The irreplaceable value of laboratory diagnostics: four recent tests that have revolutionized clinical practice

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ABSTRACT

There is a common perception that laboratory medicine may be occasionally perceived as neglected discipline by clinicians, and that laboratory tests may be considered ordinary commodities. Although there is still debate on the real contribution of diagnostic testing in care pathways, many clinical diagnoses cannot be made without laboratory data. In support of evidence-based added value of laboratory diagnostics, this article aims to discuss the over-reaching contribution of some recent tests to the clinical decision making, and the unquestionable role they have played in revolutionizing clinical practice. These paradigmatic tests include highly-sensitive cardiac troponin immunoassays for diagnosing non-ST elevation myocardial infarction, hemoglobin A1c for diagnosis and therapeutic management of diabetes, procalcitonin for diagnosing severe bacterial infections and improving antibiotic stewardship, along with natriuretic peptides for early diagnosing and managing heart failure. It is advisable that altogether these paradigms will help reaffirming the vital role of laboratory medicine in modern healthcare.

INTRODUCTION

Laboratory medicine is conventionally defined as a science devoted to generate clinically useful information by analyzing the concentration, composition and/or structure of analytes in biological fluids [1]. Throughout the relatively long history of this discipline as we currently know it, and which probably commenced around the 19th century [2], laboratory diagnostics is now providing an almost invaluable contribution to the clinical decision making. Although there is still an open debate on the real influence of diagnostic testing in care pathways, as mirrored by fierce controversies on the reiterated assumption that clinical laboratory intervenes in 70% of clinical decisions [3], it is now incontestable that many clinical diagnoses cannot be made without laboratory data. In support of the evidence-based added value of laboratory diagnostics, this article aims to discuss the over-reaching contribution of some recent tests to the clinical decision making, and the unquestionable role they have played in profoundly revolutionizing clinical practice.

CARDIAC TROPONINS

Cardiac troponins are essential components of the muscle contractile apparatus, including myocardial tissue. In myocardial cells, two unique and exclusive isoforms of cardiac troponin I (cTnT) and cardiac troponin T (cTnT) are present, so that their immunochemical measurement allows to accurately establishing whether or not the heart tissue has been injured, even in the absence of open signs and symptoms of heart damage [4]. Unlike former methods, the recent development of fourth-generation highly-sensitive immunoassays has enabled measuring physiological concentrations of both cTnI and cTnT, and to more accurately redefine the diagnostic thresholds for identifying myocardial injury, thus including acute myocardial infarction. According to recent guidelines and recommendations, when the clinical presentation is suggestive for myocardial ischemia, a dynamic elevation of cardiac troponins in the absence of any other objective finding (e.g., normal electrocardiogram) is regarded as diagnostic of non-ST elevation myocardial infarction (NSTEMI) [5,6]. The first breakthrough occurred after introducing high-sensitivity immunoassays in routine clinical practice has been a substantial decrease in the number of diagnoses of unstable angina, in favor of an increment of those of NSTEMI, thus leading the way to hypothesize that a requiem should be prepared for unstable angina [7]. On the other hand, the improved accuracy of these last generation, high-sensitivity cardiac troponin immunoassays has contributed to amplify the rate of patients diagnosed with NSTEMI (i.e., by 20-30%) [5,6], who would have been earlier discharged with inaccurate diagnosis and without appropriate medical or pharmacological treatment. Is there any doubt left that high-sensitivity cardiac troponin immunoassays have revolutionized the diagnostics of myocardial infarction and improved the managed care of this condition? Certainly not.

HEMOGLOBIN A1c

Hemoglobin A1c, also known as glycated hemoglobin, results from the nonenzymatic binding of hexose to the N-terminal amino acid of the hemoglobin molecule A1, which is contained into the erythrocytes. Its concentration is hence directly proportional to the average blood glucose level over the preceding 8-12 weeks [8]. Owing to this important biological information, hemoglobin A1c has been for long used for monitoring glucose control in diabetic patients. A major breakthrough has however occurred, when the American Diabetes Association (AHA) has published updated recommendations for classification and diagnosis of diabetes [9], according to which diabetes can now be diagnosed also

in the presence of a hemoglobin A1c value >48 mmol/mol (i.e., >6.5%) measured with an assay certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) assay. The routine assessment of hemoglobin A1c has hence enabled overcoming many of the well-known drawbacks of plasma glucose measurement (either fasting, random or during an oral glucose tolerance test), which essentially include the relative instability of glucose concentration in uncentrifuged blood samples, the high intra-individual variation of blood glucose, as well as biological (i.e., acute stress, drugs) and analytical interference [10]. Moreover, the measurement of hemoglobin A1c will now enable garnering a dual clinical information, since it not only allows to diagnosing diabetes, but will contextually provide important clinical information on medium-term glycaemic control. Recent evidence supports the conclusion that the measurement of fasting plasma glucose may underestimate the real burden of diabetes compared to hemoglobin A1c assessment, leaving this condition undiagnosed (and hence untreated) in up to one-third of pre-diabetic or diabetic patients [11,12]. Due to the clinical, social and economic burden caused by a delayed diagnosis of diabetes, it seems reasonable to conclude that routine assessment of hemoglobin A1c has the potential to generate a highly favorable impact on both diagnosis and management of diabetes.

PROCALCITONIN

The greatest drawback in sepsis diagnostics is that the current scoring systems based on integration of clinical and laboratory data, namely the host systemic inflammatory response syndrome criteria (SIRS), the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) and the quick SOFA (qSOFA) scores, have limited diagnostic efficiency, because they have been

mostly validated for predicting prognosis and death [13]. Therefore, their use for identifying sepsis would not permit an early diagnosis, and could even leave some patients underdiagnosed/ untreated.

Procalcitonin is the 141 amino acids precursor of calcitonin, the leading hormone involved in calcium homeostasis [14]. In physiological conditions, procalcitonin is produced by thyroid C cells and then converted in the mature form calcitonin into the circulation. In patients with severe infections, the synthesis of procalcitonin occurs also in many extra-thyroid tissues (i.e., liver, kidneys, lungs, pancreas), thus boosting an increase of its circulating concentration over the physiological reference range (i.e., <0.05 ng/mL) [15]. This peculiar biological behavior is now exploited for diagnosing severe infections, especially sepsis.

The number of studies and meta-analyses which have analyzed the diagnostic performance of procalcitonin for both diagnosing and managing sepsis has exponentially increased over the past decade. According to a recent meta-analysis published by Tan et al [16], procalcitonin displays 85% diagnostic accuracy (with 0.80 sensitivity and 0.77 specificity) for diagnosing sepsis, which appears sensibly higher than that of C reactive protein (e.g., 73%, with 0.80 sensitivity and 0.61 specificity). Even more importantly, in another recent meta-analysis published by Meier et al [17], procalcitonin-guided antibiotic management was found to be effective to significantly shorten the duration of antibiotic therapy (mean variation, -2.86 days), thus representing a valuable step forward toward reducing the worldwide burden of antibiotic resistance [18]. It is also worthwhile mentioning here that procalcitonin-guided antibiotic management seems also associated with substantial economic savings, as recently highlighted by Schuetz et al [19]. It is hence reasonable to conclude that the use of this simple and rapid test holds great

promise to consistently improve clinical outcomes (i.e., earlier diagnosis), reduce the risk of antibiotic resistance (i.e., tailored therapy, shortened administration), but may also generate favorable revenues on healthcare budgets.

NATRIURETIC PEPTIDES

Natriuretic peptides are a family of protein hormones exerting a vast array of metabolic functions, including natriuresis, diuresis, vasodilation and improved insulin sensitivity [20]. Among the four members of this family, b-type natriuretic peptide (BNP) and the N-terminal fragment of pro-BNP (NT-proBNP) are produced in the left ventricular myocardium in response to myocyte distension due to pressure overload or volume expansion [21]. This important biological property has catalyzed the measurement of both BNP and NT-proBNP in the diagnostics of heart failure. In the 2016 guidelines of the European Society of Cardiology (ESC) [22], the measurement of BNP or NT-proBNP has been included among the essential diagnostic tests in heart failure, alone or in combination with echocardiography. The reason underlying this assumption is that increased values of these peptides will help accelerating the diagnosis, identifying patients needing additional cardiac testing or accurately and safely ruling out heart failure in those with non-diagnostic values. Notably, in the meta-analysis of Roberts et al [23], both BNP and NT-proBNP displayed excellent performance for diagnosing acute heart failure (0.95-0.99 sensitivity and 0.94-0.98 negative predictive value, respectively). In another recent meta-analysis published by Pufulete et al [24], BNP-guided therapy was found to be effective in reducing by nearly 20% the number of further readmissions for heart failure. Even more importantly, in heart failure patients aged <75 years, BNP-guided therapy was also associated with 24% higher median survival and 13% quality-adjusted life-years gain [25].

Finally, stronger evidence was also found that BNP-guided care may be a cost-effective option to clinically-guided care in patients with heart failure and impaired ejection fraction [26]. It is hence undeniable that BNP-driven care has the great potential to improve the diagnosis of heart failure, lower the risk of developing left ventricular systolic dysfunction and ameliorate the quality of life of heart failure patients.

CONCLUSIONS

There is a common perception that laboratory medicine may be occasionally perceived as a neglected discipline by clinicians [27]. The validity of this assumption is reflected by the many publications in which a deep knowledge of the real significance of laboratory tests is lacking, so that diagnostic testing is finally considered an ordinary commodity.

For example, in a recent article published in *JAMA Internal Medicine*, Morgan et al concluded that high-sensitivity troponin testing often yields a high number of false-positive results in patients with suspected myocardial infarction [28]. In another recent article published in the *British Medical Journal*, O'Sullivan et al hypothesized that many of the vitamin D tests ordered in the UK are unnecessary screening, and this conclusion was supported by the evidence that test prescriptions have increased by over 50% between 2000/1 and 2015/16 in that country [29].

These assumptions symbolize a limited appreciation of the actual significance and implication of laboratory tests. Regarding cardiac troponins, an increased value is indeed an essential criterion for diagnosing myocardial injury, although a concentration above the diagnostic threshold does not disclose the type of underlying cardiac damage. Therefore, cardiac troponin testing can be ordered for many important reasons other than for diagnosing myocardial infarction, such as in patients with myocarditis, cardiac contusion,

Table 1	Paradigmatic examples of recent laboratory tests which have revolutionized clinical practice

Test	Disease
Highly-sensitive cardiac troponin immunoassays	Diagnosis of non-ST elevation myocardial infarction (NSTEMI)
Hemoglobin A1c	Diagnosis and therapeutic management of diabetes
Procalcitonin	Diagnosis of severe infections (sepsis) and antibiotic stewardship
Natriuretic peptides	Early diagnosis and therapeutic management of heart failure

cardiotoxicity. It is disappointing to infer that the clinical use of cardiac troponins remains still uncertain nearly 20 years after the publication of the first universal definition of myocardial infarction [6].

As regards vitamin D, the increased number of requests shall be interpreted according to the temporal trend of vitamin D deficiency. A recent study, analyzing the trends in diagnosing vitamin D deficiency in the UK, has concluded that this condition has increased by over 15-fold between 2008-2014, as consequence of many environmental factors [30]. Since vitamin D deficiency not only is a major contributor of skeletal health (by lowering the risk of osteoporosis and fractures), but also seems to play an essential role in decreasing the risk of many human pathologies (e.g., cancer, cardiovascular disease, autoimmune and infectious diseases, and so forth) [31], an increasing number of prescriptions is not certainly unexpected or unreasonable, and cannot be straightforwardly associated with inappropriateness.

This paradigmatic examples underscore the fact that clinical reasoning is unavoidable for accurate interpretation of laboratory test results, and that a deep knowledge of the real significance of each laboratory test is essential for preventing a deplorable underestimation of the added value of in vitro diagnostic testing.

In conclusion, although it is predictable that the extent to which laboratory testing informs the clinical decision making will remain controversial [3], it cannot be denied that the contribution of laboratory medicine in modern healthcare remains pivotal, since it helps predicting susceptibility to disease, making accurate diagnoses, prognosticating and monitoring diseases [32], and will become even more important in the future for the ongoing diffusion of disruptive technologies (i.e., genomics, proteomics, theranostics) and personalized (precision) medicine [33].

The four paradigmatic cases described in this article (Table 1) represent just some arbitrary examples of how irreplaceable is the value of laboratory diagnostics, and in which way some diagnostic tests have recently revolutionized clinical practice. Indeed, many other examples could be brought here, even more straightforward than those discussed in this article. It is advisable that altogether these paradigms will help reaffirming the vital role of laboratory medicine in modern healthcare [34].

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