel metabolic pathways and biomarkers for further exploration (14). One notable application of metabolomics is in infectious diseases, where it elucidates host-pathogen metabolic

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interactions and reprogramming during infection. Numerous studies have demonstrated metabolomics' ability to identify specific metabolic fingerprints associated with bacterial infections (15). These fingerprints reflect dynamic reprogramming of metabolic pathways in both host and pathogen, driven by immune responses and microbial survival strategies (14). Lipidomic analyses reveal that bacterial sepsis significantly alters lipid profiles particularly phospholipids and sphingolipids with changes correlating to systemic inflammation and endothelial dysfunction (16, 17). Specific phosphatidylcholine and sphingomyelin species decrease by 30–50% during septic shock. Such metabolic signatures not only aid infection diagnosis but also differentiate bacterial infections from viral or fungal ones, providing critical insights into pathogen-specific adaptations (4). Metabolomic profiling further enables detection of AMR by identifying metabolic markers characteristic of resistant bacterial strains (9).

Elevated levels of metabolites linked to efflux pump activity or biofilm production have been correlated with multidrug-resistant phenotypes. Monitoring metabolite changes during antimicrobial therapy also allows real-time assessment of treatment response (18), supporting personalized medicine through adaptive antibiotic regimens (14). Moreover, combining metabolomics with genomics, transcriptomics, and proteomics enhances diagnostic accuracy and comprehensiveness (19).

Table 1. A list of metabolites found in bacterial Infection using metabolomics.

Bacterial Infection	UTI	Tuberculosis			Clostridium difficile Infection	
Clinical sample	Plasma	Serum	Serum	Sputum	Stool	Stool
Analytical approaches	Capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS)	'H-NMR	'H-NMR	GC-MS	LC-MS	UPLC-MS
Metabolic biomarkers for diagnosis	Glutamate; Arginine, Asparagine, Inosine monophosphate, Citrulline and Glutamine	Alanine, Lysine, Glutamate, Glutamine, Citrate and Choline	Sugars and Sugar-Related: Glucose, Mannose, Fucose Amino Acids and Derivatives: Glutamate, Aspartate, Serine, Valine, Ornithine, 2-Aminobutyrate Energy Metabolism Intermediates: Lactate Purine Metabolites: Hypoxanthine, Inosine; Citrate, 3-Hydroxybutyrate, 3-Hydroxylsobutyrate, Asparagine, Methionine, Threonine, Cysteine, Creatine, 2-Fructose	Fatty acids (nonadecanoic acid, oleic acid, sebacic acid, C17:1ω7c), Carbohydrates (glucosamine, N-acetylglucosamine, 2-deoxyerythro-pentitol, glucopyranose, mannopyranose, gluconic acid & lactone), and other compounds (citramalic acid, glutaric acid, ethane, butanal, γ-aminobutyric acid, 3,4-dihydroxybutanoic acid).	Cholate and Chenodeoxycholate; Litocholate and Deoxycholate	Sphingosine, Chenodeoxycholic acid, Phenylalanine, Lysophosphatidylcholine (C16:0) and Propylene glycol stearate; Fatty amide, Glycochenodeoxycholic acid, Tyrosine, Linoleyl Carnitine, and Sphingomyelin
References	(20)	(21)	(22)	(23)	(24)	(25)

Black font:increase; red font:decrease

NMR: nuclear magnetic resonance; GC-MS: Gas Chromatography Mass Spectrometry; LC-MS: Liquid chromatography-mass-spectrometry; UPLC-MS: ultra-performance liquid chromatography-tandem mass spectrometry.

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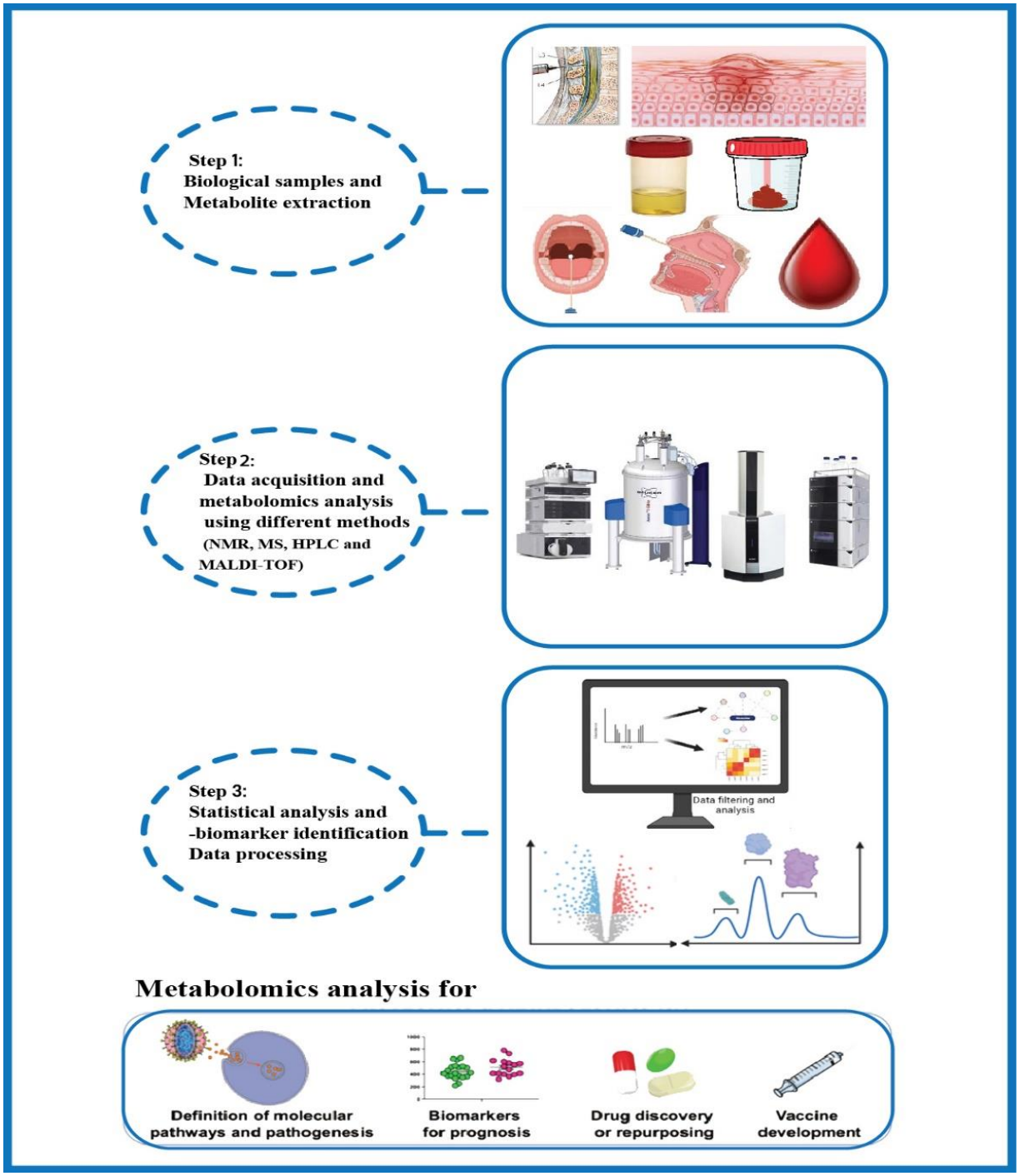

Figure 1. Schematic of key process in metabolomics analysis workflow

One notable application of metabolomics is in infectious diseases, where it elucidates host-pathogen metabolic interactions and reprogramming during infection. Numerous studies have demonstrated metabolomics' ability to identify specific metabolic fingerprints associated with bacterial infections (15). These fingerprints reflect dynamic reprogramming of metabolic pathways in both host and pathogen, driven by immune responses and microbial survival strategies (14).

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Clinical Applications of Metabolomics in Sepsis

Metabolomics shows promise for early sepsis detection, addressing a critical clinical challenge. Metabolic profiling can detect perturbations up to 24–48 hours before clinical signs emerge. Key altered pathways include energy metabolism (e.g., lactate increase by 2- to 3-fold), amino acid metabolism, and lipid metabolism (26). Changes in lactate and TCA cycle intermediates quantitatively reflect impaired tissue perfusion and cellular energetics preceding organ dysfunction (27). Distinct metabolic phenotypes associate with sepsis severity and mortality risk, enabling patient stratification (28).

Elevated acylcarnitines and disrupted tryptophan metabolism (e.g., kynurenine-to-tryptophan ratio increase by 40%) link to immune activation during bacterial infection (29-31). Such signatures facilitate earlier, targeted interventions. Wang et al. applied LC/MS-based metabolomics to analyze the metabolic profile of *E. coli* isolated from patients' blood. Over 70 differential metabolites were identified between septic and non-septic patients, indicating that *E. coli* metabolites may play a role in the onset and progression of sepsis.

The summary of metabolites and their clinical correlations is shown in Table 2 (32).

Table 2. Summary of Metabolites and Their Clinical Correlations in Sepsis.

Metabolite	Associated Clinical Indicator	Correlation (p<0.01)
Natamycin, Tyramine, D-Tagatose, Tryptophol, Glycerophosphocholine, 5-Hydroxy-L-tryptophan, Hypoxanthine, Uracil	SOFA, APACHE II, Creatinine	Positive
L-Glutamic Acid, Sucrose, Glycerol, D-biotin, D-Mannose, Indole, D-Ornithine, 5-Hydroxy-L-tryptophan, Glycerophosphocholine, Tyramine	C-reactive protein (CRP)	Positive
5-Hydroxy-L-tryptophan	Body temperature	Positive
Indole, 3-Hydroxypropanal	Red blood cell count	Positive
Glycerol, D-biotin, D-Mannose, D-Ornithine, 3-Hydroxypropanal	Platelet count	Positive
L-Glutamic Acid, Glycerol, 3-Hydroxypropanal	Aspartate aminotransferase (AST)	Positive
Glycerol, 4-Hydroxybenzaldehyde, Glycerophosphocholine, Natamycin	Coagulation function	Positive
Sucrose, D-Biotin, D-Ornithine	Lactic acid	Positive

Proteomic and metabolomic analyses revealed that elevated bacterial levels of malate, citrate, pectinesterase (YbhC), coenzyme Q10, glutamate transport proteins, and regulatory systems including PhoP, CpxR, NarL, and the ferrienterobactin receptor FepA may contribute to sepsis.

These UPEC-derived metabolites, proteins, and genetic regulators could serve as potential biomarkers for assessing sepsis risk (33). Tracking metabolic responses allows clinicians to monitor therapeutic efficacy dynamically and tailor treatments (4, 34). Metabolomic profiles also identify patient subgroups most likely to benefit from specific therapies, enhancing precision medicine (35, 36).

Despite progress, clinical implementation faces challenges including the need for protocol standardization, reduced analysis time and costs, and user-friendly data interpretation tools. Large multicenter validation studies are required to confirm biomarker robustness across populations and settings (36, 37).

Metabolomics in Meningitis

Meningitis, a severe condition with high mortality and morbidity, poses diagnostic challenges. Metabolomic analysis of CSF and biofluids via MS and NMR elucidates host-pathogen interactions, disease mechanisms, and differential diagnosis (38, 39). Elevated CSF lactate (often >3 mmol/L) and reduced glucose levels (below 2.2 mmol/L) reliably indicate bacterial meningitis, reflecting bacterial metabolism and immune activation (12, 40, 41). Alterations in

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amino acids such as increased glutamine and decreased tryptophan correlate with inflammation and neuronal injury (42). Viral meningitis exhibits distinct metabolomic profiles, including changes in nucleoside metabolism and oxidative stress markers, allowing differentiation from bacterial etiologies (43).

Advanced neurolipidomics identify lipid metabolites such as carnitine and phospholipids as potential diagnostic and therapeutic targets (44). Longitudinal CSF metabolomics tracks treatment responses, with normalization of lactate and other metabolites paralleling antibiotic efficacy and improved outcomes (44, 45). Persistent metabolic abnormalities, such as elevated kynurenine and lactic acid, characterize tuberculosis meningitis (TBM), despite therapy, highlighting the need for host-directed interventions (46). Collaborations among institutions such as Radboud University Medical Center, Oxford University, and The Broad Institute have produced multi-omics models, including an 18-protein LASSO regression classifier distinguishing bacterial and viral meningitis with >90% sensitivity and specificity (47, 48).

Metabolomics in TB

Conventional TB diagnostics are limited by sensitivity, specificity, and slow turnaround. Metabolomics identifies distinct plasma signatures, especially in tryptophan and glutamine metabolism, distinguishing active TB from latent infection with accuracies above 85% (49, 50). Treatment response assessment currently relies on culture conversion after weeks, but metabolomics detects early biochemical changes signaling successful therapy (45). This enables identification of patients at risk of treatment failure or relapse for personalized management (51).

Metabolomics reveals metabolic adaptations in drug-resistant TB strains, uncovering pathways implicated in resistance and suggesting novel drug targets. It also predicts drug susceptibility patterns, informing tailored therapy (7, 49). Host-pathogen metabolic interplay shows *Mycobacterium tuberculosis* (*M. tuberculosis*) alters host nutrient usage and metabolic pathways to facilitate persistence.

In pediatric TB, metabolomic profiling of urine and plasma offers non-invasive diagnostic and monitoring tools overcoming sample collection challenges. Additionally, metabolomics clarifies metabolic alterations due to HIV co-infection and diabetes, aiding management of these complicated cases (52). Recent studies have highlighted the potential of urine metabolites as diagnostic biomarkers for pulmonary tuberculosis (PTB). Using UHPLC-MS/MS, they screened urine from PTB, lung cancer (LCA), community-acquired pneumonia (CAP), and healthy controls (HCs), identifying five differentially abundant metabolites (DAMs) per group with AUC $\geq$ 0.71 and $p < 0.01$. A combined biosignature of these metabolites effectively distinguished PTB from CAP, LCA, and HCs. These DAMs, primarily by-products of amino acid, nucleotide, and lipid metabolism, reflect oxidative stress and inflammation, supporting non-invasive, high-accuracy PTB diagnosis through metabolomic profiling (53, 54).

Metabolomics in NTM Pulmonary Disease

NTM infections are rising, especially among immunocompromised and patients with lung diseases. Metabolomics differentiates NTM pulmonary disease from other respiratory conditions, a diagnostic challenge (55). Distinct metabolic profiles in sputum, blood, and bronchoalveolar lavage fluid correlate with infections by *Mycobacterium avium* complex and *Mycobacterium abscessus*, offering faster and more accurate diagnostics than culture (56). Serum metabolomics highlights disease-specific metabolic pathways and host-microbe interactions (55). Metabolomics also elucidates AMR mechanisms in NTM strains, identifying pathways contributing to drug resistance (57). Furthermore, studies link metabolic adaptations with risk factors such as lung disease, immune status, and environmental exposures, facilitating risk stratification and prevention (58).

Metabolomics in RTIs

RTIs, including pneumonia and bronchitis, contribute substantially to global morbidity and mortality, particularly in vulnerable groups. Community-acquired pneumonia (CAP) has been extensively studied via metabolomics, revealing pathogen-specific host metabolic signatures. For example, infections with *Streptococcus pneumonia* and *Mycoplasma pneumoniae* show distinct metabolite alterations, supporting targeted therapy (59). Moreover, metabolomic profiling has revealed systemic metabolic disruptions in severe RTIs, such as sepsis secondary to pneumonia, which can aid in risk stratification and prognosis (60, 61). In severe RTIs,

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including sepsis secondary to pneumonia, metabolomic profiling has uncovered systemic metabolic disruptions, such as altered levels of energy metabolism intermediates like lactate and citrate, indicative of mitochondrial dysfunction and hypoxic stress. Additionally, changes in lipid metabolites, such as lysophosphatidylcholines (LPCs), have been associated with inflammation and immune modulation (62).Research has shown that LPC levels decrease during acute stages of CAP, with evidence suggesting a potential protective role against pneumonia development.

The dynamic nature of LPC concentration changes has been proposed as a more stable biomarker compared to traditional inflammatory markers such as IL-6 and C-reactive protein (CRP) (63). Microbiome-metabolome interactions are crucial in RTIs. CAP patients display significantly reduced microbial diversity in lower respiratory tracts, with increased Gammaproteobacteria and decreased Bacilli, Bacteroidia, and Actinobacteria (64, 65). These compositional shifts correlate with altered lipid metabolism (65). Specific metabolites such as oleic acid and dimethyldisulfide, alongside LPC and phosphatidic acid, show high diagnostic accuracy for CAP (58). Certain bacterial genera (e.g., *Moraxella*, *Fusobacterium*, *Lautropia*, *Neisseria*) correlate strongly with these metabolites, highlighting the potential for integrated metabolomic and microbiome diagnostics (65).

Tristán et al. developed metabolite-based panels for COVID-19 management. A diagnostic panel of isoleucine, TMAO, and glucose distinguished patients from healthy individuals with high accuracy (AUC = 0.91, sensitivity 86%, specificity 84%). For disease severity, combining clinical factors (obesity, dyslipidemia, lymphocyte count) with metabolites (ethanol, TMAO, tyrosine, betaine) improved classification (AUC = 0.825, sensitivity 85%, specificity 72%), emphasizing the benefit of integrating clinical and metabolic data (66).

Metabolomics in UTIs

Traditional culture-based UTI diagnostics require 24–48 hours, whereas metabolomics enables rapid pathogen identification and antimicrobial susceptibility profiling through distinct metabolic signatures, potentially reducing diagnosis time to hours (5, 67). Quantitative metabolomics can also detect polymicrobial infections and estimate bacterial load by measuring metabolite concentrations (68, 69). Host response monitoring via metabolomics identifies inflammatory markers, immune-related metabolites, and indicators of tissue damage, facilitating assessment of infection severity (14).

Several urinary biomarkers have been proposed for UTIs, including trimethylamine (TMA) and acetic acid; TMA derives from microbial reduction of trimethylamine N-oxide (TMAO) in the bladder and serves as a robust marker of bacterial metabolic activity(5, 70). *E. coli*, responsible for most UTIs, utilizes glycolysis and the TCA cycle to metabolize amino acids and peptides for growth within the urinary tract. UPEC utilizes L-serine dehydratase to catabolize urinary L-serine into pyruvate and ammonium, which subsequently serve as sources of carbon and nitrogen to support bacterial metabolism (68, 71, 72).

Metabolomic analyses have identified metabolites linked to virulence factors, such as iron carrier biosynthesis, that distinguish UPEC from non-pathogenic strains, underscoring metabolomics' potential in diagnostics and pathogen biology understanding. In TBM, a related metabolomics study revealed gut microbiota disruption with eight urinary metabolites, including 2-methylbutyrlglycine and 4-hydroxyhippuric acid, linked to gut dysbiosis and inflammation in pediatric patients, suggesting novel biomarkers for TBM-associated gut alterations (73).

Clinical application of metabolomics in UTI management necessitates standardization of sample collection, processing protocols, and quality control, alongside optimized data analysis workflows (74). For pediatric populations, metabolomics provides non-invasive early detection tools, reducing reliance on invasive sampling (75).

In elderly patients, metabolomic profiling aids in complex UTI presentations and comorbidity assessment (76). An untargeted metabolomics analysis of clinical samples from patients with suspected UTIs identified agmatine and N6-methyladenine as reliable predictors of culture-positive cases. Using a rapid 3.2-minute LC–MS assay, these metabolites accurately detected UTIs caused by 13 Enterobacterales and 3 non-Enterobacterales species, representing over 90% of infections (agmatine AUC > 0.95; N6-methyladenine AUC > 0.89). The consistent diagnostic performance of agmatine across four independent cohorts indicated its strong potential as a clinical

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biomarker for Enterobacterales infections (77, 78) (Table 3).

Metabolomics in *H. pylori* Infections

Chronic *H. pylori* infection is a leading cause of non-cardia gastric cancer, but the metabolic mechanisms linking infection to carcinogenesis remain partially understood (79, 80). Metabolomics reveals distinct metabolic signatures in *H. pylori*-positive gastric carcinogenesis, including altered metabolic scores derived from transcriptomic and principal component analyses correlating with clinical outcomes and immune phenotypes (8, 81, 82). Key metabolism-related genes such as *GSS*, *GMPPA*, *OGDH*, *SGPP2*, and *PIK3CA* have been implicated in these metabolic alterations, affecting patient survival and therapeutic response. Untargeted metabolomics highlights pathways involving carbohydrate metabolism and the citric acid cycle as potential regulators (79, 83).

Regional metabolomic variations within gastric tissue reflect infection dynamics: organic acids increase during active infection, whereas amino acids and sugars decrease during and post-infection (81, 84). These metabolite shifts correlate quantitatively with disease severity and progression, contributing to gastritis, peptic ulcers, and gastric cancer development (85, 86).

Table 3. Summary of bacteria-specific metabolic pathways in UTIs.

Bacterium	Substrate Used	Enzyme/Pathway	Final Product
Pseudomonas aeruginosa	Nicotinic acid	Hydrolytic reaction	6-hydroxynicotinic acid
Klebsiella pneumoniae	Glycerol	glycerol dehydrogenase (gly DH-1)	1,3-Propanediol
Escherichia coli	Lactose	Glycolytic pathway	Lactate
Proteus mirabilis	Methionine	Oxidative deamination	MOBA (Methionine-derived compound)

**P. aeruginosa* converts nicotinic acid to 6-hydroxynicotinic acid (6-OHNA) via dehydrogenation. *K. pneumoniae*: Glycerol is metabolized through oxidative and reductive routes, producing dihydroxyacetone phosphate (DHAP) and 1,3-propanediol (1,3-PD), respectively. *E. coli:* Lactose is hydrolyzed by β-galactosidase into glucose and galactose and further converted to lactate through the Embden–Meyerhof–Parnas (EMP) pathway under oxygen-limited conditions. *P. mirabilis* metabolizes methionine to methional (MOBA) via oxidative deamination.

Metabolomic Insights into Antibiotic Resistance

Antibiotic resistance poses a major global health challenge requiring innovative molecular understanding (87, 88). Integrative *omics* approaches including genomics, transcriptomics, proteomics, and metabolomics generate large-scale data that elucidate the molecular mechanisms underlying antimicrobial resistance AMR. Metabolomics captures dynamic metabolic adaptations in resistant bacteria, revealing how pathogens reprogram central carbon metabolism to meet energy demands of resistance mechanisms such as efflux pumps, which actively expel antibiotics (89, 90). Alterations in amino acid and nucleotide metabolism further promote biofilm formation and stress responses essential for resistance. Lipidomic analyses demonstrate changes in membrane phospholipids and fatty acids that enhance rigidity and reduce antibiotic permeability (52).

Elevated metabolites like polyamines and specific short-chain fatty acids serve as markers of resistance in pathogens such as *E. coli* and *Klebsiella pneumoniae(91).* Metabolomics also elucidates resistance in polymicrobial infections, where microbial community interactions modulate virulence and resistance(92). Ramzan *et al.* demonstrated that chemometric analysis identified eleven metabolites significantly linked ($p < 0.05$) to antibiotic resistance in *A. baumannii* isolates. Among them, pyochelin and L-serine levels showed a stepwise increase corresponding to higher MIC values of ciprofloxacin and cefixime, respectively. These findings highlight a clear metabolic correlation with resistance patterns in *A. baumannii*, suggesting that specific metabolites could serve as promising targets or biomarkers for developing novel therapeutic approaches against multidrug-resistant strains (78).

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Dixon et al. investigated metabolic differences between carbapenemase-producing Enterobacterales (CPE) and non-CPE isolates, based on the link between cellular phenotype and metabolome. Their analysis revealed distinct alterations in pathways such as arginine and purine metabolism, ABC transporters, and biofilm formation, offering insight into resistance mechanisms. Moreover, metabolite biomarkers enabled discrimination between CPE and non-CPE within seven hours, suggesting potential for rapid diagnostic development (93).

Mass spectrometry techniques offer rapid, sensitive, and early detection of AMR both on proteomics and metabolomics levels. A recent study examined how bacterial growth rate and metabolic state influence antibiotic lethality, indicating that low metabolic activity underlies antibiotic tolerance. Modulating bacterial metabolism may therefore restore susceptibility in tolerant cells (Figure 2) (94). In examining metabolite patterns associated with antibiotic resistance, several main trends of metabolite increase or decrease have been observed. Increased levels of glycine and TMAO are frequently reported under antibiotic stress and appear to contribute to protein stabilization, osmotic stress regulation, and adjustment of antibiotic susceptibility.

Additionally, acetone, sarcosine, N-acetylcysteine, and 3-hydroxybutyrate are among the metabolites that typically increase and may participate in oxidative stress management, energy supply, and modulation of cell-wall structure.In contrast, reductions in betaine and imidazole indicate cellular utilization of osmoprotective resources and disruption of pathways related to cell-wall structure or nucleotide synthesis.

Furthermore, higher levels of creatinine and trimethylamine derivatives suggest alternative metabolic pathways that support survival under drug pressure. Overall, increased metabolites associated with osmoprotection and oxidative stress, alongside decreased resources for cell-wall integrity and nitrogen balance, provide an integrated picture of metabolic adaptation and survival under sub-inhibitory antibiotic concentrations (Table 4) (95).

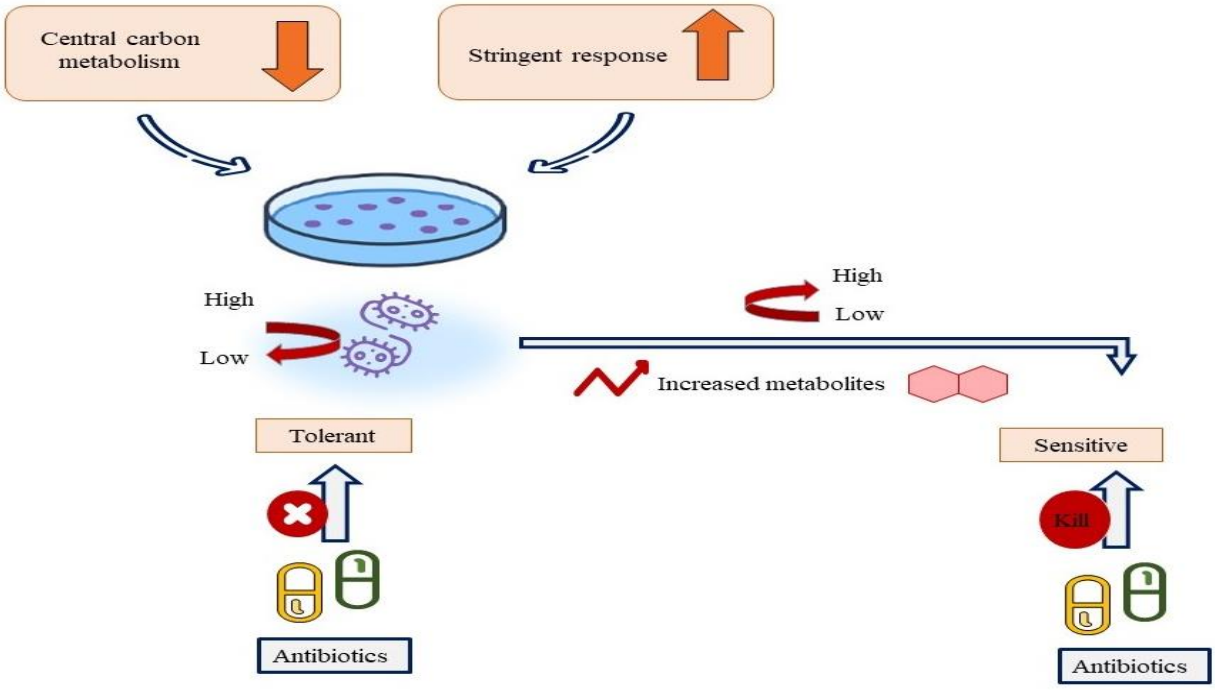

Figure 2. Enhanced bacterial metabolism can reverse antibiotic tolerance. Suppression of central carbon metabolism and activation of the stringent response inhibit bacterial metabolic activity, promoting tolerance. Supplementation with specific exogenous metabolites restores metabolic activity in tolerant cells, converting them into metabolically active bacteria and re-establishing susceptibility to antibiotic killing.

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Table 4. Summary of Metabolite Changes Linked to Antibiotic Resistance.

Metabolite	Trend (↑/↓)	Potential Functional Role
Glycine	↑	Osmoprotection, protein stabilization, modulation of susceptibility
TMAO	↑	Osmoprotection, protein stabilization, altered antibiotic sensitivity
Acetone	↑	Stress-induced energy metabolism
Sarcosine	↑	Oxidative stress handling, metabolic adaptation
N-Acetylcysteine	↑	Antioxidant defense, redox balance
3-Hydroxybutyrate	↑	Alternative energy source, stress signaling
Creatinine	↑	Influence on DNA replication under stress
Trimethylamine derivatives (TMA/TMAO)	↑	Nitrogen metabolism, stress adaptation
Betaine	↓	Osmoprotectant depletion, carbon/nitrogen utilization
Imidazole	↓	Disrupted nucleotide-related pathways, stress sensitivity

Biofilm formation is closely associated with extensive metabolic reprogramming. Compared to planktonic cells, biofilms show altered glycolysis, TCA cycle activity, and membrane-related metabolism. Key metabolites and signaling molecules, such as c-di-GMP, promote matrix production and biofilm persistence, while glycolytic enzymes (e.g., GAPDH) and TCA intermediates support early biofilm development. Additionally, metabolites like glucose-6-phosphate enhance polysaccharide synthesis through regulatory proteins, leading to stronger biofilm structure. Overall, metabolomic changes drive biofilm formation, improve stress tolerance, and represent potential targets for anti-biofilm strategies(96).

Discussion

Metabolomics is positioned to transform AMR management by providing tools for diagnosis, monitoring, and drug development. Continued technological advances, interdisciplinary collaboration, and translational research focus will enable metabolomics to address this critical global health threat more effectively.

Rapid, point-of-care diagnostic tools based on metabolic biomarkers could provide clinicians with timely resistance profiles, guiding targeted therapies and reducing inappropriate broad-spectrum antibiotic use. Metabolomics can also identify unique metabolic vulnerabilities in resistant pathogens, facilitating novel antimicrobial agent discovery targeting essential survival pathways. Multi-omics integration combining metabolomics with genomics, proteomics, and transcriptomics offers holistic insights into resistance by capturing genetic, protein, and metabolic interplay. Advances in ML and bioinformatics will accelerate pattern discovery and predictive modeling for resistance evolution and treatment outcomes.

Recently, metabolomics has played a larger role in dissecting host–microbiome metabolic dynamics, largely via the use of isotope tracing experiments. Isotope tracing approaches track the flow of stable isotope-labeled nutrients (typically 13C, 15N or 2H) through microbial communities and their exchange with the host. This strategy has been used to identify

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microbe-specific biomarkers, demonstrate nutrient exchange from microbes to the host, and reveal syntrophic relationships among microbes. Such methodologies provide a practical framework to distinguish microbial and host metabolic signatures in complex systems (97) . In addition, it is important to note that a lack of standardized workflows in clinical metabolomics remains a major practical limitation. Variability across sample handling, analytical procedures, quality control practices, and data processing can impede internal validity and reproducibility. Given the increasing logistical, instrumental, and computational demands of metabolic phenotyping, the development of harmonized guidelines, robust quality assurance frameworks, and automated data-mining strategies is urgently needed to ensure reliable translation of metabolomic findings into clinical infectious disease research. Overcoming these challenges requires coordinated efforts among researchers, clinicians, and policymakers to build infrastructure, promote training, and foster innovation.

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