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LINEZOLID-INDUCED THROMBOCYTOPENIA IN A PATIENT WITH RENAL IMPAIRMENT: A CASE REPORT

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1. INTRODUCTION

Linezolid was the first oxazolidinone antibiotic to reach clinical use, and its value is easy to understand. It is active against methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and many penicillin-resistant streptococci, it is almost completely absorbed when taken by mouth, and it reaches lung and soft tissue well [1, 2]. Randomised trials in skin infection and nosocomial pneumonia placed it alongside vancomycin as a standard option for resistant Gram-positive disease [3, 4]. More recently its role has widened to drug-resistant tuberculosis, where treatment courses run for

Abstract

Thrombocytopenia is the most common serious haematological adverse effect of linezolid, and it is reported far more often when kidney function is reduced. This narrative review draws on published trials, cohort studies, pharmacokinetic work and case reports to describe how linezolid is handled by the body, why platelet counts fall, which factors raise the risk, and how the event is recognised and managed. Accumulation of the drug and its metabolites, longer courses and critical illness emerge as recurring explanations. Evidence for dose reduction and drug monitoring is promising but based mostly on observational data. The article reports no individual patient and no new data.

months and not days [5, 6]. That longer exposure has brought its main weakness into sharper focus.

The weakness is bone-marrow toxicity. Early clinical experience showed that platelet counts fall in a proportion of patients, usually after the second week of treatment, and that

red cells and neutrophils may be affected too [7, 8]. The effect is generally reversible once the drug is stopped. Even so, a low platelet count in an acutely ill patient raises the risk of bleeding, forces transfusion decisions, and often compels a change of antibiotic at an unhelpful moment. Reports in people with chronic kidney disease or on dialysis described unusually high rates of the problem, and the association has been confirmed in many later cohorts [9, 10, 11].

This review addresses linezolid-induced thrombocytopenia in the setting of renal impairment, a topic usually met in the literature as isolated case reports and small retrospective series. It synthesises what is known about the drug's disposition, the likely mechanisms, the risk factors, and practical approaches to detection and management. No individual patient is described, and nothing here derives from new clinical observation. The emphasis is on what a pharmacist or prescriber can take from the published record when a patient with reduced kidney function needs, or already receives, linezolid, together with a frank account of what remains uncertain.

2. PHARMACOLOGY AND RENAL HANDLING

Renal impairment is defined, for the purposes of most of the studies discussed here, by estimated glomerular filtration rate. The KDIGO classification places chronic kidney disease at an eGFR below 60 mL/min per 1.73 m² for more than three months, or at markers of kidney damage, and stages severity from G3 to G5 according to the fall in filtration [12]. Dosing guidance for many drugs is organised around the same categories [13]. Linezolid is awkward in this respect, since its label contains no renal adjustment, so prescribers cannot rely on a standard table. They have to interpret a small and uneven body of research, and this accounts for much of the variation in practice between hospitals.

The standard adult dose of linezolid is 600 mg every twelve hours, given orally or intravenously, with no adjustment recommended by the manufacturer for renal impairment. Absorption is nearly complete, protein binding is low at around 30 per cent,

and the volume of distribution is close to total body water [1, 14]. Elimination is mixed. About a third of a dose appears unchanged in urine, while the rest is oxidised in a non-enzymatic process to two inactive carboxylic acid metabolites that are excreted mainly by the kidney [14]. Because only part of clearance is renal, the parent drug is not affected as dramatically by kidney failure as drugs eliminated entirely by that route, and this partly explains why the unadjusted dose became standard.

The antibacterial properties explain why the drug is so often chosen for patients whose kidneys are already compromised. Linezolid is bacteriostatic against staphylococci and enterococci and bactericidal against most streptococci, and its binding site on the 50S subunit means that cross-resistance with other classes is rare [1, 2]. Resistance remains uncommon and arises mainly through mutations in the 23S rRNA gene or acquisition of the *cfr* methyltransferase. Unlike vancomycin, it needs no level-guided adjustment to avoid nephrotoxicity, and unlike aminoglycosides it carries no renal penalty [3, 4]. A patient with infected pressure sores, a dialysis catheter infection or a diabetic foot is a very typical recipient, and often one in whom treatment is prolonged.

Detailed pharmacokinetic work in volunteers with different degrees of renal dysfunction showed what was missing from that simple picture. Systemic exposure to the parent drug rose only modestly as renal function declined, but the two main metabolites accumulated substantially, by several-fold in severe impairment, and haemodialysis removed a large fraction of linezolid and its metabolites [15]. At the time, the metabolites were considered inactive, so the finding was not viewed as clinically important. Subsequent studies in patients, as opposed to healthy volunteers, found higher trough concentrations of the parent compound in those with low creatinine clearance, and it is now clear that exposure varies widely [9, 16].

The relationship between exposure and effect gives the pharmacokinetics their clinical meaning. Antibacterial efficacy is best predicted by the ratio of the area under the concentration curve to the minimum

inhibitory concentration, and a ratio around 80 to 120 has been associated with good outcomes in seriously ill patients [1, 17]. Toxicity, on the other hand, follows trough concentration and cumulative exposure. Studies that measured plasma levels found that thrombocytopenia occurred more often when troughs exceeded roughly 7 to 8 mg/L, and that patients with impaired kidneys were over-represented in that group [18, 19]. A fixed dose therefore means efficacy that is adequate for most patients and toxicity that is unpredictable in some.

Population pharmacokinetic modelling has tried to put numbers on this. Models built from hospital patients identify creatinine clearance as the most important covariate for linezolid clearance, with body weight and age adding smaller effects [16]. When these models were used to simulate dosing in renal impairment, reduced daily doses brought exposure back toward the range seen in people with normal kidney function, and the predicted risk of platelet depression fell [20]. These are simulations and need confirmation, since a lower dose could fall short of the antibacterial target for organisms with higher minimum inhibitory concentrations, but the direction of the evidence is consistent across groups.

Linezolid is also a weak reversible inhibitor of monoamine oxidase, which has no bearing on platelets but matters whenever the drug is prescribed to patients with complex medication lists. Serotonin syndrome has been described when it is combined with serotonergic antidepressants, and hypertensive responses with sympathomimetics [2, 21]. In renal impairment the polypharmacy is typically heavier, because patients with chronic kidney disease take many agents for blood pressure, anaemia, mineral disorders and mood. A medication review at the time of starting linezolid is therefore valuable for several reasons, only one of which concerns the haematological risk discussed here.

3. MECHANISMS OF THROMBOCYTOPENIA

Two broad explanations have been proposed for the platelet fall, immune destruction and

suppressed production, and the evidence leans toward the second. In a report of mechanisms in humans, bone-marrow findings in affected patients resembled those seen with other drugs that reduce marrow output, with some patients showing reduced megakaryocytes, and the time course (onset after one to two weeks, recovery after stopping) pointed away from the rapid immune reactions typical of drug-dependent antibodies [22]. Immune thrombocytopenia due to drugs generally appears within days of re-exposure, and it is detected by drug-dependent antibody tests, whereas linezolid-associated cases usually follow a dose- and duration-related pattern [23].

The favoured mechanism involves mitochondria. Linezolid acts by binding to the 23S ribosomal RNA of the bacterial 50S subunit and blocking formation of the initiation complex. Mitochondrial ribosomes retain many features of their bacterial ancestry, and experiments in cultured mammalian cells showed that oxazolidinones inhibit mitochondrial protein synthesis and reduce the activity of respiratory chain complexes, with a clear concentration-response relationship [24, 25]. Cells with high energy demands and rapid turnover, such as haemopoietic precursors, would be expected to suffer first. This model is consistent with the other toxicities of long linezolid courses, namely lactic acidosis and neuropathy, which are also attributed to mitochondrial injury [21, 26].

Kinetic modelling has added support to the production hypothesis. In a population analysis of hospitalised patients, platelet counts over time were best described by a semi-mechanistic model in which linezolid reduced the rate of platelet production in proportion to its concentration, with a delay reflecting transit through the precursor compartments, and creatinine clearance and baseline count were important covariates [16]. The model reproduced the usual pattern of a nadir about two weeks into treatment and recovery after stopping. This does not prove the mechanism, since other models might fit as well, but it gives a framework in which exposure, duration and baseline marrow reserve act together, as clinical data suggest

they do.

How mitochondrial injury translates into thrombocytopenia specifically is less certain. Possible routes include reduced proliferation or maturation of megakaryocytes in the marrow, impaired platelet shedding from megakaryocytes, and toxicity to circulating platelets, whose mitochondria are needed for activation. Early clinical data suggested that the platelet count fell gradually and that neutrophils and haemoglobin often moved in the same direction, which favours a general marrow effect [7, 22]. Direct human marrow studies are scarce, so statements about megakaryocyte numbers rest on very few observations, and in vitro work in other cell types cannot be extrapolated safely to the megakaryocyte lineage.

Why kidney failure should aggravate the process has two plausible answers, which may operate together. The first is simple pharmacology: higher parent concentrations and larger metabolite loads mean more mitochondrial inhibition [9, 15]. The second concerns the host. Uraemia itself impairs platelet function and survival, haemodialysis exposes platelets to membrane contact and heparin, and anaemia of chronic kidney disease reflects a marrow already under strain [10, 11]. A patient with these baseline features has less reserve, so the same degree of marrow suppression produces a lower nadir. Untangling the two contributions would require studies that measure drug concentrations alongside baseline marrow function, and such studies have not been done in any systematic way.

Metabolite accumulation deserves special comment. Because the carboxylic acid metabolites were classed as inactive against bacteria, they were largely ignored in toxicity discussions. Whether they inhibit mitochondrial protein synthesis is not clear from the published experiments, which have mostly used the parent compound [24, 25]. If they contribute even slightly, their several-fold accumulation in advanced renal failure could be important [15]. It is an open question that could be answered in simple cell-based assays, and it would help to decide whether monitoring of the parent drug alone is enough in patients with severely reduced

clearance. Targeted laboratory work of this kind is cheap relative to the clinical questions it could settle.

4. RISK FACTORS AND THE ROLE OF RENAL IMPAIRMENT

Incidence figures vary greatly with the way thrombocytopenia is defined and the population studied. In the pooled early trials, where courses seldom exceeded four weeks, clinically relevant platelet reductions were seen in a few per cent of patients, and the comparator-controlled phase III studies reported higher rates of thrombocytopenia with linezolid than with comparators, though with broadly similar rates of serious events [7, 27]. Routine hospital cohorts tell a different story, with a substantially higher frequency, often from a fifth to a third of patients treated for longer than a week [28, 29, 30]. Findings from the studies that have tried to identify risk factors are summarised in table 1, and the way that evidence divides by type is shown in fig. 1.

Table 1: Published evidence on linezolid-associated thrombocytopenia and renal impairment

Study type focus	Reported finding	Ref.
Pharmacokinetic study renal dysfunction	Parent drug exposure rose modestly; carboxylic acid metabolites accumulated several-fold; dialysis removed drug.	[15]
Population PK modelling hospital patients	Creatinine clearance was the main covariate of clearance; reduced doses restore normal exposure.	[16, 20]
Plasma concentration cohorts monitoring	Higher trough levels linked to thrombocytopenia; kidney impairment common in the high-trough group.	[18, 19, 31]
Dose individualisation critical care	Monitoring-guided dosing reduced platelet toxicity without evident loss of effect.	[18, 32]
Renal insufficiency cohort Taiwan	Thrombocytopenia far more frequent with renal insufficiency than with normal function.	[10]
End-stage renal disease cohort dialysis	High frequency of thrombocytopenia and anaemia in dialysis patients.	[11]

Study type focus	Reported finding	Ref.
Higher exposure study renal dysfunction	Greater drug exposure and more thrombocytopenia with reduced renal function.	[9, 33]
Retrospective risk-factor analyses adults	Duration, low baseline platelets and renal function were the consistent predictors.	[28, 29, 30]
Early trial data safety summaries	Reversible platelet falls, mainly after two weeks of therapy.	[7, 8, 27]
In vitro cell studies mitochondria	Oxazolidinones inhibited mitochondrial protein synthesis in mammalian cells.	[24, 25]
Mechanism review clinical features	Time course pointed to reduced production, not immune destruction.	[22]

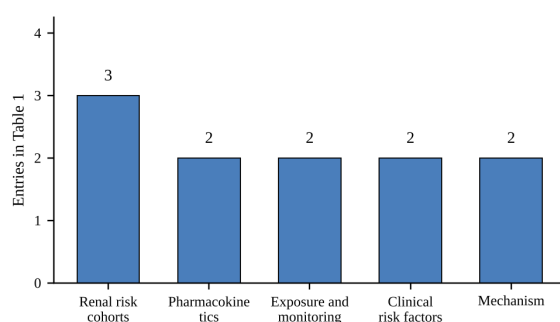


Fig. 1: Number of entries in table 1 by type of evidence

Definitions deserve attention because they drive the numbers. Some investigators define thrombocytopenia as a count below $100 \times 10^9/L$, others as below $150 \times 10^9/L$, and others as a relative fall of 25 or 30 per cent from the baseline value, with the choice of definition noticeably changing the reported incidence in the same data set [27, 28, 29]. A relative definition tends to capture more events in patients who start with low counts, which is the case for many patients with chronic kidney disease. Readers comparing studies should check the definition first. A clearer standard, such as a common grading scale for cytopenias, would be a minor improvement with large benefits for synthesis.

Duration of therapy is the most consistent predictor. Risk is low in the first week, climbs steadily thereafter, and is highest beyond fourteen days. The relationship is almost linear in some analyses, which fits with a cumulative mitochondrial effect [7, 29]. Baseline platelet count is the second strong

predictor, because a patient who begins with a count near the lower limit of normal has less distance to fall before crossing the threshold of $100 \times 10^9/L$ or a fall of 25 to 30 per cent from baseline, which many studies use as the definition [28, 29, 30]. Both factors are practical to apply, since duration is planned and baseline count is checked before starting.

Renal impairment ranks alongside them. In a series from a Taiwanese centre, patients with renal insufficiency developed thrombocytopenia far more often than those with normal function, and a follow-up report in end-stage renal disease described very high frequencies of both thrombocytopenia and anaemia [10, 11]. A Japanese study that stratified patients by creatinine clearance found that exposure to the drug was higher and thrombocytopenia more frequent in those with reduced function [9]. Others have confirmed that low estimated glomerular filtration rate and high plasma concentration independently predict the event [33]. The effect holds after adjusting for treatment duration, suggesting that it is not just an artefact of longer courses in sicker patients.

Concomitant therapy contributes in ways that are difficult to quantify. Patients with chronic kidney disease frequently receive heparin during dialysis, erythropoiesis-stimulating agents, iron preparations, antiplatelet drugs and other antibiotics, and several of these can themselves influence platelet counts or complicate their interpretation [11, 34, 35]. Studies that adjusted for such factors generally still found renal function and linezolid exposure to be independent predictors [9, 33]. Even so, residual confounding is likely, since sicker patients both receive more drugs and have lower platelets. For the clinician, the point is that a multidrug regimen widens the differential diagnosis and makes it more important to keep the timeline clear.

Other recognised risk factors include low body weight, older age, liver disease, concurrent critical illness and sepsis, and previous exposure to other drugs that suppress the marrow [28, 29, 30]. Critical illness is a particular source of confusion. Thrombocytopenia is common in intensive care for many reasons, with sepsis,

disseminated intravascular coagulation, haemodilution and drugs all contributing, and a systematic review noted that its presence is associated with higher mortality independent of the cause [36]. In this setting a drop in platelets during linezolid therapy is not by itself proof of causation, and the attribution depends on the timing, the dose, the plasma concentration and the response to withdrawal.

Several groups have tried to combine these predictors into scores or rules. Models based on baseline platelet count, renal function, treatment duration and sometimes serum albumin or concomitant drugs reached moderate discrimination in their derivation cohorts [28, 30]. External validation has been limited, so such tools are best viewed as ways of drawing attention to patients who need closer monitoring, not as devices for deciding who may receive the drug. They also remind clinicians that a patient with several risk factors, for example a dialysis patient with a low baseline count and an expected course of three weeks, is in a quite different position from one with a single risk factor and a one-week course.

Haemodialysis introduces its own pharmacokinetic wrinkle. Since linezolid is removed by dialysis, the timing of the dose relative to the session affects exposure, and giving it after dialysis avoids loss of drug during the procedure [15]. Patients on continuous renal replacement therapy show wide variation in clearance depending on the intensity of treatment, and plasma concentration measurements in those patients have shown both under-exposure and accumulation [16, 18]. The wide spread of values is one of the better arguments for measuring drug levels in critically ill patients with kidney injury, whose clearance changes from one day to the next.

5. RECOGNITION, MONITORING AND MANAGEMENT

Recognition begins with an expectation. Anyone starting linezolid for longer than a few days should have a baseline full blood count, and counts should be repeated at least weekly, with more frequent checks (two or three times a week) in patients with renal impairment, low baseline platelets or other

risk factors [7, 37]. Thrombocytopenia is usually asymptomatic until counts are quite low, so the laboratory is the main means of detection. Bruising, mucosal bleeding or petechiae are late signs. The pattern to watch for is a steady fall over several days, which should prompt a review before the count reaches the usual action thresholds.

A structured assessment helps to separate drug effect from other causes. The differential diagnosis for a falling platelet count in a hospitalised patient includes sepsis and disseminated intravascular coagulation, heparin-induced thrombocytopenia, immune thrombocytopenia, drug-dependent antibodies due to other agents such as beta-lactams or vancomycin, haemodilution, and marrow infiltration [23, 34, 35]. The 4Ts score offers a rapid assessment of heparin-induced thrombocytopenia, which is of obvious relevance in dialysis patients exposed to heparin [35]. A Naranjo-type causality assessment can then be recorded, noting that it is a crude instrument and that a probable rating usually depends on timing and recovery after withdrawal [38].

Platelets are not the only cell line affected, and monitoring should be broad. Anaemia and, less often, neutropenia accompany thrombocytopenia in a substantial minority, and in patients with end-stage renal disease the anaemia of treatment may be difficult to separate from that of the underlying disease [7, 11, 22]. Longer courses bring other toxicities as well. Peripheral and optic neuropathy appear after weeks to months of exposure and are often only partly reversible, while lactic acidosis can present abruptly with nausea, vomiting and breathlessness [21, 26]. A patient receiving a prolonged course should therefore be asked regularly about numbness, visual change and unexplained malaise, in addition to having the laboratory results checked.

Once linezolid is judged the likely cause, the first decision is whether it can be stopped. If an alternative active agent exists, switching is the safest course, and platelet counts typically begin to recover within several days of discontinuation, returning to baseline in one to three weeks [7, 8, 37]. If linezolid is needed, for example in a drug-resistant

infection where options are limited, then continuing with a reduced dose, with close monitoring, is a reasonable alternative that has been described in tuberculosis programmes [5, 39]. Transfusion is reserved for bleeding or very low counts, and there is no evidence to support routine platelet administration for asymptomatic mild thrombocytopenia.

Dose adjustment guided by drug monitoring is the most active area of research. Several centres have reported that individualising the dose to keep the trough in a window of about 2 to 7 mg/L reduced the proportion of patients developing thrombocytopenia, without obvious loss of clinical effectiveness [18, 19, 32]. Proposed regimens for severe renal impairment typically halve the daily dose, for instance 300 mg twice daily or 600 mg once daily, then adjust according to measured levels [13, 20]. The evidence comes from observational cohorts and modelling, not from randomised comparison, and not every hospital has a laboratory able to measure linezolid, which limits uptake.

The choice of alternative agent in renal impairment is rarely trivial. Glycopeptides require trough-guided dosing and carry a nephrotoxic risk that is unattractive in someone whose kidneys are already damaged, and the evidence base for newer options in prolonged therapy is smaller than for linezolid [3, 4]. In tuberculosis the alternatives may simply not exist, which is why dose adjustment has been explored so extensively [5, 6]. The prescriber therefore weighs a known and manageable haematological risk against less predictable alternatives. Documenting this reasoning, and the agreed monitoring plan, is a sensible habit, as it makes later review easier and gives a clear reference point if the platelet count starts to fall.

Experience in tuberculosis supports the idea of dose reduction. A trial of highly drug-resistant tuberculosis compared linezolid at different doses and durations within a combination regimen, and found that lower doses were associated with fewer episodes of myelosuppression and neuropathy with outcomes that remained favourable, while an earlier trial in extensively

drug-resistant disease had shown a clear dose-related trend in adverse effects [5, 6]. A review of the narrow therapeutic index of the drug in this setting concluded that monitoring and dose adjustment were likely to be more helpful than empirical use of the full dose [39]. These conclusions are extrapolated to renal patients with caution.

6. GAPS AND PRACTICE IMPLICATIONS

Several gaps limit confident recommendations. Most studies are retrospective, single-centre and small, and they differ in how they define thrombocytopenia, which makes pooling hazardous. Patients with end-stage renal disease or on renal replacement therapy are under-represented in trials and over-represented in reports of toxicity. Few studies report drug concentrations with the platelet data, and fewer still report metabolite concentrations. Pharmacokinetic studies in volunteers cannot reproduce the changes in protein binding, fluid balance and organ function seen in the acutely ill [15, 16]. Reporting bias is also likely, since an unusual or severe event is more likely to be published than a routine one.

Research that would be most informative is not hard to describe. Prospective cohorts of patients with defined grades of renal impairment, with scheduled platelet counts and trough sampling, would clarify exposure-response relationships. A pragmatic randomised trial comparing standard and reduced dosing in advanced renal impairment, with efficacy and haematological end points, would provide the evidence that modelling cannot [20, 32]. Mechanistic work on megakaryocyte biology and on the contribution of metabolites would address the question of why kidney function matters. Pharmacogenetic studies have so far been unrewarding, and there is little reason to expect that genotyping will help in routine care soon.

For practice, the published record supports a handful of simple measures. Check a baseline blood count, and record renal function. Limit the duration to what the infection requires, and review at one week. Monitor counts more

often in patients with kidney disease, and have a plan before the count falls. Consider a reduced dose or drug monitoring in advanced impairment, particularly when a course longer than two weeks is expected [18, 20, 37]. Choose an alternative where one of comparable effect exists. None of these steps is costly, and together they address most of the avoidable harm described in the literature.

Pharmacovigilance has a part to play. Spontaneous reports are the origin of most knowledge about rare effects, but they are weak for common ones, in which underreporting is the rule and numerators are not matched with denominators. Structured reporting of suspected cases, with causality assessed by a recognised method and with dose, renal function, drug concentration and outcome recorded, would make the reports far more useful [37, 38]. Hospital pharmacists are well placed to organise this, since they see both prescribing and laboratory data. Repeated, consistently documented reports from different centres could confirm or refute the signal for specific subgroups such as patients receiving haemodialysis, in whom trials will probably never be large.

Patient information is easily overlooked. People who receive linezolid at home, for example for tuberculosis or osteomyelitis, need to know which symptoms deserve prompt attention, including unusual bruising, nosebleeds, black stools, numbness in the feet and changes in vision, and they need access to a laboratory for regular blood tests [26, 39]. Dialysis units can include a blood count in routine pre-dialysis sampling. Taking these steps costs little in comparison with the consequences of an unrecognised complication, and they are a natural role for community and hospital pharmacists working with the prescriber. Pharmacy-led telephone follow-up during the second week is one approach that some services have adopted.

7. CONCLUSION

Linezolid-induced thrombocytopenia in patients with reduced kidney function is best understood as a predictable, exposure-related effect, not an idiosyncratic reaction. The drug and its metabolites accumulate when clearance falls, the likely mitochondrial

mechanism depends on concentration and duration, and published cohorts show consistently higher event rates in patients with renal insufficiency or dialysis dependence [9, 10, 11, 15, 24]. Longer courses, low baseline counts and critical illness add to the risk. Recovery after withdrawal is usual, although a few patients experience clinically important bleeding before the problem is noticed. Early recognition therefore depends on awareness of these predictors at the time of prescribing.

The practical response is anticipatory care rather than avoidance. Baseline and frequent blood counts, limits on treatment duration, early review of alternatives, and consideration of reduced dosing or concentration monitoring in advanced renal impairment are all supported by the available evidence [18, 20, 32, 37]. That evidence remains observational, and trials of reduced dosing would settle the matter more securely. Until they exist, clinicians should combine the published signals with local resources and the needs of the individual infection, and should report suspected cases so that the evidence base continues to grow.

8. ABBREVIATIONS

ADR-Adverse drug reaction, AUC-Area under the concentration–time curve, CKD-Chronic kidney disease, MIC-Minimum inhibitory concentration, MRSA-Methicillin-resistant *Staphylococcus aureus*, PK-Pharmacokinetic, rRNA-Ribosomal RNA, TDM-Therapeutic drug monitoring, 4Ts-Thrombocytopenia, timing, thrombosis, other causes score, eGFR-Estimated glomerular filtration rate

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Nil

10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

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