Editorial

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The ten commandments of laboratory testing for emergency physicians

Keywords: appropriateness; effectiveness; emergency department; patient safety; stat testing.

In this issue of the journal, we publish a series of articles that deal with the rapidly evolving field of the use of cardio-specific troponin testing in the emergency department (ED). Two of these are “opinion papers”, which provide a different and somehow controversial perspective about the clinical usefulness of high-sensitivity (HS) troponin immunoassays in diagnosing myocardial infarction (MI) in the ED [1, 2]. The third paper by Jellema et al. is an interesting study about the complementary value of clinical and laboratory diagnostics for investigation of chest pain patients in the ED [3]. The results of this study are particularly intriguing, wherein it is demonstrated that the diagnostic performance of the HEART score (i.e., acronym for History, ECG, Age, Risk factors and Troponin) outperform that of either troponin or clinical evaluation alone for predicting major adverse cardiac event (MACE), within 6 weeks of initial presentation. In a recent issue of this journal we have also published another “opinion paper”, which contains practical recommendations about the use of the latest generation of cardiac troponins immunoassays in emergency room settings for the diagnosis and rule-out of MI in patients with suspected acute coronary syndrome (ACS) and without persistent ST-segment elevation (NSTE-ACS) [4].

Although the outcome of the study of Jellema et al. should not be considered really unexpected [3], since the notion that clinical data and laboratory testing should always go hand in hand within the clinical diagnostic reasoning is probably as old as laboratory medicine, this series of articles gives us the opportunity to discuss a hot topic, that is the prescription of diagnostic testing in the ED. The ED is a challenging environment, probably the most complex in healthcare, where clinical decision(s) must be rapidly undertaken to diagnose or rule out a given disease, and thereby assure the best care to the patient, avoid litigations with patients or relatives, and prevent overcrowding. It is common experience that diagnostic testing in this scenario may often be prescribed without fulfilling some basic criteria that would finally grant an exclusive clinical usefulness to test result(s). With the obvious humility that we are unable to provide a thoughtful solution to this problem, we list here an essential “Decalogue” of recommendations that, in our expectation, may guide the emergency physician to a more appropriate prescription of laboratory tests (Figure 1).

Consider that you can not diagnose everything with laboratory testing

There is a widespread perception, often boosted by laboratory professionals themselves, that diagnostic testing may be a sort of “magic bullet”, i.e., a foolproof tool that can virtually lead to diagnose everything. Although it is undeniable that quality and volume of laboratory diagnostics have both consistently improved over the past decades [5], there is no single test that is able to univocally diagnose (or rule out) the presence of disease, with very few and notable exceptions. In the specific field of MI diagnostics, a large number of research has paved the way to a general belief that non-diagnostic values of HS troponin at ED admission may virtually exclude the presence of myocardial injury. Recent articles have demonstrated, however, that a consistent proportion of patients with MI – up to one quarter – may have non-diagnostic values at presentation [6]. Beside this specific consideration about MI, a broader consideration can be made about the fact that the diagnostic performance of conventional laboratory tests is generally (much) lower than optimal (i.e., only approximates, but rarely met, 1.00 negative-predictive value and 1.00 positive-predictive value). There are also some conditions, such as intracranial hemorrhage (to be differentiated from stroke) or appendicitis, for which laboratory diagnostics is of little help to the emergency physician. Keeping this foremost concept in mind would probably help reduce the number of avoidable prescriptions. It is also noteworthy that there is no single test that is also able to definitely identify the “healthy status”, so
that diagnostic testing only prescribed to satisfy patient’s wishes should be avoided.

**Defensive medicine is not a good reason for prescribing a test**

The ED is at greater risk of malpractice claims than any other healthcare setting, due to the quick pace, episodic and fast patient-physician relationship, as well as for the high demand and expectation of care. Moreover, the relationships between patients and emergency physicians are, at variance with many other areas of medicine, definitely asymmetric (i.e., the patient can not choose “his trusted doctor”). This fact plays a central role in fuelling defensive medicine and redundancy of testing, so that it is understandable that some tests may be simply prescribed for reasons of defensive medicine, with poor consideration on the negative consequences that this may carry in terms of global diagnostic efficiency (see below) and resources (either human and economical) utilization. It is noteworthy that in a large US-based survey, the vast majority of physicians (i.e., 92%) admitted the prescription of tests and diagnostic procedures as an “assurance behavior” [7], with serious implications for expenditure, access, technical and interpersonal quality.

**Excessive testing can be harmful for your patient**

In several fields of medicine, excessive testing can lead to definite harm for patients. A good example is represented by testing for pulmonary embolism (PE). Harms and benefits in medical testing often coexist in a delicate balance, but measurable medical harms of excessive and often unnecessary test prescriptions are tangible and include malignancy due to diagnostic imaging (e.g., the attributable increase in cancer due to CT pulmonary angiography is approx. five case per 10,000 persons tested for PE, half of which are projected to be fatal) [8, 9], renal injury caused by contrast media (e.g., acute renal failure and death may occur in up 2% of cases) [10], along with other iatrogenic complications of treating patients with positive results (e.g., anticoagulants are associated with a 6-month bleeding risk of 2.8%) [11]. The benefits, however, are more elusive. When patients with possible PE present with physiologic abnormalities (hypotension, hypoxia, etc), the importance of establishing diagnosis and treatment seems clear. Nevertheless, emergency physicians frequently tend to perform a thorough PE testing also in physiologically normal patients, for whom the actual PE poses no major health threat. It is in fact often overlooked that several emboli spontaneously dissolve by endogenous fibrinolysis. Although the exact value of each data input about harms and benefits may be debatable and will vary according to patient characteristics, extensive testing is unlikely to produce a net benefit. Presuming an optimistic 80% efficacy of anticoagulation in lowering death, and accepting a fatality rate of 3.8% for PE missed by testing, a recent study concluded that the current model of testing causes roughly six times as many deaths as lives saved [12].

**Use a Bayesian approach for requesting diagnostic testing**

Who has ever heard about Thomas Bayes? If anyone in the ED knows the answer, raise the hand, please. Thomas Bayes was a Presbyterian minister, but especially an English statistician, universally known for developing a specific theorem that bears his own name – the Bayes’s theorem – and which states that “The probability of any event is the ratio between the value at which an expectation depending on the happening of the event ought to be computed, and the value of the thing expected upon its happening”.

The diagnostic performance of each test are dramatically influenced by the prevalence of disease and, thereby, by its pre-test probability. The generalized prescription of a panel of diagnostic tests regardless of disease probability is perhaps the worst action that can be done in
an ED. It may be helpful to provide here a paradigmatic example. The reported diagnostic sensitivity and specificity of HS troponin immunoassays are approximately 0.95 and 0.50 in a general population of patients admitted to the ED with chest pain. In the most frequent instance, wherein MI is diagnosed in approx. 15/100 patients with chest pain (i.e., prevalence of 0.15), the post-hoc probability (odds) of disease for a diagnostic value of HS troponin is 25%. Consider now the ideal and worst circumstances, where patient selection before testing is very accurate (i.e., disease prevalence of 0.50) or very poor (i.e., disease prevalence of 0.01). In such cases, the post-hoc probabilities increase to 66% in the former scenario, but decrease to 2% in the latter. It is hence understandable that widespread request of testing, as may occasionally occur in overcrowded EDs, is associated with a poor diagnostic yield and, especially, leads to an unjustified waste of human and economical resources. The use of diagnostic algorithms, where pre-test probability anticipates laboratory testing as in the case of D-dimer in patients with suspected venous thromboembolism (VTE), is a good example on how unnecessary testing may be prevented according to disease probability, since D-dimer values are frankly meaningless in patients with a high pre-test likelihood of disease and do not influence the clinical decision-making [13]. The risk of false-positive and false-negative results also increases in parallel with the number of tests requested [14], and this poses other problems, both clinical and ethical. Due to genuine economical reasons, in several hospitals patients now receive a battery of tests at presentation to the ED, even before they are approached by a clinician. These tests are hence ordered with no assessment of the likelihood that the patient has or not any particular disease, and results are then unlikely to be helpful, but can be paradoxically harmful, as previously appreciated [15].

The timing of prescription is essential

The different biomarkers conventionally used in clinical practice are characterized by a highly exclusive series of biological properties, which include the time of increase in blood or other fluids after disease onset, the relative increase over baseline, the peak concentration, the half-life and the time to return to normal. All these conditions must be carefully considered before prescribing whatever type of test. D-dimer testing for ruling out VTE is again an appropriate example. In an ideal condition, the sensitivity of D-dimer for excluding the presence of VTE (either deep vein thrombosis or PE), ranges between 0.98 and 1.00 [13]. Since the diagnostic cut-off of D-dimer is typically 500 ng/mL (FEU), a patient that develops an episode of VTE with a low “baseline” value (e.g., 100 ng/mL) will need as much as 2–4 h to display a significant increase, that may definitely overcome the diagnostic threshold. Therefore, prescription of D-dimer at early patient admission (e.g., 1–2 h after onset of symptoms) may be virtually misleading and carries a high risk of producing false-negative results. Then, considering that the half-life of D-dimer in plasma is approximately 4–8 h, serial sampling with 2-h intervals is clearly inappropriate during monitoring of different coagulopathies, especially disseminated intravascular coagulation (DIC).

Some practical decisions should be undertaken after weighting the implications of time pressure in the ED with overcrowding and need to perform timely and accurate diagnosis or treatments. The simplest thing is often the best: observe your patient! As former Nobel prize Bernard Lown (inventor and developer of the defibrillator, and co-discoverer of the Lown-Ganong-Levine syndrome) stated, “Technology is erroneously considered a substitute for time” [16]. Therefore, a paradigm shift is advisable when discussing about the appropriateness of laboratory testing, i.e., from “potentially inappropriate” to “really harmful for patients”. When a given test is not sufficiently accurate to change the clinical management in a particular setting, it should not be prescribed.

Be aware of the limitations of the test

Although most physicians, thus including those working in the ED, have an adequate knowledge of the diagnostic implications of tests, what they frequently ignore are the inherent limitations, especially for newly introduced biomarkers. These include both technical and clinical aspects, which may impair the ultimate efficiency of testing. A reliable example in this context is neutrophil gelatinase-associated lipocalin (NGAL) [17]. This emerging and attractive biomarker is used for diagnosing acute kidney injury (AKI), on the basis that it is expressed by tubular cells and its concentration increases by several orders of magnitude after acute tubular injury. What is frequently overlooked, however, is that NGAL is actively synthesized by several other cell types, including neutrophils, and the current commercial immunoassays can not distinguish one isoform from the others [18]. Therefore,
increased values in serum or plasma of patients with several comorbidities associated with suspected renal injury must be carefully interpreted, especially in the presence of acute neutrophilia.

Consider the influence of preanalytical problems on test results

Although relatively infrequent, the results of some tests may be occasionally unexpected or frankly aberrant according to the clinical status of the patient. Once biological causes have been excluded, the most plausible explanation is indeed a preanalytical problem, thus including identification errors (e.g., the right test on the wrong patient), processing of unsuitable samples (e.g., measuring potassium in spuriously hemolyzed samples), along with the presence of various types of interferences (e.g., rheumatoid factor, heterophilic antibodies, turbidity, undue clots, etc) [19]. It is clearly implausible that the emergency physicians are aware of every type of problem that may occur in blood samples. Nevertheless, whenever test results do not go hand in hand with the clinics, the negative impact of some preanalytical variables should always be suspected before starting a litigation with the laboratory or – even worse – an accusation of analytical error, which is always a possibility, however. In this circumstance, a constructive cooperation between the emergency physicians and the laboratory personnel would be effective to troubleshoot the problem and eventually identify the most probable source(s) of bias.

Avoid litigation and reinforce partnership

The clinical and laboratory interface is often critical, wherein emergency physicians are pressurized for producing accurate and fast diagnoses, whereas laboratory professionals often perceive their role as passive “executors” rather than being an essential part of the whole “system” of care. It is hence nothing that unlikely that the right word pronounced in the wrong way may trigger open litigation between parties [20]. This is clearly censurable, since litigation inevitably delays the clinical decision-making, is often counterproductive for the problem solving and – even worse – contributes to loose concentration for interpreting data. A constructive debate should guide whatever type of communication between the ED and the laboratory. In this circumstance, a “collaborative” partnership, designed around specific clinical and analytical competency, is indeed the key for success.

Do not just read this paper. Go and spread the word

The authors of this article, all notoriously affected by the obsessive-compulsive scientist’s disorder [21], are now clinically worsening, and so they are self-convincing to be invested the role of mentors of medical science and practice. However, they are convinced that medical literature should not solely serve as a publication tool for academic careers, but also – and probably more importantly – as an educational tool for improving clinical practice.

Conflict of interest statement

Authors’ conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.
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