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Review Article

Antibiotic-Related Immune Haemolysis Integrating Drug-Dependent Antibodies NIPA Concepts Diagnostics and Management

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ABSTRACT

Drug-induced immune haemolytic anaemia (DIIHA) is a rare, unpredictable adverse effect of pharmacotherapy, most often linked to antibiotics—especially second- and third-generation cephalosporins—and may present abruptly with anaemia, jaundice, and laboratory evidence of haemolysis. Incidence is pragmatically near one to two cases per million annually, with cephalosporins dominating modern series. Pathobiology spans drug-independent autoantibody formation (methyldopa-type) and drug-dependent reactions in which antibodies require the drug's presence, classically the drug-adsorption/hapten ('penicillin-type') and immune-complex ('quinidine-type') patterns; a related non-immune protein adsorption phenomenon can yield DAT positivity without demonstrable drug-specific antibodies. Diagnosis integrates a careful drug timeline with mechanism-aware serology: polyspecific/monospecific DAT, eluate behaviour, and testing with drug-coated RBCs or soluble drug. An eluate that fails to react with untreated RBCs suggests drug dependence, and DAT positivity alone does not equate to DIIHA. Management prioritizes immediate cessation of the suspect agent, clinical stabilization, and transfusion when indicated, while anticipating intravascular haemolysis and complications such as acute kidney injury, disseminated intravascular coagulation, and thrombotic microangiopathy. Steroids show no consistent benefit in classic drug-dependent DIIHA and are best reserved for refractory disease or when drug-independent autoantibodies are implicated; long-term safety hinges on rigorous documentation and lifelong avoidance of the culprit and close analogues to prevent rapid, life-threatening recurrence. With timely recognition, prompt drug withdrawal, targeted serology, and judicious supportive care, outcomes are generally favourable; recovery commonly begins within one to two weeks even if the DAT remains positive as immune reactants clear.

INTRODUCTION

Drug-induced immune haemolytic anaemia (DIIHA) is an uncommon but clinically important

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entity, typically estimated at roughly one case per million persons per year, and is best understood as a rare, unpredictable adverse effect of pharmacotherapy. [1],[2],[7] It is characterized by immune-mediated destruction of red blood cells (RBCs) triggered by exposure to an offending drug and may present abruptly with anemia, jaundice, dark urine, and laboratory evidence of hemolysis—features that demand prompt recognition. [3]

Accurate contemporary incidence figures are difficult to generate because cases are under-recognized, under-reported, and true population drug-exposure denominators are hard to establish. [4] Nevertheless, the spectrum of potential culprits is broad: approximately 130 medications have been implicated, with antibiotics featuring prominently among reported triggers. [5] Commonly cited classes include cephalosporins, penicillins, macrolides, fluoroquinolones, tetracyclines, and lincomycin. [2] Among these, second- and third-generation cephalosporins account for most cases in modern series. [6] Notably, 3–4% of patients receiving very high-dose intravenous penicillin or first-/second-generation cephalosporins develop a positive direct antiglobulin test (DAT), yet only a minority progress to clinically overt hemolysis—underscoring that DAT positivity alone does not equal DIIHA. [6] From a diagnostic standpoint, a meticulous drug history and appropriate serologic testing are central. A useful early clue is that an eluate prepared from DAT-positive patient RBCs may fail to react with normal RBCs, suggesting the presence of an antibody that is primarily drug-dependent rather than broadly RBC-reactive. [6] Because immune-mediated RBC lysis can evolve rapidly, early suspicion and timely withdrawal of the suspected agent are critical to mitigating morbidity. [3]

When viewed against related hematologic drug reactions, DIIHA remains the least well quantified. Drug-induced immune thrombocytopenia and neutropenia have better established incidence ranges—approximately 10–18 and 2–15 cases per million, respectively—whereas robust population data for DIIHA are lacking; pragmatic estimates place it near one to two cases per million worldwide. [8],[7] Compared with autoimmune (non-drug-induced) hemolytic anaemia, which occurs at about 1 in 80,000 people, DIIHA appears markedly rarer; in long clinical experience, autoimmune hemolysis is encountered roughly an order of magnitude more often. [9] In sum, DIIHA is rare, unpredictable, and often under-detected, yet potentially severe—particularly with contemporary cephalosporin exposure—making early recognition, drug cessation, and targeted serologic evaluation essential components of care. [1-9]

MECHANISMS INVOLVED IN DIIHA:

There are two different types of drug-related antibodies. Drug-independent antibodies can be discovered *invitro* without using another drug; as a result, the characteristics of these antibodies in vitro and in vivo are the same as those of RBC-based auto-antibodies. The mechanism are controversial involved in the serological and clinical findings. yet unclear how or why some medications can impact the immune system and lead to the development of RBC autoantibodies, Whether or not HA. [10] The prototype medication is methyldopa, which only results in the development of a HA in 0.5% to 1% of patients but causes the creation of RBC auto-antibodies in about 15% of those taking it. The medication most frequently used to cause RBC auto-antibodies is fludarabine.

One mechanism for the drug-dependent processes is generally acknowledged. A patient may produce

an IgG antibody to a drug, which will adhere to the medication on RBC and cause the macrophages to interact, causing extravascular RBC destruction through FC; complement may also occasionally be involved. This does not harm the RBCs. However, if the patient develops an IgG antibody to the medication, the medicine on the RBC will bind to the antibody and cause harm to the RBCs.The patient's serum or an eluate from the RBCs can be tested in vitro for the presence of these antibodies by comparing them to drug-coated RBCs (prepared in vitro). Penicillin is the model medication; cefotetan, but not ceftriaxone, can react in this way. Sadly, the majority of medications that induce immediate, severe intravascular hemolysis and renal failure with disseminated intravascular coagulation can occur occassionally, and mortality appear to operate by a different mechanism, which typically involves drug-dependent antibodies that activate complement.With medications in this class, it is frequently impossible to produce drug-coated RBCs in vitro, and the antibodies can only be found by combining the drug with the patient's blood (which contains drug antibodies) and RBCs.

A POSSIBLE NEW MECHANISM FOR DIIH:

One more idea that has gained popularity during the past ten years is this one. Some medications seem to have the ability to alter the RBC membrane, causing proteins to be non-immunologically adsorbed . The first cephalosporin was the medication initially identified as responsible for non-immune protein adsorption (NIPA) (cephalothin).After being incubated in normal plasma, RBC treated with cephalothin Adsorb IgG, C3, Albumin and fibronogen, and other proteins, as demonstrated by Spathet al. [11]; the anti-globulin test may be used to identify the proteins.They thought NIPA might contribute to hemolytic anaemia. [12-13] Positive outcome from monocyte monolayer assays(MMA) on RBCs with IgG on their membrane via non-immunologic adsorption imply that macrophages would interact with these coated RBCs, decreasing RBC survival. [14]They have reported that individuals using medications containing -lactamase inhibitors (clavulanate, sulbactam, and tazobactam) and medications in the platinum family[15] may experience lower RBC survival without the presence of drug antibodies.

These medications include tazobactam with piperacillin and sulbactam plus ampicillin; thus, the HA linked to these drugs may be caused by one or both of these pathways . Antibiotics (penicillins) can cause DIIHA by well-described mechanisms.Cisplatin, carboplatin, and oxaliplatin are only a few of the chemotherapy drugs that have been linked to DIIHA and/or positive DATs. [9] [18] Although the exact mechanisms have been debated over the years, it is now known that patients may develop antibodies to the medication and/or that NIPAs potential involvement in the Hemolytic process.

Mechanisms Involved in DIIHA (extended with the same reference numbers)

Drug-independent (autoantibody) mechanism — the "methyldopa-type"

In the drug-independent mechanism, the drug's primary action is to disrupt immune tolerance, upon which the patient creates warm-reactive RBC auto-antibodies detectable in vitro in the absence of the addition of the drug. Serologically, this corresponds to typical warm autoimmune haemolytic anaemia: the DAT is IgG positive (usually with C3), and an eluate will react with untreated reagent RBCs since the target of the antibody is an RBC antigen, not a drug–RBC complex. Clinically, onset is insidious over weeks

to months; anaemia can be absent or mild initially and can last for weeks beyond drug withdrawal, indicating the time required for autoantibody production to decline. The mechanism of tolerance breakdown is not yet settled—suggested mechanisms are polyclonal activation, bystander inflammation, epitope spreading, and modified antigen processing—but these remain interpretative and not definitive. What is firmly established is the epidemiology: methyldopa causes RBC auto-antibodies in ~15% of recipients but overt haemolysis in only ~0.5–1%; fludarabine is another drug commonly involved in the production of drug-independent RBC auto-antibodies. These facts serve to illustrate a major clinical message: DAT positivity does not equal DIIHA, and correlation with haemolysis markers and drug timeline is necessary. [10]

Drug-dependent antibody mechanisms — antibodies need the presence of the drug

By contrast, drug-dependent antibodies identify determinants that exist only when drug is in the circulation. Two serologic patterns account for the majority of cases and produce different clinical pictures.

Drug-adsorption (hapten) mechanism — the "penicillin-type"

Certain drugs adsorb firmly (frequently covalently) to RBC membrane proteins and thereby coat the RBC with drug. The patient generates IgG anti-drug, which binds to such drug-coated RBCs and targets them for Fc-receptor–mediated splenic macrophage removal, resulting in mainly extravascular haemolysis (jaundice, increased bilirubin, spherocytes may be visible). The DAT is highly IgG positive (± C3). A key laboratory finding is that the eluate is not reactive with normal untreated RBCs but will be reactive with in-vitro drug-coated RBCs. Penicillin is the paradigm of this hapten mechanism; cefotetan may work similarly, but ceftriaxone generally doesn't operate through this route. Since coating density is important, in-vitro experiments should mimic therapeutic drug concentrations and have negative controls to prevent over-interpretation of weak responses. [10]

Immune-complex mechanism — complement-mediated ("quinidine-type")

Soluble immune complexes with free circulating antibody are formed by other drugs; these complexes bind transiently to RBCs, fix complement, and induce intravascular haemolysis. The clinical presentation may be sudden and dramatic, with haemoglobinaemia/haemoglobinuria, acute LDH elevation, haptoglobin loss, and danger of acute kidney injury or DIC. Serologically, the DAT is usually C3-dominant with weak or negative IgG. An operational trap is that pre-coating RBCs with drug may not mimic the immune-complex kinetics; detection is usually done by adding soluble drug to patient serum and RBCs in the same system. This complement-activating pathway accounts for most acute haemolytic crises following exposure to certain agents; ceftriaxone is a prototypic example. Because complement amplification may be explosive, timing of the collection of specimens relative to drug exposure is crucial for in vitro demonstration of reactivity. [10]

Cross-cutting diagnostic clue in drug-dependent forms: an eluate that does not react with normal (untreated) RBCs favors drug dependence over a genuine RBC autoantibody and should induce specific testing with drug-coated RBCs (hapten pathway) and soluble-drug systems (immune-complex pathway). [10]

A potential second mechanism — Non-immune protein adsorption (NIPA)

A third, more recently defined concept is non-immune protein adsorption (NIPA). Here, some drugs modify the RBC membrane in a way that plasma proteins non-immunologically bind to the surface even in the absence of drug-specific antibodies. Pioneering studies with cephalothin demonstrated that drug-treated RBCs incubated in normal plasma adsorb IgG, C3, albumin, fibrinogen, and other proteins, resulting in a positive DAT that is an expression of coated proteins but not an acute immune response. This finding generated the hypothesis that NIPA shortens RBC survival by rendering RBCs "opsonized" to the mononuclear phagocyte system. [11],[12–13] Consistent with this, monocyte monolayer assays (MMA) show that IgG-carrying RBCs generated by NIPA are seen and ingested by macrophages, suggesting extravascular removal in the absence of classical drug-dependent antibody. [14] Notably, β-lactamase inhibitors (clavulanate, sulbactam, tazobactam) and platinum compounds have been linked with decreased RBC survival and/or positive DATs with no demonstrable drug-dependent antibodies, consistent with the NIPA model. Clinically, this translates to a patient who has haemolysis and a positive DAT but all drug-antibody studies negative—a picture that is explained by protein adsorption rather than traditional antigen–antibody binding. [15]

Drug classes showing overlapping pathways and heterogeneous serology

Antibiotics are the most common offenders in current series and reflect the heterogeneity of mechanism. Penicillins and some cephalosporins (e.g., cefotetan) represent the hapten mechanism with extravascular haemolysis mediated by IgG, whereas ceftriaxone is associated with immune-complex complement activation resulting in precipitating fulminant intravascular haemolysis. Combination drugs like piperacillin–tazobactam and ampicillin–sulbactam can induce profiles that are compatible with NIPA, drug-dependent antibodies, or both, to account for the occurrence in some patients of a DAT with IgG and C3 but no detectable drug-specific antibody. Outside the antimicrobials, platinum chemotherapy (cisplatin, carboplatin, oxaliplatin) has been associated with DIIHA and/or isolated DAT positivity; the reports involve drug-dependent antibodies and NIPA-type membrane alterations, which can cooccur in the same patient over time or upon re-exposure. These realities highlight the importance of mechanism-aware serology and an accurate drug history for causality attribution and future safe prescribing. [9],[10],[15],[18]

Practical laboratory practice rooted in mechanism

A step-wise serologic approach enhances diagnostic yield and avoids misclassification. Begin with a polyspecific DAT, followed (if positive) by monospecific IgG and C3 testing to imply pathway (IgG-dominant for hapten/autoantibody; C3-dominant for immune-complex). Conduct an eluate:

- Eluate reacts with untreated panel cells (no drug available) → drug-independent autoantibody (methyldopa-type).
- Eluate does not react with untreated cells but with in-vitro drug-coated RBCs → hapten mechanism.
- Eluate weak/negative, DAT C3-dominant, and reactivity needs soluble drug with patient serum and RBCs → immune-complex.
- When drug trials are negative but the DAT is positive for widespread protein deposition (IgG ± C3), think of NIPA. For drug testing

itself, add parallel controls, utilize therapeutically relevant concentrations of drug, and provide complement-sufficient serum when an immune-complex mechanism is suspected.

- Lastly, keep in mind that hospitalized patients may have a positive DAT without haemolysis; interpretation must be rooted in clinical and biochemical proof of haemolysis and drug exposure time course. [10],[11–15]

Mechanism-based clinical implications and management priorities

In all presentations, the most crucial intervention is the immediate withdrawal of the suspected drug. Hapten and NIPA patterns characteristically cause extravascular haemolysis that responds to withdrawal; management is directed against the anaemia and jaundice. Immune-complex type cases can occur as medical emergencies with intravascular haemolysis, haemoglobinuria, and organ damage; these need immediate supportive interventions (close transfusion therapy, control of haemolysis, and protection of the organs) and careful avoidance of re-exposure. NIPA is of clinical value since it accounts for situations of positive DAT without demonstrable drug-specific antibody, leading the clinicians to withdraw the drug despite futile attempts at antibody studies. Mechanistic classification also guides patient counseling regarding risks of cross-reactivity within a class (e.g., between cephalosporins) and assists in clear documentation to avoid future adverse reactions. [10],[11–15]

A Possible New Mechanism for DIIHA: Non-Immune Protein Adsorption (NIPA)

Over the past decade, non-immune protein adsorption (NIPA) has emerged as a compelling explanation for some cases of drug-induced immune haemolytic anaemia (DIIHA) in which no drug-specific antibody can be demonstrated. In this model, certain medications appear to modify the red blood cell (RBC) membrane so that plasma proteins adhere non-immunologically to the cell surface. The concept was anchored by observations with the early cephalosporin cephalothin: RBCs exposed to cephalothin and then incubated in normal plasma acquire a surface coat of IgG, C3, albumin, fibrinogen, and other proteins, detectable by the antiglobulin (DAT) test. These experiments, classically associated with Späth and colleagues, suggested that membrane alteration alone—without a specific anti-drug antibody—can generate a DAT-positive phenotype and led to the proposal that NIPA contributes to haemolysis in exposed patients. [11], [12–13]

Mechanistically, NIPA shifts the focus from antigen–antibody specificity to biophysical changes in the erythrocyte membrane. Drug exposure is posited to perturb the outer membrane leaflet (for example, by altering local charge distribution, hydrophobic interactions, or membrane microviscosity), thereby increasing the passive adsorption of circulating proteins. Because the adsorbed IgG and complement fragments are not bound through a classical immune epitope, standard drug antibody assays are often unrevealing. Nonetheless, the coated surface functionally mimics opsonization: splenic macrophages recognize Fc-bearing IgG on the RBC and remove the cell from circulation, producing predominantly extravascular haemolysis. The monocyte monolayer assay (MMA) provides functional corroboration—RBCs that carry IgG on their membranes via non-immunologic adsorption trigger monocyte/macrophage interaction, implying shortened RBC survival even in the absence of a demonstrable drug-dependent antibody. [14]

The laboratory phenotype that follows from NIPA is distinctive. Patients typically have a positive DAT (commonly IgG with or without C3) but show weak, non-specific, or negative eluates, and targeted drug studies fail to prove drug dependence: antibodies do not bind to in-vitro drug-coated RBCs (as in the hapten pathway) and reactivity is not rescued by adding soluble drug to patient serum and cells (as in immune-complex cases). When these findings align with a clear temporal link between drug exposure and haemolysis, the parsimonious interpretation is that protein coating—not specific antibody—drives clearance. Because DAT positivity can persist transiently after the culprit is stopped, repeating testing after drug withdrawal can help confirm the diagnosis and avoid over-calling autoimmune haemolysis. [11–15]

Drug classes repeatedly implicated in NIPA-like behaviour include β-lactamase inhibitors—clavulanate, sulbactam, and tazobactam—often encountered in combinations such as piperacillin–tazobactam and ampicillin–sulbactam. In these settings, patients may demonstrate reduced RBC survival and/or a positive DAT without detectable drug-dependent antibodies, a profile that maps closely to NIPA. In oncology practice, platinum compounds—cisplatin, carboplatin, and oxaliplatin—have been linked to DIIHA and/or isolated DAT positivity as well; the broader literature indicates that some cases reflect bona fide drug-dependent antibodies, while others fit an adsorption-driven pattern, and a subset likely reflects both processes operating together. This mechanistic overlap helps explain the heterogeneity of clinical severity and serology observed across reports. [15], [9], [18]

Clinically, NIPA tends to produce a picture dominated by extravascular haemolysis—progressive anaemia, jaundice, reticulocytosis, and elevated indirect bilirubin—with intravascular features being less typical than in complement-driven immune-complex reactions. Severity varies with the agent, exposure intensity and duration, and the efficiency of the mononuclear phagocyte system. Importantly, because some of the same drugs capable of NIPA can also elicit classical drug-dependent antibodies, an individual patient may exhibit different serologic patterns at different times or upon re-exposure, underscoring the importance of integrating serology with a precise drug timeline. [11–15], [9], [18]

Diagnosis in suspected NIPA rests on correlating exposure with haemolysis and excluding other immune mechanisms through methodical serology. A polyspecific DAT followed by monospecific IgG and C3 testing sets the stage; an eluate that is non-reactive or non-specific, coupled with negative drug studies using both drug-coated RBCs and soluble-drug systems, supports NIPA when the clinical timeline fits. Where available, an MMA adds functional evidence by demonstrating that the IgG-coated (but antibody-nonspecific) RBCs engage macrophages. This stepwise approach prevents misclassification as idiopathic AIHA and avoids unnecessary immunosuppression when drug cessation is the decisive therapy. [11–15], [14]

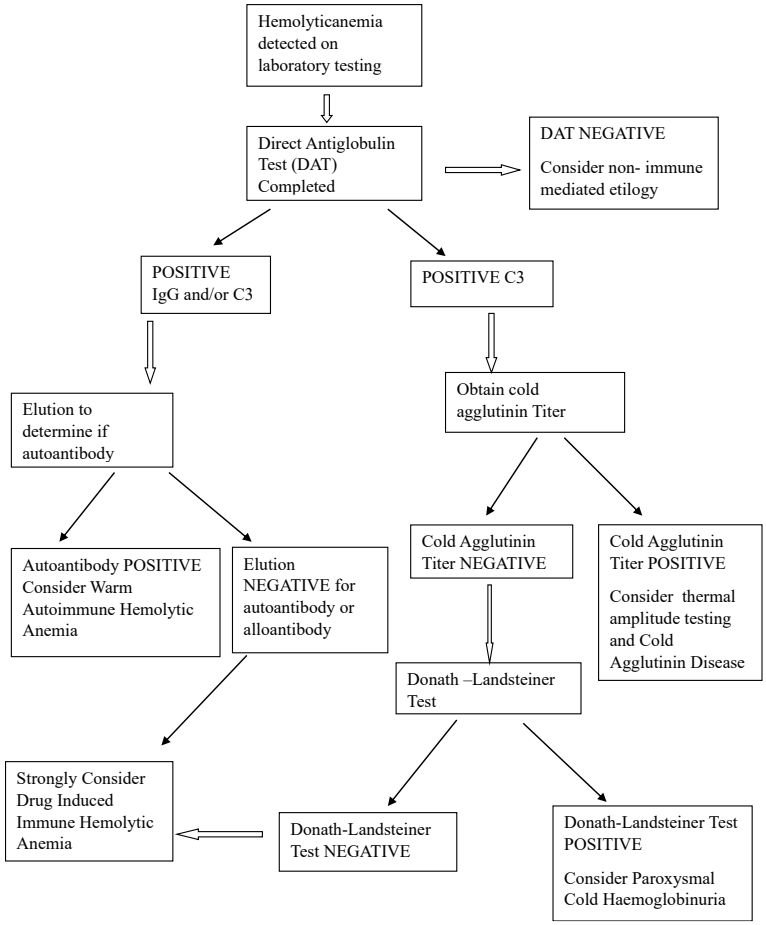

FIGURE 1: DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA WORKUP

Drug-Specific Reports of Drug-Induced Immune Haemolytic Anaemia (DIIHA)

Ceftriaxone-induced haemolytic anaemia

Ceftriaxone classically produces a drug-dependent, immune-complex (quinidine-type) reaction that fixes complement on red cells and precipitates abrupt intravascular haemolysis. Patients often present with sudden back/abdominal pain, haemoglobinuria, rapidly falling haemoglobin, markedly elevated LDH, undetectable haptoglobin, and can progress to AKI or DIC in severe episodes. Serology typically shows a DAT strongly positive for C3 with weak/negative IgG; eluates are often non-reactive with untreated cells, and in-vitro reactivity requires soluble ceftriaxone added to patient serum and RBCs. Re-exposure risks recurrence and can be life-threatening, so the drug should be listed as a permanent contraindication. Supportive care (cessation, transfusion as needed, organ support) is central. [19],[20],[21]

Amoxicillin-induced haemolytic anaemia

Amoxicillin follows the hapten (drug-adsorption, "penicillin-type") paradigm: the drug binds to RBC membrane proteins, and patients form IgG anti-drug that opsonizes drug-coated RBCs for extravascular clearance. The DAT is IgG-positive (± C3); the eluate does not react with untreated cells but does react with amoxicillin-coated RBCs prepared in vitro. The clinical course is often subacute—fatigue, jaundice, reticulocytosis—with improvement after prompt withdrawal. High-dose or prolonged exposure increases risk; future

class cross-reactivity within penicillins should be considered. [22],[23]

Cephalosporin-induced haemolytic anaemia (class overview)

Cephalosporins as a group can trigger DIIHA via two dominant pathways. Agents such as cefotetan act by the hapten mechanism with IgG-mediated extravascular haemolysis; others—most notably ceftriaxone—act via immune complexes with complement-driven intravascular haemolysis. Accordingly, serology spans IgG-dominant DAT with eluate reactive only to drug-coated cells (hapten) to C3-dominant DAT requiring soluble drug for in-vitro detection (immune-complex). Many cases occur around perioperative prophylaxis or repeated dosing; re-exposure can provoke brisk recurrence. Management hinges on immediate cessation and mechanism-aware testing to guide counselling on future β-lactam use. [24],[25]

Piperacillin-induced haemolytic anaemia

Piperacillin can cause DIIHA through drug-dependent IgG antibodies, and in combinations containing tazobactam there may also be contributions from non-immune protein adsorption (NIPA). Patients tend to show extravascular haemolysis (jaundice, splenic clearance) with DAT IgG ± C3; drug studies can demonstrate piperacillin-dependent reactivity, although some cases remain antibody-negative and fit a NIPA phenotype. Ill, hospitalized patients (e.g., with renal impairment or long courses) are over-represented. Stopping the drug is the key step; document the reaction clearly to avoid future exposure. [26],[27],[28]

Levofloxacin-induced haemolytic anaemia

Levofloxacin-associated DIIHA is rare, typically reported as drug-dependent immune haemolysis with variable serology. Presentations range from moderate anaemia with jaundice to more acute drops in haemoglobin. DAT patterns may show IgG and/or C3, and confirmatory testing seeks levofloxacin-dependent reactivity; however, negative drug studies do not exclude the diagnosis when the clinical timeline is compelling. Withdrawal and supportive care are usually sufficient, with avoidance of future levofloxacin exposure. [29]

Cefazolin-induced haemolytic anaemia

Cefazolin cases are uncommon but fit β-lactam-associated patterns. Mechanistically, many resemble the hapten pathway seen with other first-generation agents, yielding IgG-positive DAT and extravascular haemolysis; immune-complex features are less typical but possible. Episodes often occur in the postoperative prophylaxis setting with improvement after cessation. As with other cephalosporins, re-challenge is discouraged, and future cephalosporin use should be risk-assessed. [30],[31]

Amoxicillin–clavulanate (amoxiclav)–induced haemolytic anaemia

With amoxiclav, haemolysis may reflect one or both mechanisms. The amoxicillin component can drive hapten-type IgG responses, while clavulanate has been implicated in NIPA-like membrane changes that yield a positive DAT without demonstrable drug-specific antibody. Clinically, patients present with anaemia, jaundice, and reticulocytosis; serology may show IgG ± C3 with non-specific/weak eluates and negative drug-antibody testing, pointing toward an adsorption-driven process. Stopping the combination leads to recovery; list the product

(and close analogues) as an allergy in the record. [32]

Ceftazidime-induced haemolytic anaemia

Ceftazidime, a third-generation cephalosporin, has been reported to cause DIIHA via drug-dependent antibodies; some cases resemble immune-complex, complement-mediated haemolysis with C3-dominant DAT and brisk anaemia, while others are more consistent with hapten-type extravascular clearance. Confirmation may require soluble-drug testing if immune complexes are suspected. As always, immediate drug cessation is essential, with transfusion support as needed and strict avoidance of re-exposure. [33],[34]

Copyable summary table (keeps your reference numbers)

Drug	Likely mechanism	Key serology (DAT / eluate)	Typical presentation & course	Management notes	References
Ceftriaxone-induced haemolytic anaemia	Drug-dependent immune-complex, robust complement activation (quinidine-type)	DAT C3-dominant, IgG weak/−; reactivity often requires soluble ceftriaxone; eluate usually non-reactive with untreated cells	Abrupt intravascular haemolysis: back/abdominal pain, haemoglobinuria, rapid Hb fall, ↑LDH, ↓/0 haptoglobin; may progress to AKI/DIC	Immediate cessation; transfusion/organ support as needed; strict avoidance of re-exposure	[19]–[21]
Amoxicillin-induced haemolytic anaemia	Hapten (drug-adsorption, "penicillin-type") with IgG anti-drug to drug-coated RBCs	DAT IgG+ (±C3); eluate non-reactive with untreated cells but reactive with amoxicillin-coated RBCs	Subacute extravascular haemolysis (jaundice, reticulocytosis); risk ↑ with high/prolonged dosing	Stop drug; monitor recovery; consider penicillin class cross-risk	[22], [23]
Cephalosporin-induced haemolytic anaemia (class)	Mixed: hapten (e.g., cefotetan) and immune-complex (e.g., ceftriaxone) pathways	Hapten: DAT IgG+, eluate reacts with drug-coated cells; Immune-complex: DAT C3-dominant, needs soluble drug	Range from subacute extravascular to fulminant intravascular haemolysis; often peri-operative/prophylaxis setting	Stop agent; define mechanism to guide future β-lactam use; avoid re-challenge	[24], [25]
Piperacillin-induced haemolytic anaemia	Drug-dependent IgG; with tazobactam may also show NIPA (non-immune protein adsorption)	Typically DAT IgG ± C3; drug studies may show piperacillin dependence; some cases DAT+ but antibody tests − (NIPA pattern)	Usually extravascular; commonly in hospitalized/renal patients or long courses	Stop drug; document clearly; avoid future piperacillin(±tazobactam)	[26]–[28]

Levofloxacin-induced haemolytic anaemia	Drug-dependent immune haemolysis (rare)	DAT IgG and/or C3; variable; confirm if possible with levofloxacin-dependent testing	Moderate to acute haemolysis; improves after withdrawal	Discontinue; supportive care; avoid future levofloxacin	[29]
Cefazolin-induced haemolytic anaemia	Likely hapten-type (first-gen cephalosporin)	DAT IgG+ (±C3); eluate tends to react only with drug-coated cells	Extravascular pattern; often around post-op prophylaxis	Stop cefazolin; caution with future cephalosporins	[30], [31]
Amoxicillin–clavulanate (amoxiclav)–induced haemolytic anaemia	Combination of hapten (amoxicillin) and possible NIPA (clavulanate)	DAT IgG ± C3; weak/non-specific eluate; drug-antibody studies may be negative (supports NIPA)	Extravascular haemolysis; anaemia/jaundice; resolution after cessation	Stop combination; record product as allergy; avoid close analogues	[32]
Ceftazidime-induced haemolytic anaemia	Drug-dependent antibodies; some cases immune-complex; others hapten-like	Immune-complex: DAT C3-dominant, needs soluble ceftazidime; Hapten: DAT IgG+ with drug-coated cell reactivity	From moderate to brisk haemolysis; timeline close to exposure	Immediate cessation; transfuse/support as needed; no re-exposure	[33], [34]

MANAGEMENT

Initial stabilization and drug withdrawal: The first and most decisive intervention in suspected drug-induced immune haemolytic anaemia (DIIHA) is the immediate cessation of the offending agent; this alone drives recovery in the majority of cases and should not be delayed while serologic confirmation is pursued. [35,36] Patients with acute presentations require prompt stabilization: establish intravenous access, begin fluid resuscitation, and initiate close monitoring of vital signs, urine output, renal function, and haemoglobin to detect progression to haemodynamic instability or haemoglobinuric kidney injury. Many patients—particularly those with intravascular haemolysis—benefit from management in a higher-acuity setting, and a subset may require short-term dialysis if acute kidney injury develops. [37]

Transfusion support: Red cell transfusion should be given whenever clinically indicated, and should not be withheld because of a positive direct antiglobulin test (DAT) or difficulty in identifying fully compatible units. [37,38] In practice, transfusion decisions follow standard thresholds and symptoms: patients with severe, symptomatic anaemia (e.g., haemoglobin ≤7 g/dL) generally require urgent transfusion, with careful selection of the best-match/least-incompatible units and close post-transfusion monitoring. Exchange transfusion is rarely required and is reserved for exceptional circumstances such as profound shock unresponsive to conventional measures. [37] Serious complications of intravascular

haemolysis—including thrombotic microangiopathy (TMA), disseminated intravascular coagulation (DIC), and acute kidney injury—should be anticipated and managed proactively. [37]

Antithrombotic considerations: Despite anaemia, patients with DIIHA are often hypercoagulable, especially in the context of brisk haemolysis and immobilization; therefore, the need for thromboprophylaxis should be actively assessed once bleeding risk is evaluated. [37] Individualized decisions (e.g., pharmacologic vs. mechanical prophylaxis) should be revisited frequently as haemolysis resolves.

Glucocorticoids and other immunomodulators: Steroids have no proven, consistent benefit in classic drug-dependent DIIHA, and many patients improve with drug withdrawal alone. Nevertheless, short courses are commonly used in refractory cases; if chosen, limit the duration to ~1–3 weeks, and reserve intravenous dosing for severe haemolysis requiring rapid effect. [36,39–40,37,40] Intravenous immunoglobulin (IVIG) and immunosuppressants such as cyclophosphamide or azathioprine may be considered when drug-independent autoantibodies are present and haemolysis persists despite stopping the culprit medication, reflecting a pathophysiology closer to warm autoimmune haemolysis. [36,40] Plasmapheresis is rarely indicated, but it may be contemplated in selected patients—particularly those with renal failure—when rapid reduction of putative pathogenic factors is desired and other measures have not sufficed. [36]

Expected time course and special scenarios: With prompt discontinuation of the offending drug, clinical and haematologic improvement usually occurs within 1–2 weeks, although the DAT may remain positive during that interval as immune reactants clear from the red cell surface. [37,39,40] In ceftriaxone-associated cases, haemolysis typically abates after drug cessation; antibodies can remain detectable for 1–2 weeks, but ongoing haemolysis is uncommon unless re-exposure occurs, which can provoke rapid recurrence. [37] Children may experience more severe reactions, and one study reported fatal outcomes in 36% of drug-induced IHA cases, underscoring the need for early recognition and decisive treatment. [42] Observational data suggest that about 55% of patients with DIIHA require transfusion support (Garbe et al., 2011), and although steroids were administered to 105/124 (85%) in that series, any apparent benefit is difficult to disentangle from the effect of drug withdrawal, which remains the cornerstone of therapy (Garbe et al., 2011).

Prevention of re-exposure and long-term safety: After recovery, lifelong avoidance of the offending medication is essential, and the patient's allergy/adverse reaction profile must be updated across their medical records. [36,41] Given the possibility of class cross-reactivity, clinicians should also avoid closely related agents within the same pharmacologic class and provide clear documentation to guide future prescribing. [36,41] Patient counselling should emphasize the risk of brisk, potentially life-threatening recurrence upon re-exposure and the importance of communicating the history to all healthcare providers.

Practical summary: Management of DIIHA hinges on rapid drug cessation, supportive care with transfusion when needed, thoughtful thromboprophylaxis, and judicious use of immunomodulation only in situations consistent with drug-independent autoantibody–mediated haemolysis or refractory disease. Most patients improve within 1–2 weeks once the culprit drug is stopped, but vigilance for complications of intravascular haemolysis and for renal

compromise is crucial during the acute phase. [35–41,42]

CONCLUSION:

In summary, this review underscores that drug-induced immune haemolytic anaemia (DIIHA) is rare but potentially life-threatening, with antibiotics—especially β-lactams such as penicillins and cephalosporins—being prominent culprits; accurate diagnosis hinges on marrying a meticulous drug timeline with mechanism-aware serology (polyspecific/monospecific DAT, eluate behavior, testing with drug-coated RBCs or soluble drug) to distinguish drug-independent autoantibodies, hapten (penicillin-type) and immune-complex (quinidine-type) pathways, and the increasingly recognized non-immune protein adsorption (NIPA) phenomenon that can explain DAT-positivity without demonstrable drug-specific antibodies; management is anchored in immediate cessation of the offending agent, supportive care and transfusion as indicated, vigilance for complications such as intravascular haemolysis, AKI, or DIC, and judicious, mechanism-guided use of steroids or other immunomodulators (primarily when autoantibodies are implicated), while long-term safety requires rigorous documentation and avoidance of re-exposure or close analogues to prevent severe recurrence.

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