



Anaplasmosis in Animals- Advances in Molecular Epidemiology, Pathogenesis, Diagnostics and Integrated One Health Control Strategies: A Review

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ABSTRACT

Anaplasmosis is an important tick-borne disease affecting livestock, companion animals, wildlife and humans worldwide. The disease is caused by obligate intracellular bacteria of the genus *Anaplasma*, which infect different hematopoietic cells and produce diverse clinical manifestations depending on the host species, pathogen strain, immune status and environmental conditions. In recent years, the epidemiology of anaplasmosis has evolved considerably because of climate change, expansion of tick vectors, increasing animal movement, emergence of novel *Anaplasma* species and growing zoonotic concerns. Advances in molecular epidemiology, genomics and diagnostic technologies have improved understanding of pathogen diversity, host-pathogen interactions and disease transmission dynamics. This review critically synthesizes recent advances in the epidemiology, genomics, pathogenesis, diagnostics, therapeutics, vaccine development and integrated one health control strategies of anaplasmosis in animals. Recent molecular studies have revealed substantial genetic diversity among circulating *Anaplasma* isolates and highlighted the emergence of zoonotic species such as *Anaplasma phagocytophilum* and *Anaplasma capra*. The pathogenesis of anaplasmosis involves sophisticated immune evasion mechanisms including antigenic variation, intracellular persistence, apoptosis inhibition and modulation of host immune signaling pathways. Molecular diagnostics such as polymerase chain reaction and next-generation sequencing have improved detection sensitivity, limitations remain in field applicability and carrier-state detection. Therapeutic management continues to rely primarily on tetracyclines; however, persistent carrier states, antimicrobial resistance concerns and incomplete pathogen clearance remain major challenges. Integrated control strategies involving vector management, vaccination, surveillance, biosecurity and climate-resilient approaches are essential for sustainable disease control. Anaplasmosis remains a major constraint to livestock productivity and public health globally. Future control will depend on integrated multidisciplinary approaches combining molecular surveillance, precision diagnostics, vaccine innovation, vector ecology and One Health policy frameworks to address the evolving epidemiology of this economically and zoonotically important disease.

Key words: *Anaplasma*, Antimicrobial resistance, Diagnostics, Genomics, Molecular epidemiology, One health, Pathogenesis, Vector control.

Anaplasmosis is one of the most important tick-borne diseases affecting domestic animals, wildlife and humans worldwide (Kumar *et al.*, 2023a; Ierardi *et al.*, 2025). The disease is caused by bacteria of the genus *Anaplasma*, members of the family Anaplasmataceae, which are obligate intracellular pathogens that infect haematopoietic cells (Rikihisa, 2011). The disease causes substantial economic losses in livestock production systems because of reduced milk yield, weight loss, reproductive inefficiency, treatment costs, mortality and restrictions on animal trade (Ierardi *et al.*, 2025). Bovine anaplasmosis caused by *Anaplasma marginale* is particularly important in tropical and subtropical regions where tick infestation is common and vector populations remain active throughout the year. The global significance of anaplasmosis has increased considerably during the last decade because of several interrelated ecological, epidemiological and socioeconomic factors. Climate change has facilitated the expansion of tick vectors into previously non-endemic regions, thereby increasing disease transmission risk (Maharana *et al.*, 2016; Huang *et al.*, 2025). Intensification of livestock production systems, unrestricted movement of animals, wildlife-livestock

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interactions and inadequate vector control practices have further contributed to the emergence and persistence of the disease (Babu *et al.*, 2025). In addition, increasing reports of zoonotic *Anaplasma* species such as *A. phagocytophilum* and *A. capra* have expanded the public health relevance of anaplasmosis under the One Health framework (Acosta-Espana *et al.*, 2025). Although several review articles have previously discussed the epidemiology, diagnosis, or control of anaplasmosis, recent advances in molecular epidemiology, genomics, host-pathogen interactions, immune evasion mechanisms and integrated one health surveillance have substantially transformed the understanding of the disease. Furthermore, increasing concerns regarding antimicrobial resistance, acaricide resistance, vaccine limitations and emerging zoonotic infections necessitate an updated and critical synthesis of current evidence. Therefore, the present review integrates recent developments in genomics, molecular diagnostics, pathogenesis, therapeutics, vaccine research, vector ecology and one health control strategies across multiple host species, with particular emphasis on recent findings from India and tropical production systems.

Etiology and taxonomy

The genus *Anaplasma* comprises gram-negative, obligate intracellular bacteria belonging to the order *Rickettsiales* and family *Anaplasmataceae*. These organisms are characterized by their ability to infect blood cells and survive within membrane-bound intracellular vacuoles known as morulae (Rikihisa, 2011; Reller and Dumler, 2015). Unlike many gram-negative bacteria, *Anaplasma* species lack classical peptidoglycan and lipopolysaccharide structures, which contributes significantly to their ability to evade host immune responses and persist intracellularly. Several *Anaplasma* species possess important veterinary and zoonotic significance. *Anaplasma marginale* primarily infects erythrocytes in cattle and is responsible for bovine anaplasmosis. *Anaplasma ovis* infects sheep and goats, whereas *Anaplasma phagocytophilum* targets neutrophils and causes granulocytic anaplasmosis in animals and humans (Ierardi *et al.*, 2025). *Anaplasma platys* infects canine platelets and produces cyclic thrombocytopenia in dogs (Gospodinova *et al.*, 2024). Emerging species such as *Anaplasma capra* have further complicated the taxonomy and epidemiology of the genus (Altay *et al.*, 2024).

Recent advances in molecular taxonomy and phylogenomics have improved understanding of species diversity and evolutionary relationships within the genus. Molecular markers including 16S rRNA, *groEL*, *gltA*, *msp1α* and *msp4* genes are widely used for species identification and phylogenetic analysis (Kumar *et al.*, 2023b; Bisen *et al.*, 2023). Whole-genome sequencing studies have revealed substantial genetic diversity among field isolates and suggested regional adaptation, host-associated evolution and emergence of genetically distinct strains with potential epidemiological significance. Phylogenomic studies have also demonstrated considerable antigenic variability

among circulating isolates, particularly within major surface proteins MSP2 and MSP3.

Molecular epidemiology and genomics

Global epidemiology

Anaplasmosis is widely distributed throughout tropical, subtropical and temperate regions of the world. The prevalence of infection is strongly influenced by the distribution of competent tick vectors, environmental conditions, host density and management practices (Mauri *et al.*, 2025). Regions characterized by warm temperatures and high humidity favor tick survival and therefore experience greater disease prevalence. The epidemiology of anaplasmosis has changed considerably in recent years because of climate-driven expansion of tick populations. Tick species such as *Rhipicephalus microplus*, *Dermacentor* spp. and *Ixodes* spp. have expanded into new ecological zones, increasing transmission risk in previously non-endemic regions. Ecological disturbances, deforestation, wildlife migration and changing agricultural practices have also contributed to altered vector dynamics.

Epidemiology in India

India represents one of the major endemic regions for bovine anaplasmosis because of favorable climatic conditions for tick survival and widespread livestock farming systems. Studies from Northern India, particularly Uttar Pradesh, Haryana, Rajasthan and Punjab, have reported significant prevalence of *Anaplasma* infection in cattle and buffaloes (Paramanandham *et al.*, 2019). Recent molecular epidemiological studies from Western Uttar Pradesh demonstrated considerable prevalence of bovine anaplasmosis associated with breed susceptibility, seasonal tick abundance and farm management practices. Indigenous breeds generally exhibit greater resistance compared with crossbred animals, which are more susceptible to severe clinical disease. Poor tick control, inadequate biosecurity and intensive farming systems further contribute to disease persistence in endemic areas (Atif, 2016; Kumar *et al.*, 2023; Gong *et al.*, 2025).

Molecular epidemiology

Molecular epidemiology has substantially improved understanding of strain diversity and transmission dynamics of *Anaplasma* spp. Polymerase chain reaction-based genotyping and sequencing approaches have revealed extensive diversity among circulating isolates. MSP1α genotyping has been particularly useful for studying strain variation and epidemiological linkage among outbreaks. Phylogeographic studies indicate that genetically diverse *Anaplasma* strains circulate simultaneously within endemic regions, contributing to reinfection, persistent carrier states and vaccine challenges (Kumar *et al.*, 2021).

Genomics and evolutionary adaptation

Recent genomic studies have provided important insights into pathogen adaptation, virulence and host specificity. Whole-genome sequencing has identified genes associated

with intracellular survival, antigenic variation, secretion systems and immune modulation. Comparative genomics suggests that selective evolutionary pressure exerted by both vertebrate hosts and tick vectors contributes significantly to genomic diversification. Transcriptomic and proteomic analyses have further revealed differential expression of virulence-associated proteins during host infection and vector transmission.

Host-pathogen interactions and pathogenesis

The pathogenesis of anaplasmosis involves complex interactions between the pathogen, host immune system and tick vector. Infection typically begins when an infected tick introduces *Anaplasma* organisms into the bloodstream during feeding. Tick saliva contains immunomodulatory molecules that facilitate pathogen establishment by suppressing local immune responses and inflammation. Following entry into the host, *Anaplasma* organisms invade target cells and replicate within membrane-bound intracellular vacuoles. The organisms manipulate host cellular pathways to establish a favorable intracellular environment. Intracellular survival involves inhibition of phagolysosomal fusion, alteration of host gene expression, nutrient acquisition and prevention of programmed cell death (Fig 1). One of the most important pathogenic mechanisms employed by *Anaplasma* spp. is antigenic variation. Major surface proteins, particularly MSP2 and MSP3, undergo continuous genetic variation, allowing the pathogen to evade host immune recognition (Severo *et al.*, 2012; Alberdi *et al.*, 2016). This sequential antigenic switching contributes significantly to persistent infection, chronic carrier states and failure of sterilizing immunity.

In addition to antigenic variation, *Anaplasma* organisms interfere with innate immune responses by

suppressing oxidative burst activity and modulating cytokine production (Rana *et al.*, 2023). *A. phagocytophilum* specifically targets neutrophils and disrupts their antimicrobial functions, thereby impairing host defense mechanisms. The pathogen also manipulates apoptosis signaling pathways to prolong survival of infected cells and maintain intracellular replication niches. The infection produces significant hematological and biochemical alterations including anemia, leukopenia, thrombocytopenia, oxidative stress and inflammatory tissue injury. In bovine anaplasmosis, destruction of infected erythrocytes by the reticuloendothelial system results in severe hemolytic anemia, jaundice, hypoxia and reduced productivity. Persistent carrier states represent one of the major epidemiological challenges associated with anaplasmosis.

Species-specific manifestations

Bovine anaplasmosis

Bovine anaplasmosis caused primarily by *A. marginale* is characterized by fever, progressive anemia, icterus, weakness, weight loss, abortion and decreased milk production (Kumar *et al.*, 2015; Das *et al.*, 2022). Adult cattle are generally more susceptible to severe disease compared with younger animals, which often develop mild or subclinical infections (Ierardi *et al.*, 2025). Persistent carrier states are common and play a critical role in disease transmission.

Ovine and caprine anaplasmosis

Sheep and goats are mainly infected with *A. ovis*. Infections are frequently subclinical, although stress, malnutrition and concurrent infections may precipitate clinical disease characterized by anemia, fever, weakness and reduced productivity. Small ruminants may also serve as reservoirs for tick-mediated transmission.

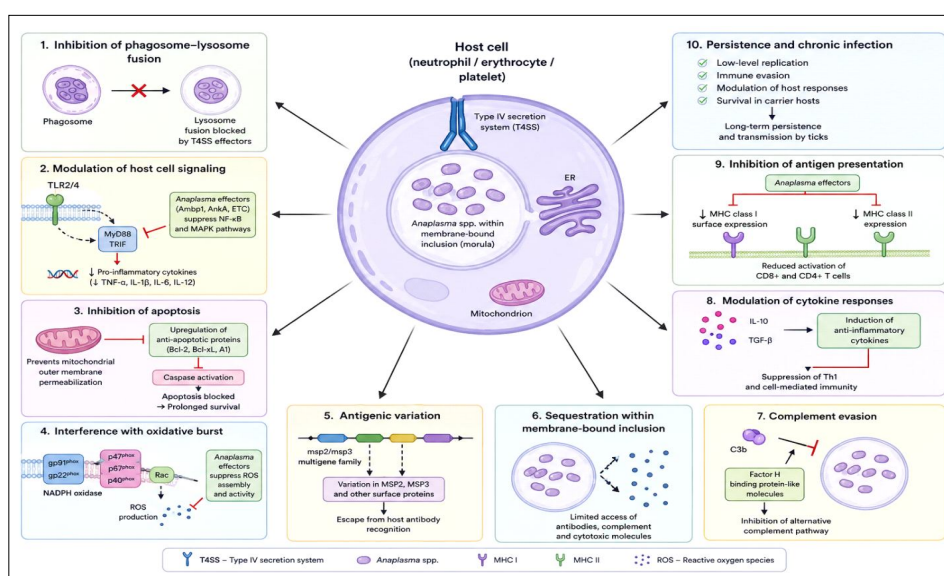


Fig 1: Cellular mechanisms of immune evasion and intracellular persistence in *Anaplasma* spp.

Canine anaplasmosis

Canine anaplasmosis is caused primarily by *A. platys* and *A. phagocytophilum*. Clinical manifestations include fever, lethargy, anorexia, thrombocytopenia, lymphadenopathy and occasional bleeding disorders (Atif *et al.*, 2021). Cyclic thrombocytopenia is a characteristic feature of *A. platys* infection.

Equine granulocytic anaplasmosis

Equine anaplasmosis caused by *A. phagocytophilum* is characterized by fever, depression, limb edema, ataxia, reluctance to move and occasionally neurologic manifestations. Disease occurrence is often seasonal and associated with vector activity.

Wildlife reservoirs

Wildlife species including deer, wild ruminants, rodents and other free-ranging animals play important roles in maintaining *Anaplasma* organisms within natural ecosystems. Wildlife reservoirs contribute significantly to pathogen persistence, vector infection and cross-species transmission at the wildlife-livestock-human interface.

Advances in diagnostics

Accurate diagnosis of anaplasmosis remains essential for effective therapeutic management, epidemiological surveillance and disease control. Conventional diagnostic approaches include microscopic examination of Giemsa-stained blood smears and serological assays such as enzyme-linked immunosorbent assay and indirect fluorescent antibody tests (Shabana *et al.*, 2018). Although these methods are relatively inexpensive and suitable for field application, they suffer from limited sensitivity, particularly during chronic or carrier-stage infections. Molecular diagnostic techniques have substantially improved detection sensitivity and specificity. Conventional PCR, nested PCR, multiplex PCR and quantitative real-time PCR assays enable species-level identification and detection of low-level parasitemia (Colasante *et al.*, 2024). PCR-based assays targeting 16S rRNA, MSP genes and other conserved genomic regions are widely used in epidemiological investigations (Pan *et al.*, 2011; Altay *et al.*, 2026). Despite their superior sensitivity, molecular diagnostics face several practical limitations in endemic field conditions. High cost, infrastructure requirements, need for trained personnel and limited portability restrict their widespread use in resource-constrained settings. Furthermore, PCR-based methods may not reliably distinguish viable from non-viable organisms (Table 1).

Recent advances in genomics and sequencing technologies have expanded diagnostic possibilities. Next-generation sequencing, metagenomics and nanopore sequencing facilitate comprehensive pathogen detection, strain characterization and genomic surveillance. These technologies are particularly useful for identifying emerging species, mixed infections and novel genetic variants. Point-of-care diagnostics are

emerging as promising alternatives for field-level disease detection. Loop-mediated isothermal amplification (LAMP), CRISPR-Cas-based diagnostics, portable PCR systems, biosensors and microfluidic platforms offer rapid and sensitive detection under field conditions.

Therapeutics and antimicrobial resistance

Therapeutic management of anaplasmosis primarily relies on tetracycline antibiotics because of their ability to penetrate host cells and inhibit bacterial protein synthesis. Oxytetracycline remains the most commonly used therapeutic agent in cattle, whereas doxycycline is widely used in small animals because of superior bioavailability and tissue penetration. Both the drugs act primarily by inhibiting bacterial protein synthesis through binding to the 30S ribosomal subunit (Lacasta *et al.*, 2022; Rai *et al.*, 2024; Kumar *et al.*, 2026). Imidocarb dipropionate also exhibits efficacy against bovine anaplasmosis and provides partial prophylactic activity. Its mechanism of action is not fully understood but is believed to involve interference with nucleic acid metabolism in the parasite (Doyle *et al.*, 2016). However, toxicity concerns including cholinergic side effects, necessitating careful dosing and monitoring, prolonged withdrawal periods and incomplete pathogen clearance limit its routine application. Macrolides and fluoroquinolones have been investigated as alternative antimicrobial agents, although their use remains limited because of variable efficacy and concerns regarding antimicrobial stewardship (Maurin *et al.*, 2003). Rifampicin has shown some *in vitro* activity against *Anaplasma phagocytophilum*; however, its clinical application in veterinary practice is not well established (Thomas *et al.*, 2009).

Pharmacokinetics and treatment regimens

The efficacy of antimicrobial therapy is influenced by pharmacokinetic and pharmacodynamic factors, including drug absorption, tissue distribution and intracellular penetration. Tetracyclines exhibit favourable intracellular accumulation, which is essential for targeting *Anaplasma* organisms that reside within host cells (Semenova *et al.*, 2025). Long-acting formulations of oxytetracycline have been widely adopted in field conditions because of their convenience and sustained therapeutic levels. Treatment regimens vary depending on the species, severity of infection and regional practices; however, early intervention remains a key determinant of therapeutic success.

Antimicrobial resistance and emerging concerns

The emergence of antimicrobial resistance in *Anaplasma* spp. is a growing concern, although it remains less well characterised than other bacterial pathogens. Reports of reduced sensitivity to tetracyclines have emerged in certain endemic regions, raising questions about the long-term efficacy of current treatment protocols (Curtis *et al.*, 2021). Resistance mechanisms are thought to involve genetic mutations affecting ribosomal binding sites and efflux pump systems that reduce intracellular drug concentrations

Table 1: Comparative analysis of conventional, molecular and emerging diagnostic methods used for detection of anaplasmosis in animals, including their principles, sensitivity, specificity, advantages, limitations and field applicability.

Diagnostic method	Principle	Target/marker	Sensitivity	Specificity	Advantages	Limitations	Field applicability
Microscopic examination (Giemsa-stained blood smear)	Direct visualization of intraerythrocytic or intracytoplasmic inclusions	Morulae or inclusion bodies in blood cells	Low to moderate	Moderate	Rapid, inexpensive, minimal equipment required	Low sensitivity during chronic/ carrier stage; requires skilled personnel; difficult differentiation from artifacts	High in resource-limited settings
Buffy coat examination	Concentration of infected leukocytes/platelets	Infected leukocytes or platelets	Moderate	Moderate	Improved detection compared with direct smear	Limited sensitivity in low parasitemia; labor-intensive	Moderate
Complement fixation test (CFT)	Detection of specific antibodies	Serum antibodies	Moderate	Moderate	Historically important diagnostic tool	Poor sensitivity in early infection; cross-reactivity	Limited
Indirect fluorescent antibody test (IFAT)	Fluorescent detection of antibodies	Species-specific antibodies	High	High	Useful for epidemiological surveillance	Cannot differentiate active from past infection; subjective interpretation	Moderate
ELISA	Detection of antibodies against <i>Anaplasma</i> antigens	MSP proteins and other antigens	High	High	Suitable for herd-level screening; relatively rapid	Cross-reactivity possible; limited value in acute infection	High
Conventional PCR	Amplification of target DNA sequences	16S rRNA, <i>msp1a</i> , <i>msp4</i> , <i>groEL</i>	High	High	Sensitive and species-specific	Requires laboratory infrastructure and trained personnel	Moderate
Nested PCR	Two-step amplification for enhanced detection	Conserved genomic targets	Very high	Very high	Detects low parasitemia and carrier animals	Increased contamination risk; time-consuming	Moderate
Multiplex PCR	Simultaneous amplification of multiple targets	Multiple tick-borne pathogens	High	High	Detects co-infections efficiently	Requires optimization and specialized equipment	Moderate
Quantitative real-time PCR (qPCR)	Real-time amplification and quantification	Species-specific DNA targets	Very high	Very high	Quantitative, rapid, highly sensitive	High cost and infrastructure requirements	Moderate to low in field conditions
Digital PCR (dPCR)	Partition-based nucleic acid quantification	Genomic DNA targets	Extremely high	Extremely high	Absolute quantification; highly accurate	Expensive instrumentation; limited accessibility	Low

Table 1: Continue...

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High-resolution melt (HRM) analysis	DNA melting profile differentiation	Sequence polymorphisms	High	High	Rapid strain differentiation	Requires advanced instruments	Moderate
Loop-mediated isothermal amplification (LAMP)	Isothermal DNA amplification	Conserved DNA sequences	High	High	Rapid, simple, field-friendly	Primer design complexity; limited multiplexing	High
CRISPR-Cas-based diagnostics	CRISPR-mediated nucleic acid detection	Species-specific genomic sequences	Very high	Very high	Rapid, highly specific, portable potential	Still under validation for routine veterinary use	Emerging field applicability
Nanopore sequencing	Real-time sequencing of nucleic acids	Whole genomic material	Very high	Very high	Portable sequencing; rapid pathogen identification	High analytical complexity; bioinformatics expertise required	Moderate
Next-generation sequencing (NGS)	High-throughput genomic sequencing	Whole genome/metagenome	Extremely high	Extremely high	Comprehensive pathogen characterization; detects mixed infections	Expensive; requires advanced bioinformatics field use	Low for routine
Metagenomic analysis	Untargeted sequencing of all nucleic acids	Mixed microbial genomes	Extremely high	Very high	Detects novel and emerging pathogens	High computational demand and cost	Low
Biosensors and microfluidic platforms	Rapid molecular or immunological detection	DNA/protein biomarkers	Moderate to high	High	Portable and rapid	Limited commercial availability	Emerging field applicability
Portable PCR systems	Field-deployable PCR amplification	Pathogen DNA	High	High	On-site diagnosis possible	Battery/infrastructure dependency	High in remote settings

(Chavarria-Bencomo *et al.*, 2023). The widespread and often indiscriminate use of antibiotics in livestock production systems has likely contributed to the development of resistance, emphasising the need for judicious antimicrobial use in livestock (Kumar *et al.*, 2012; Sharma *et al.*, 2015 and Fig 2). Another important consideration is the persistence of *Anaplasma* organisms despite the use of antimicrobial therapy. This persistence is not necessarily indicative of classical resistance but reflects the ability of pathogens to evade host immunity and survive in intracellular niches. Consequently, treated animals may continue to serve as reservoirs of infection, complicating the control efforts. Table 2 highlights that tetracyclines, particularly oxytetracycline and doxycycline, remain the most reliable therapeutic agents because of their ability to penetrate host cells and inhibit bacterial protein synthesis. Imidocarb dipropionate is an alternative option, especially in bovine cases; however, its toxicity and residue concerns limit its widespread use. Emerging alternatives, such as fluoroquinolones and rifampicin, show promise but are constrained by regulatory and resistance issues. Importantly, none of the currently available drugs consistently

eliminate the carrier state, which remains a major limitation in controlling the disease.

Limitations of conventional therapy

Although antimicrobial therapy is effective in reducing clinical severity, it does not always result in complete pathogen clearance (Ierardi *et al.*, 2025; Kumar *et al.*, 2026). This limitation is particularly evident in chronic infections, where low-level parasitaemia persists despite treatment. Additionally, reliance on antibiotics raises concerns regarding drug residues in animal products, regulatory restrictions and public health implications (Chavarria-Bencomo *et al.*, 2023). The cost and accessibility of drugs also pose challenges in resource-limited settings, where livestock owners may have limited access to veterinary care. These constraints highlight the need for alternative and complementary therapeutic approaches to treat the disease. The mechanisms outlined above indicate that antimicrobial resistance in *Anaplasma* spp. is multifactorial and differs from the classical resistance observed in extracellular bacteria (Table 3). Although direct genetic resistance, such as ribosomal mutations, is beginning to

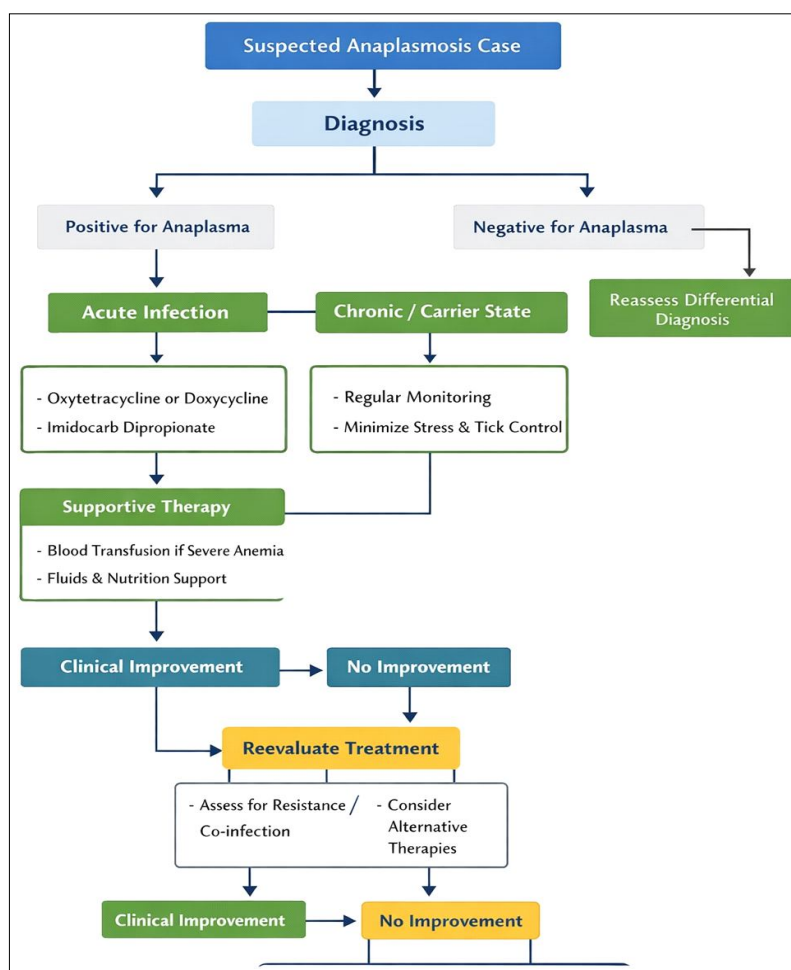


Fig 2: Treatment decision for anaplasmosis in animals.

Table 2: Therapeutic agents used for the treatment of anaplasmosis in animals: target species, mechanisms of action, advantages and limitations.

Drug	Target species	Recommended dose	Mechanism of action	Advantages	Limitations/concerns
Oxytetracycline	Cattle, sheep and goats	10-20 mg/kg IV/IM (single or repeated); long-acting: 20 mg/kg IM	Inhibits protein synthesis by binding to 30S ribosomal subunit	Highly effective, widely available, good intracellular penetration	Does not eliminate carrier state; resistance emerging; withdrawal period required
Doxycycline	Dogs and small ruminants	5-10 mg/kg orally for 7-14 days	Inhibits bacterial protein synthesis (30S ribosome)	Excellent bioavailability; preferred for <i>A. phagocytophilum</i> ; less tissue irritation	Requires prolonged treatment; cost higher than oxytetracycline
Imidocarb dipropionate	Cattle and dogs	1.2-3 mg/kg IM or SC (single or repeated dose)	Interferes with nucleic acid metabolism and parasite replication	Provides partial prophylaxis; effective in acute cases	Toxicity (cholinergic effects); long withdrawal period; does not clear infection fully
Enrofloxacin (fluoroquinolone)	Experimental use (cattle and dogs)	2.5-5 mg/kg IM/SC	Inhibits DNA gyrase and topoisomerase IV	Broad-spectrum; potential alternative in resistant cases	Limited evidence against <i>Anaplasma</i> ; regulatory restrictions; resistance concerns
Rifampicin	Experimental (dogs and humans) Cattle	10 mg/kg orally	Inhibits RNA polymerase	Good intracellular activity	Limited veterinary use; rapid resistance if used alone
Chlortetracycline (feed additive)	Limited use	1-2 mg/kg/day in feed	Protein synthesis inhibition	Useful for prophylaxis in endemic areas	Risk of resistance; not suitable for acute treatment
Amoxicillin/β-lactams		Variable	Inhibits cell wall synthesis	Widely available	Ineffective due to intracellular nature of pathogen
Herbal extracts (neem, garlic)	Experimental	Not standardized	Antimicrobial, antioxidant, immunomodulatory effects	Low cost; reduced drug residues; supportive therapy	Lack of standardized dosing; limited clinical validation
Nanoparticle-based tetracyclines	Experimental	Under research	Enhanced intracellular delivery	Improved efficacy; reduced toxicity	Not commercially available; requires further validation

Table 3: Molecular and cellular mechanisms underlying antimicrobial resistance and persistence in *Anaplasma* spp.

Resistance mechanism	Molecular basis	Target drug class	Effect on therapy	Evidence/status
Ribosomal target modification	Mutations in 16S rRNA gene altering tetracycline binding sites	Tetracyclines (oxytetracycline, doxycycline)	Reduced binding affinity leading to decreased drug efficacy	Emerging evidence from field isolates; not yet widespread but increasing concern
Efflux pump activity	Upregulation of membrane transport proteins that expel antibiotics from infected cells	Tetracyclines, possibly macrolides	Decreased intracellular drug concentration reduces effectiveness	Suggested by genomic studies; functional validation limited
Reduced membrane permeability	Alterations in host cell or bacterial membrane affecting drug entry	Multiple classes	Lower intracellular accumulation of drugs	Hypothesized mechanism; indirect evidence in intracellular pathogens
Intracellular sequestration	Localization of bacteria within membrane-bound vacuoles avoiding drug exposure	All intracellular-active drugs	Protects bacteria from therapeutic concentrations	Well-established survival strategy; contributes to persistence rather than true resistance
Antigenic variation (MSP genes)	Genetic variation in major surface proteins (MSP2 and MSP3)	Indirectly affects all therapies	Enables immune evasion, prolonging infection despite treatment	Strong evidence; key mechanism for persistence and relapse
Biofilm-like protective states (hypothetical)	Aggregation or protective microenvironments within host cells	Broad-spectrum	May reduce drug penetration	Limited evidence; requires further investigation
Metabolic dormancy/persistence	Reduced metabolic activity leading to "persister" cell formation	Bacteriostatic drugs (tetracyclines)	Drugs less effective against non-dividing organisms	Increasingly recognized in intracellular pathogens
Horizontal gene transfer (rare)	Acquisition of resistance genes via mobile genetic elements	Multiple classes	Potential for rapid resistance spread	Limited evidence in <i>Anaplasma</i> ; more common in other bacteria
Host-mediated drug inactivation	Host cell environment altering drug activity (pH and enzymes)	Multiple classes	Reduced antimicrobial activity within intracellular niche	Suggested mechanism; needs more experimental validation

emerge, much of the reduced therapeutic efficacy observed in field conditions is attributable to intrinsic survival strategies, including intracellular sequestration, antigenic variation and metabolic persistence. The obligate intracellular lifestyle of *Anaplasma* plays a central role in limiting drug efficacy, as many antimicrobial agents fail to achieve sufficient intracellular drug concentrations. Tetracyclines, which are bacteriostatic, may be less effective against dormant or slowly replicating organisms, thereby contributing to persistent infections and carrier states. Although confirmed antimicrobial resistance in *Anaplasma* remains relatively limited compared to other pathogens, the increasing reliance on tetracyclines in endemic regions raises concerns regarding the development of future resistance.

Alternative and adjunct therapeutic approaches

Phytotherapy and plant-derived compounds

Increasing interest has been directed toward plant-based therapies as potential alternatives or adjuncts to conventional treatments (Mahima *et al.*, 2012; Dhama *et al.*, 2013). Several medicinal plants have demonstrated antimicrobial, antioxidant and immunomodulatory properties that may be beneficial for managing anaplasmosis. Extracts from plants such as *Azadirachta indica* (neem), *Allium sativum* (garlic) and *Ocimum sanctum* (holy basil) have demonstrated inhibitory effects against various intracellular pathogens in experimental studies. Phytochemicals, such as flavonoids, alkaloids and terpenoids, are believed to contribute to these effects by disrupting microbial metabolism and enhancing host immune responses.

Immunomodulatory therapy

Given the importance of host immunity in disease progression, immunomodulatory approaches have been explored as adjunctive therapies. Agents such as cytokines, probiotics and nutritional supplements may enhance immune function and improve disease outcomes (Mahima *et al.*, 2013). Antioxidants, including vitamin E and selenium, have been shown to mitigate the oxidative stress associated with infection and may support recovery (Dhanasree *et al.*, 2020; Das *et al.*, 2022).

Nanotechnology-based drug delivery

Recent advances in nanotechnology have opened new avenues for improving drug delivery in intracellular infections. Nanoparticle-based formulations of antimicrobial agents have demonstrated enhanced cellular uptake and targeted delivery, potentially increased therapeutic efficacy while reducing systemic toxicity (Verma *et al.*, 2026). Although still in the experimental stage, these approaches hold promise for future treatment strategies.

Biological control and vaccine-assisted therapy

Vaccination, although primarily a preventive strategy, may also play a role in reducing disease severity and complementing therapeutic interventions (Singh *et al.*, 2014).

The use of live attenuated vaccines, such as *Anaplasma centrale*, has shown partial success in endemic regions (Shkap *et al.*, 2008; Ferm *et al.*, 2024). Emerging recombinant vaccines targeting conserved antigens offer potential for improved efficacy (Sarli *et al.*, 2020).

Ethnoveterinary practices

Traditional knowledge systems in many regions have long utilized herbal remedies for the treatment of tick-borne diseases. Ethnoveterinary practices may provide valuable insights into locally available and sustainable therapeutic options. However, scientific validation and standardization are essential to ensure safety and efficacy.

Integrated therapeutic strategies

A holistic approach to the treatment of anaplasmosis involves the integration of antimicrobial therapy with supportive care, vector control and management practices. Early diagnosis followed by prompt administration of appropriate drugs remains the cornerstone of treatment, but long-term control requires addressing the underlying epidemiological factors. Combining conventional therapy with alternative approaches such as phytotherapy and immunomodulation may enhance treatment outcomes and reduce reliance on antibiotics. Furthermore, strategic use of therapeutics in conjunction with vaccination and tick control measures can significantly reduce disease burden.

Future directions in therapeutics

Future research should focus on the development of novel therapeutics targeting specific molecular pathways involved in *Anaplasma* survival and replication. Advances in genomics and proteomics may facilitate the identification of new drug targets and vaccine candidates. Additionally, the integration of precision medicine approaches, including host genetic profiling and tailored treatment regimens, may improve therapeutic efficacy.

Vaccines and integrated control strategies

Vaccination remains one of the most promising approaches for sustainable control of anaplasmosis. The live *Anaplasma centrale* vaccine has been used in several endemic regions and provides partial protection against severe disease. However, limitations including incomplete cross-protection, residual virulence and inability to prevent carrier states restrict its effectiveness. Recent vaccine research has focused on recombinant proteins, conserved antigens, DNA vaccines, vector-based vaccines and reverse vaccinology approaches (Sarli *et al.*, 2020).

Tick control remains the corner stone of integrated disease prevention. Strategic acaricide application, pasture management, biological control, rotational grazing and use of tick-resistant breeds contribute significantly to reducing transmission. However, increasing acaricide resistance among tick populations, particularly *Rhipicephalus microplus*, represents a major emerging challenge (Makwavela *et al.*, 2025). Chemoprophylaxis may be employed

in endemic areas to reduce infection pressure, although concerns regarding antimicrobial resistance necessitate judicious use. Farm-level biosecurity measures including quarantine of newly introduced animals, sterilization of instruments, surveillance of carrier animals, vector monitoring and movement control are essential components of integrated control programs. Climate-based forecasting systems, GIS surveillance and ecological monitoring may further improve vector management strategies under changing environmental conditions.

One health and zoonotic implications

The emergence of zoonotic *Anaplasma* species has substantially increased the public health significance of anaplasmosis. *A. phagocytophilum* causes human granulocytic anaplasmosis, an emerging tick-borne disease characterized by fever, headache, myalgia, leukopenia, thrombocytopenia and occasionally severe systemic complications (Abdoli *et al.*, 2025). Recent reports of *A. capra* infection in humans further highlight the zoonotic potential of emerging *Anaplasma* species. Increasing interaction among wildlife, livestock, vectors and humans has created favorable conditions for cross-species transmission and emergence of novel zoonotic infections. Occupational exposure among farmers, veterinarians, animal handlers, forestry workers and wildlife personnel increases risk of infection. Climate change, ecological disruption, wildlife migration and expanding vector habitats are expected to further enhance zoonotic transmission risk in the future. The one health approach provides an essential framework for integrated management of anaplasmosis by linking veterinary health, human health, environmental surveillance, vector ecology and public health policy. Integrated surveillance systems incorporating molecular epidemiology, vector monitoring, wildlife ecology and climate forecasting are necessary for effective prevention and control of emerging tick-borne diseases.

Knowledge gaps and future perspectives

Despite considerable scientific advances, several important challenges continue to hinder effective control of anaplasmosis. Current vaccines fail to provide complete cross-protection and sterilizing immunity. Diagnostic limitations remain significant under field conditions, particularly for chronic carrier detection and mixed infections. The molecular basis of persistence, host specificity and pathogen adaptation also remains incompletely understood. Future research should prioritize multi-omics approaches including genomics, transcriptomics, proteomics and metabolomics to better understand pathogen biology and host-pathogen interactions. Artificial intelligence-assisted epidemiological modelling, climate-based vector forecasting and GIS surveillance may improve early warning systems and disease prediction. Development of affordable point-of-care diagnostics, CRISPR-based molecular assays, precision therapeutics and next-generation vaccines represents important future

priorities. Strengthening antimicrobial stewardship and integrated tick management programs will also be essential to mitigate resistance development. The future control of anaplasmosis will likely depend on integrated multidisciplinary strategies combining molecular surveillance, precision diagnostics, vector ecology, vaccine innovation, climate-resilient interventions and coordinated One Health policy frameworks.

CONCLUSION

Anaplasmosis remains a major constraint to livestock productivity, animal welfare and public health worldwide. Advances in molecular epidemiology, genomics, diagnostics and host-pathogen biology have substantially improved understanding of the disease; however, major challenges including persistent carrier states, antimicrobial resistance, vaccine limitations and expanding vector ecology continue to hinder effective control. Integrated multidisciplinary approaches combining molecular surveillance, precision diagnostics, vector management, vaccine development, antimicrobial stewardship and one health collaboration offer the most promising strategy for sustainable disease control. Future research should focus on genomics-informed interventions, climate-resilient surveillance systems and translational approaches capable of addressing the evolving epidemiology of this economically and zoonotically important disease.

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Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily represent the views of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided, but do not accept any liability for any direct or indirect losses resulting from the use of this content.

Informed consent

All animal procedures for experiments were approved by the Institutional Animal Ethics Committee, SVPUAT, Meerut (IAEC/SVPUAT/2025/168).

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article. No funding or sponsorship influenced the design of the study, data collection, analysis, decision to publish, or preparation of the manuscript.

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