Review Article

Investigative algorithms for disorders affecting plasma lactate dehydrogenase: a narrative review

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Background and Objective: The following article is part of a special series to aid the reader in diagnosing the cause of various plasma derangements in humans. By the end of the article, the reader will be able to order and interpret appropriate investigations when faced with a patient with low or high lactate dehydrogenase (LDH) activity in plasma.

Methods: A narrative, focused literature review was performed using Medline, OMIM and Google Scholar from April 2023 to September 2023 to identify references published from database inception to September 2023; reference lists from these articles were also used. The language was restricted to English.

Key Content and Findings: LDH is produced by all cells and can be released into plasma in a vast number of pathological processes. Liver and red blood cells are a common source as is skin, lung, muscle, and the gastrointestinal tract. A laboratory approach to the investigation of elevated LDH is presented, no algorithm was produced for low LDH activity as causes are too scarce and of unlikely clinical significance. The clinical status and condition of the patient should be considered first in order to carry out a targeted investigation however full blood count, liver and renal function tests may be used as first line tests.

Conclusions: Diagnostic flow charts have been created to help aid healthcare professionals to investigate the cause of elevated LDH activity where the cause is not immediately apparent. These algorithms have been presented and created within the limitations of the laboratory tests discussed within the paper, selected to be widely available.

Keywords: Lactate dehydrogenase (LDH); diagnosis; measurement; investigation

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Introduction

The measurement of plasma lactate dehydrogenase (LDH) initially became widespread due to its role in detecting acute myocardial infarction (1). However, LDH gained popularity in a wide range of medical and surgical specialties due to its almost ubiquitous tissue location (2). Plasma LDH activity therefore may be performed as part of screens when a clinician is faced with an unwell patient and is also part of various staging and monitoring algorithms (3). As a wide range of normal tissues and tumors can produce LDH, an isolated elevated LDH is not diagnostic of any single condition, therefore clinical clues and other investigations are required to elucidate the cause of an LDH elevation.

The following paper will discuss how to approach deviations of LDH concentrations from the normal range

Table 1 The search strategy summary

Items	Specification
Date of search	April to September 2023
Databases and other sources searched	Medline, Google Scholar, OMIM
Search terms used	LDH, lactate dehydrogenase, Low, High, Raised, Tissue, Activity, Drugs, Investigations, Algorithms, Guidelines, Diagnosis, Causes, Aetiology, Human
Timeframe	From database inception to September 2023
Inclusion and exclusion criteria	All papers and reviews were included but restricted to English. Animal data were excluded
Selection process	A.R.S. and S.B. conducted initial search, with refinement by all other authors to obtain consensus and agreement
Any additional considerations, if applicable	Seminal texts were also searched and the references of important articles and texts were obtained and checked for relevance

OMIM, Online Mendelian Inheritance in Man.

and provide a systematic laboratory algorithm, which can be used to help the clinician account for plasma LDH activity elevation when struggling to find the diagnosis. We will not cover the investigation of LDH in bodily fluids. The algorithms are designed for all healthcare professionals irrespective of their expertise, or lack of expertise, with diagnostics and are meant to provide an up-to-date suggestion to guide management steps that can be validated in the future in a variety of healthcare settings and patient populations. We present this article in accordance with the Narrative Review reporting checklist (available at https://jlpm.amegroups.org/article/view/10.21037/jlpm-23-65/rc).

Methods

The limited narrative literature review was created by searching Medline, Google Scholar, OMIM and seminal texts over the period April 2023 to September 2023. The diagnostic algorithms were then created based on the literature review by the authors. The language was restricted to English and excluded if non-human studies. For further information please see *Table 1*.

What is LDH?

LDH is a universally expressed enzyme across all cells and conserved between organisms. LDH concentrations are highest in high energy consuming organs such as muscles, liver, kidneys, lungs, heart, and blood cells (4). LDH is involved in the anaerobic metabolic pathway (*Figure 1*) (3,4). LDH reversibly converts pyruvate to lactate, and hydrogenated nicotinamide adenine dinucleotide (NADH) to nicotinamide adenine dinucleotide (NAD+), and generates adenosine triphosphate (ATP) when oxygen supplies dwindle (3,4). At the molecular level, LDH is a tetramer comprising two common subunits, A and B, with subunit C predominating in sperm and testes. Chromosomes 11 and 12 host the genes encoding these subunits and various combinations—homo- or heterotetrameric—yield a diverse assortment of five LDH isoforms, called LDH1 to LDH5 (3,4). Although all these isoenzymes facilitate the same catalytic reaction, their structural composition, substrate affinity, temperature responsiveness, and tissue-specific distributions diverge markedly (3,4). Distinguishing between them however is not a test commonly available to most clinicians.

How is LDH measured?

LDH is quantified by measurement of the enzymatic activity of the specimen rather than concentration of the enzyme. When measuring the enzyme activity one can either detect the formation of lactate from pyruvate, which is the internationally recommended reference method described as “forward” or “lactate pyruvate (LP)”, or vice versa [“backward” or “pyruvate lactate (PL)”] (5,6). This has allowed reference material to be produced and therefore an ability to harmonize assays internationally making reference intervals potentially comparable (7,8). However, there is a variety of methods used internationally (6). In addition to the direction of the reaction, different reagents and buffers can be used resulting in very discrepant results between

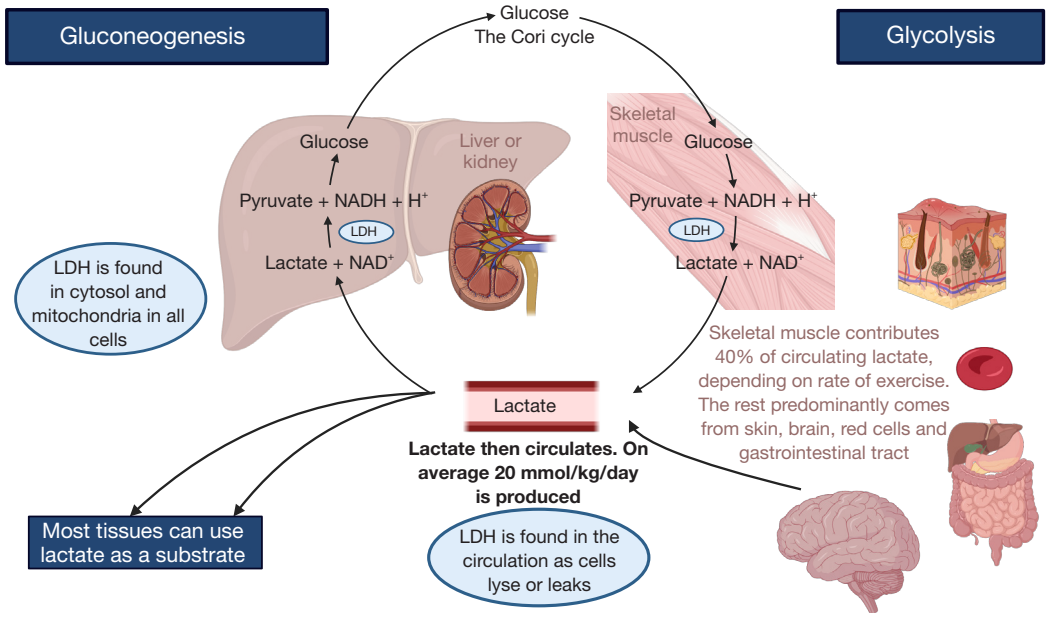

Figure 1 Lactate production and the Cori cycle. Figure to show LDH activity in glycolysis and gluconeogenesis. LDH is involved in energy production in muscle (and other tissues) and whilst lactate will be found in normal circulation (with levels increasing with exercise). LDH should only be present in the circulation if cells are lysed. LDH, lactate dehydrogenase; NAD, nicotinamide adenine dinucleotide; NADH, hydrogenated nicotinamide adenine dinucleotide.

assay manufacturers preventing harmonization (9).

LDH isoenzymes can be separated and quantified by electrophoresis but other biomarkers have replaced this test and it is no longer routinely performed (10). Electrophoresis may also detect 'macroLDH', a spurious cause of increased activity (11). In the "macro" condition antibody or cell wall components bind LDH preventing clearance and hence causing accumulation that is not related to an increased rate of release from the tissue of origin (12).

Although antibody binding can cause increased accumulation of LDH, and hence an increase in serum activity which can be spuriously attributed to tissue damage, it may also inhibit enzymatic activity analytically causing a spuriously low measured level even in the face of an increased serum concentration (13,14). Other causes of spurious results include *in vitro* haemolysis releasing LDH into the tube and elevating LDH activity in the specimen (15). Spuriously raised LDH activities have also been reported secondary to triamterene (16). Potentially spuriously low LDH activities have been reported secondary to hyperlipidaemia, aspirin and vitamin C (17-19). Small elevations in activity of LDH in lymphoma may not always be indicative for change in tumour burden (20).

Causes of raised LDH activity

Elevated LDH activity arises due to multiple aetiological factors affecting almost every organ system (2). Commoner organ system causes of LDH elevation are either because the tissue has greater mass, more LDH expression or because the diseases are the most common. For example, in one study of 500 people with elevated LDH activity the pathology identified, in descending order of frequency, was (21):

- Cardiorespiratory diseases;
- Malignancy;
- Fracture;
- Central nervous system disease;
- Infection/inflammation;
- Hepatic cirrhosis and/or alcoholism;
- Trauma without fracture;
- Infectious mononucleosis;
- Hypothyroidism;
- Uraemia;
- Necrosis;
- Pseudo-mononucleosis;
- Viraemia;
- Intestinal obstruction;
- Idiopathic in 3%.

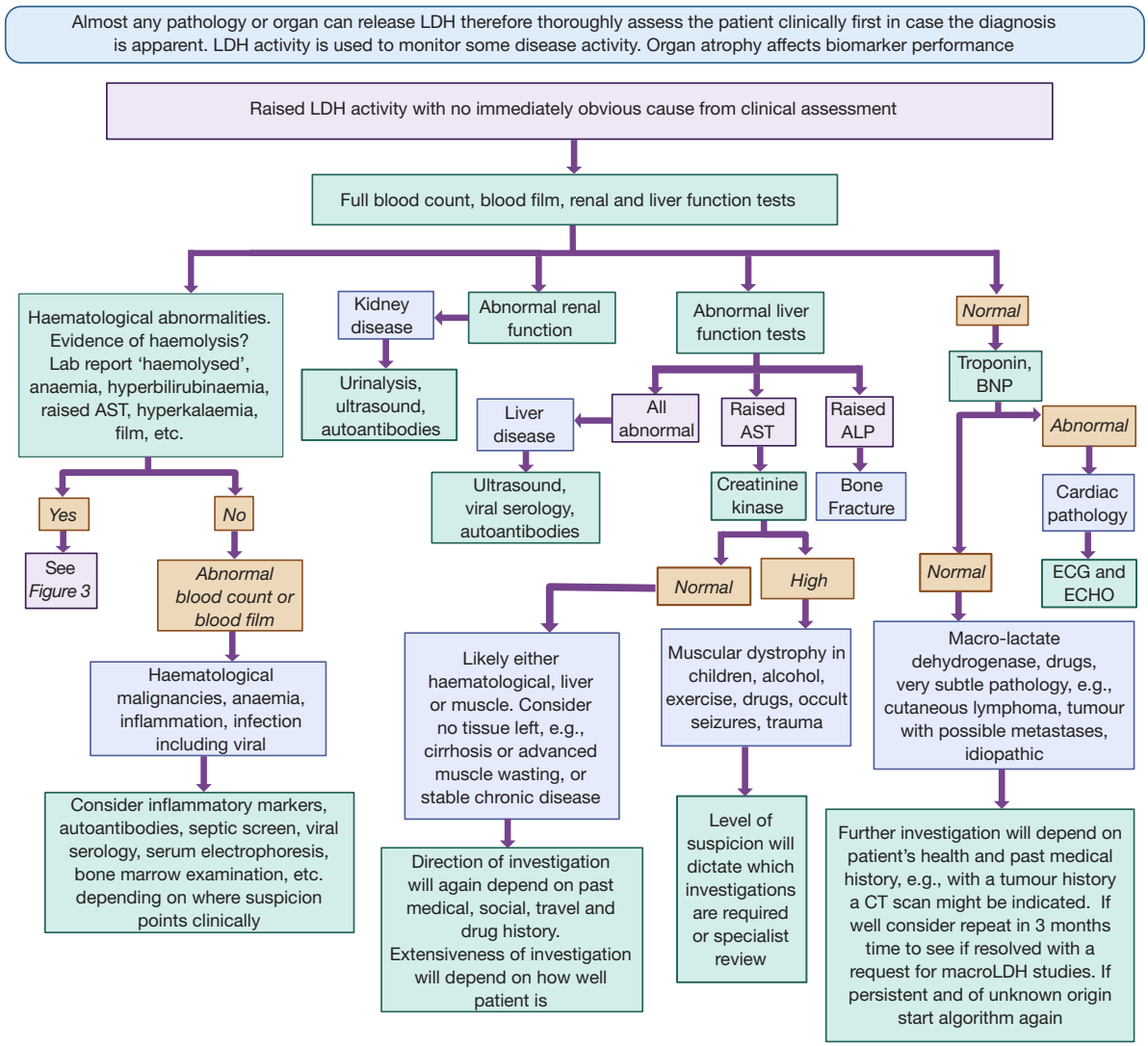

Figure 2 Diagnostic algorithm for elevated LDH activity. LDH is produced in all tissue and so elevation of activity in human sera is not, alone, a helpful diagnostic biochemical marker. The algorithm presented here is to help someone find a reason for LDH elevation if the cause if not instantly obvious in the patient's clinical presentation. It includes an approach to appropriate investigations that might be required along with clues from history and examination. LDH, lactate dehydrogenase; AST, aspartate transaminase; ALP, alkaline phosphatase; BNP, brain natriuretic peptide; ECG, electrocardiogram; ECHO, echocardiogram; CT, computed tomography.

One group tried to see if an elevated LDH activity on admission to hospital could provide any diagnostic or prognostic advantage (22). The cases were defined as those at hospital admission with LDH >800 IU/L [and aspartate transaminase/alanine transaminase (AST/ALT) <60 U/L] and the control group was those admitted with LDH <800 IU/L (and AST/ALT <60 U/L). Diagnoses were similar between the groups, the main notable exceptions were that infections (predominantly pulmonary), solid tumors, liver metastases, and haematological malignancies were more frequent in the case group and cardiovascular disease more common in the controls. With 158 patients in the case group and 188 in the control, and 14 main diagnoses driving admission, power was limited but confirms the fact that LDH remains a non-specific marker and other tests are required to reach a diagnosis. Therefore, whilst we present an algorithm (*Figure 2*) to help diagnose the cause of an elevated LDH if one is uncertain after

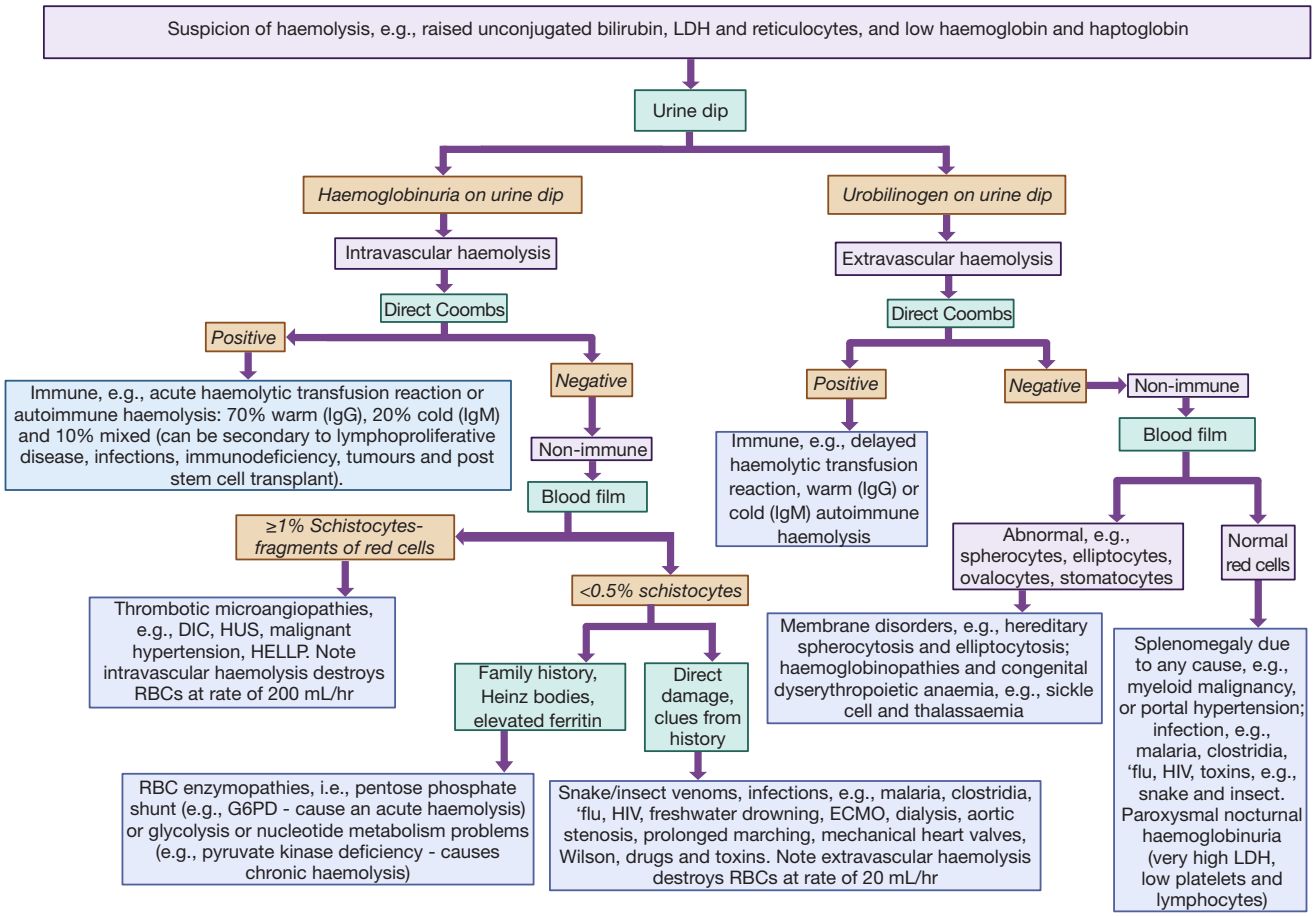

Figure 3 Investigative algorithm for determining the cause of haemolysis. Figure to show an algorithm of laboratory tests a clinician can use to determine the cause of haemolysis if they are uncertain of the aetiology. LDH, lactate dehydrogenase; IgG, immunoglobulin G; IgM, immunoglobulin M; DIC, disseminated intravascular coagulation; HUS, haemolytic uraemic syndrome; HELLP, haemolysis, elevated liver enzymes and low platelets; RBC, red blood cells; G6PD, glucose 6-phosphate dehydrogenase; ECMO, extracorporeal membrane oxygenation; 'flu, influenza; HIV, human immunodeficiency virus.

clinical assessment, it is important to remember that LDH in general is perhaps better employed as a marker of disease activity, rather than a specific diagnostic tool.

Connective tissue

Adipocytes contain LDH however obesity alone does not seem to cause an elevation in circulating LDH (23). In conditions of underweight patients, elevations to LDH are due to a multitude of causes, e.g., in cancer cachexia the tumor, tissue breaks down and drugs commonly elevate LDH (24). In anorexia nervosa elevated LDH may be due to skeletal muscle breakdown, mediated by low T3 (25). Elevated LDH was also shown by other groups in anorexia nervosa patients (compared to normal controls) but the LDH was also elevated, perhaps not unexpectedly, in a comparator group of those who were anorectic due to bowel surgery or malignancy (26,27). However, another study demonstrated lower LDH in anorexia nervosa compared to controls (28). Perhaps these contradictory results reflect other tissue damage that can occur in anorexia nervosa meaning low body weight alone is insufficient to cause a disturbance compared to, e.g., muscle breakdown, cardiac stress or liver damage (29).

All five LDH tetramers are expressed in skin but LDH-5 is the most common form (30). Burns elevate

LDH and the deeper the burn the higher the LDH as the tissue anaerobically respires secondary to the tissue damage (31). However extensive and common skin diseases, such as psoriasis and eczema, do not seem to cause a clinically significant increase in LDH (32-34) However a correlation with LDH activity and the severity of eczema in children has been noted and higher LDH activity predicting poorer response to treatment in these patients (35,36).

LDH measurement has been recommended in various guidelines for skin malignancies, e.g., cutaneous lymphoma and melanoma (37). Elevated LDH levels have demonstrated a correlation with unfavourable prognosis with cutaneous lymphoma and LDH has also been integrated into the tumor-node-metastasis (TNM) staging system for melanoma (38-40). Insights gleaned from cancer databases demonstrate the consistent elevation of LDH expression in malignancies, thereby accentuating its potential role in the meticulous monitoring of metastatic cutaneous tumours (41). The interpretation of LDH measurements within cutaneous malignancy warrants thoughtful consideration and caution, given the absence of definitive trials to substantiate its specific role (3,41).

LDH is also elevated in connective tissue disease conditions characterized by extensive tissue damage, including dermatomyositis, myositis, and panniculitides. This connection means that LDH levels could potentially be used to track disease activity within these contexts (41). Other more traditional rheumatological disorders such as systemic sclerosis might elevate LDH, correlating with a more aggressive and multiorgan disease (42). However cutaneous only sclerosis or lupus do not seem to be related to an elevated LDH in the literature. A spectrum of rheumatological diseases have not related to LDH elevation in one small case series (43) however there are papers of LDH being related to disease activity of Adult Still disease, rheumatoid arthritis and vasculitis for example (44-49).

Bone is another source of LDH and injuries, particularly fractures, will lead to elevation. In athletes, a raised LDH might point towards stress fractures for example with the correct history (50). Raised LDH is a poor prognostic indicator in hip fracture patients, although whether the LDH levels is related to the degree of bone injury or rather muscle death from ischaemia, haemorrhage, long lie, cardiac stress, etc. is not certain (51). Certainly, an early study showed that operative repair of hip fractures did not cause a significant change in LDH and therefore, whilst the bone fracture and muscle damage can increase LDH serum activity levels, if there is a significant elevation of LDH then the clinician needs to consider if there are other sources, e.g., a cardiac event (52). LDH has also been shown to rise in rare sclerosing bone pathologies (53).

Nervous and muscular systems

Lactate metabolism increases in brain injury and multiple pathologies have been related to elevated LDH in serum including intracerebral haemorrhage, ischaemic or haemorrhagic stroke, post-epileptic seizures (and indeed can be used as a biochemical marker to distinguish an epileptic versus non-epileptic seizure), infectious meningitis and encephalitis, cerebral oedema, encephalopathy related to pre-eclampsia, post brain surgery with complications and traumatic brain injuries (54-63).

Cardiac muscle is another common source of LDH elevation, with LDH once being used as a marker for myocardial infarction before being replaced with troponin T (64,65) and so will be elevated post cardiac arrest, shock and hypoxia. Cardiomyopathies, heart failure, valve disease, QTc prolongation, pulmonary hypertension, arrhythmia such as atrial fibrillation, rheumatic heart disease (66), prosthetic valves (particularly if leaking) and trauma causing intravascular haemolysis and pre-eclampsia can all cause LDH elevation and again LDH is often not used diagnostically but as a marker of disease activity or prognostication (67-74).

It should be noted that LDH is in smooth muscle too (75), so whilst perhaps a rarer cause of serum LDH elevation any damage to smooth muscle can contribute to LDH elevation. Smooth muscle is present in blood vessels, uterus, ureteric tracts to name just a few systems. Smooth muscle pathologies are unusual, but a few examples include:

- Autoimmune diseases, e.g., anti-smooth muscle antibodies often associated with autoimmune hepatitis;
- Tumours, e.g., leiomyomas and leiomyosarcomas, the latter often causing a greater elevation in LDH (76-78).

Skeletal muscle breakdown will release LDH into the serum. Any cause of muscle breakdown will trigger this, e.g.,

- Alcoholic myopathy (79);
- Inflammatory myositis (80);
- Muscular dystrophy (81);
- Strenuous exercise (82);
- Drug induced, e.g., steroids, statins, quinines (83).

As muscle is destroyed there is less tissue to release LDH and so if a disease has already caused significant muscle atrophy but is still active it may not produce high LDH

activity (unless for other reasons, e.g., increased cardiac stress due to failing skeletal muscles).

Haematological

Haemolysis is a common cause of LDH elevation. *Figure 3* shows a laboratory diagnostic algorithm approach to haemolysis (from sister article in this series on bilirubin investigation with identical methodology). Severe pernicious anaemia can cause an LDH elevation (84) as can megaloblastic anaemia (85), sickle cell (86,87), Epstein-Barr virus (88), thrombocythaemia (89), haematological malignancy (90), polycythaemia (91), splenic necrosis (92) and paroxysmal nocturnal haemoglobinuria (93). However, a normal LDH does not preclude a haematological malignancy, for example, up to 80% of patients with myeloma will have normal LDH activity (94). The worse the disease the more likely the elevation of LDH and higher LDH is a clue to a worse prognosis. It should be noted that it also possible for inflammatory diseases with high lymphocyte activity to lead to a raised LDH, e.g., T lymphocytes in psoriasis (32) or lymphadenopathy in sarcoidosis (95).

Other viscera

A study demonstrated elevated LDH in 204 newly diagnosed cervical cancer patients but unfortunately, they were compared to healthy controls rather than to those with cervical dysplasia or HPV infections, and whilst statistically significant the median LDH values were 194 U/L [interquartile range (IQR), 65.25 U/L] in patients compared to 180 U/L (IQR, 40.75 U/L) in controls (96). However, another study demonstrated a higher LDH pre-cervical cancer treatment was associated with a worse prognosis (97). Ovarian tumors can elevate LDH, and in children point towards dysgerminomas in particular (98) but LDH is also elevated in benign gynaecological disease (99). Whilst LDH activity will be elevated more in malignant gynae pathology the degree of elevation is not great enough to allow for a confident discrimination from benign disease using LDH activity alone (100).

Renal transplant rejection has also been noted to cause an elevation in LDH (101) and LDH has been noted to increase post dialysis although mechanical trauma might be the reason for this elevation (102). Nephropathies and chronic kidney disease of any cause can also elevate LDH, of course the more severe disease, especially if there is infarction, the greater the elevation (103-109). LDH can be used a poor prognostic marker in acute kidney injury and renal cell carcinoma and also a marker of multiple organ involvement in a particular illness (110,111).

LDH can be used as a prognostic marker for the refractory nature of mycoplasma pneumonia, for example in children a cut off 408 IU/L has an area under the receiver operating characteristic curve (AUROC) of 0.812 (sensitivity of 75% and specificity of 72.2%), i.e., LDH higher than 408 IU/L predicts the pneumonia will be refractory to treatment (112). One group showed that elevated LDH after subarachnoid haemorrhage statistically significantly predicted post operative pneumonia (113) however their LDH values overlapped (pneumonia group 261.26±126.51 U/L *vs.* no pneumonia group 189.00±69.20 U/L) perhaps reflecting that the brain injury itself plus any seizures, surgery etc. might also be putting the LDH up in this situation.

Pulmonary embolus and infarction will elevate LDH (114) but not of a degree to help distinguish between myocardial and pulmonary infarct in the setting of chest pain and breathlessness (115). LDH elevation does seem to distinguish between children with asthma, compared to controls (116) and there may be a correlation of LDH with prognosis in chronic obstructive pulmonary disease in adults and interstitial lung disease (117,118). LDH elevation is perhaps more closely link to pneumonia compared to other causes of infection in acute hospital admissions but the actual difference between LDH levels does not render it a useful clinical test in this setting (119).

The gastrointestinal tract is another source of LDH in the serum. Pancreatitis, pancreatic necrosis or mesenteric ischaemia cause LDH elevation as does bowel gangrene (120-122). Any liver pathology can elevate LDH including hepatitis, cholestasis, trauma and cirrhosis, and again higher levels are more likely to be related to poor prognosis and mortality in both liver disease and peritonitis (123,124). Stomach pathologies do not seem to elevate LDH, whether benign or malignant (125).

Hypothyroidism can lead to an elevated LDH due to skeletal muscle breakdown and hyperthyroidism to a relative decrease (126,127). LDH is an important enzyme in phaeochromocytoma (128) and has also been shown to be raised in diabetes mellitus and Cushing syndrome (129,130).

Diseases

Tumours, particularly the malignant and metastatic, often

Table 2 Current known genetic conditions which result in low lactate dehydrogenase concentrations in serum

Genotype	Title	Phenotype
LDHA, autosomal recessive, chromosome 11	Glycogen storage disease XI or lactate dehydrogenase A deficiency	Exertional myoglobinuria, easy fatigue, exercise-induced elevation of lactate, pyruvate, creatine kinase with myoglobinuria. Can develop renal failure. Skin rash—non-pruritic erythemato-squamous patches
LDHB, chromosome 12	Lactate dehydrogenase B deficiency	Does not seem to cause a disease, just a low reading of lactate dehydrogenase activity than normal values
LDHC, chromosome 11	Lactate dehydrogenase C deficiency (testicular form)	Impaired sperm motility
LDHD, chromosome 16, autosomal recessive	D-lactic aciduria with gout	Elevated D-lactate in plasma and urine, elevated serum uric acid, low urinary uric acid levels, reduced renal clearance of uric acid and gouty arthropathy

LDHA, lactate dehydrogenase A gene; LDHB, lactate dehydrogenase B gene; LDHC, lactate dehydrogenase C gene; LDHD, lactate dehydrogenase D gene.

have a higher metabolism so take up more glucose [hence the rationale of positron emission tomography (PET) imaging] and produce more lactate, via LDH activity. The higher the LDH the more active the cells metabolically but also the LDH activity seems to suppress immune surveillance and therefore helps the tumour survive (131). This review will not tackle the prognostic indication that LDH might provide with cancer monitoring but it is widely used in the oncology setting, partly as a marker of tumour burden and monitoring changes to the levels indicating treatment success or relapse. LDH activity has been shown to be elevated in many tumours, particularly metastatic breast, colorectal, germinal testicular, gastric, hepatoma, lung, ovarian, pancreatic, melanoma, prostatic, renal, sarcoma, seminoma and thyroid (132,133). Chemotherapy can lead to LDH rises initially, as expected, due to tumor breakdown (134).

Infection can cause LDH elevation, e.g., human immunodeficiency virus (HIV), usually in acquired immunodeficiency syndrome (AIDS)-defining infections or coronavirus disease 2019 (COVID-19) (135,136). There is an unusual LDH elevating virus, although this seems to be specific to mice (137). Malaria is a cause of LDH elevation, partly due to its effects on red cells (138). Again, the worse the infection the more likely one will detect an LDH elevation.

Low LDH

There are multiple different genetic conditions described as causing an LDH deficiency. In most, there is no disease and instead what happens is that there is an unusually low LDH activity than expected on laboratory testing (*Table 2*) (139,140). However, the lack of LDH, as could be expected, can impair the person's ability to perform physical activity and progress in labour (141). Clinically low LDH is not something that is ever a cause for clinical concern.

Special circumstances

Pregnancy

A normal pregnancy does not increase LDH and if LDH activity increases then one needs to consider disease like pre-eclampsia, pregnancy induced hypertension and cholestasis of pregnancy (142-144).

Childhood

LDH activity is higher in children, dropping as they age and reaching adult levels by the age of 22 (145). An idea of the range in paediatric population is therefore helpful to guide if a child needs further investigation or not (*Table 3*) (146).

Conclusions

Elevated LDH activity is a common finding and is not diagnostic for any single disease process in isolation. The most common causes included cardiorespiratory diseases, any malignancy, fracture or trauma, infection, inflammation and any cause of hepatitis. Low LDH activity is rare and genetic causes might be considered if testing is available. If a thorough clinical assessment does not reveal a cause of LDH elevation then the included algorithm is presented to

Table 3 Lactate dehydrogenase concentration (IU/L) depending on age and sex in children

Age	Lower limit		Upper limit		Sample size		Lower confidence limit		Upper confidence limit	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
0–14 days	309	309	1,222	1,222	197	197	267, 360	267, 360	1,116, 1,257	1,116, 1,257
15 days to <1 year	163	163	452	452	145	145	94, 173	94, 173	428, 483	428, 483
1 to <10 years	192	192	321	321	370	370	189, 199	189, 199	314, 333	314, 333
10 to <15 years	157	170	272	283	141	141	130, 162	138, 175	258, 308	277, 286
15 to 19 years	130	130	250	250	227	227	124, 142	124, 142	239, 257	239, 257

help support a systematic approach to determine possible reasons. There may be no single cause, or rather multiple tissue sources of the LDH, and in the setting of a well person the result may be spurious. Specialist knowledge, experience and local guidelines all remain vital in elucidating the cause. It is recommended that LDH is not measured unless the clinician has a very specific question in mind due to the non-specificity of serum LDH activity.

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