

Liquid Chromatography-Tandem Mass Spectrometry in the Clinical Laboratory

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The advent of soft ionization techniques such as electrospray ionization (ESI) and matrix assisted laser desorption ionization (MALDI) in the late 1980s, for which the inventors were jointly awarded the 2002 Nobel prize in Chemistry, rendered liquid chromatography-tandem mass spectrometry (LC-MS/MS) an indispensable tool for analyses of small and macro-molecules in biological fluids. Recent improvements in sensitivity and affordability have encouraged the adoption of this technology for routine applications in the clinical laboratory. However, the major driving force for the rapid expansion of this technology in the last decade remains the advantages it offered in comparison with other technologies, such as gas chromatography-mass spectrometry (GC-MS) and immunoassays. Unlike GC-MS, LC-MS/MS does not require laborious sample preparation procedures, which often involve tedious derivatization, or lengthy chromatographic run times. In fact, it is now common to see published LC-MS/MS methods that require only protein precipitation, solid-phase extraction or liquid-liquid extraction with chromatographic run times not exceeding 5 minutes. In addition, LC-MS/MS widened the spectrum of analytes that can be measured by MS because it is not limited by molecular mass or polarity of the target analytes compared to GC-MS [1]. As a result, LC-MS/MS has found numerous applications in particularly challenging areas like endocrinology (steroids), therapeutic drug monitoring (immunosuppressants), inborn errors of metabolism (organic acids and acylcarnitines), clinical and forensic toxicology (drugs of abuse testing), and nutrition assessment (vitamins). Also, with the advancement in MALDI-TOF and orbitrap technologies, these applications have been expanded to microbiology, metabolomics, proteomics and lipidomics [2,3]. On the other hand, in comparison with immunoassays, LC-MS/MS offers much lower throughput but requires lower reagent cost per test with a much higher specificity for most applications, which is why this technique is often considered the "gold standard". For instance, the American Endocrine Society issued a statement in 2007 recommending the use of LC-MS/MS over immunoassays for the determination of steroid hormones [4].

Major areas for improvement of this technology remain, including throughput, complexity, standardization, instrument cost, field service, and interfacing with laboratory information systems (LIS). Manufacturers are gearing up the effort to increase the throughput of LC-MS/MS with some manufacturers introducing multiplexing capabilities that allow connection of up to four parallel LC systems synchronized to a single MS analyzer, which allows multiple samples to be analyzed simultaneously. Others have partnered with the automation industry to work on fully automate solutions from sample preparation to analysis. Nevertheless, the number of LC-MS/MS instruments currently in use in clinical laboratories is still limited when compared with other diagnostic analyzers for several reasons. First, the Achilles' heel of LC-MS/MS is its complexity and the need for highly skilled laboratory staff to assist with method development and thorough validation as well as maintaining the instruments. While some manufacturers are now assisting with the process and are offering "kits" that include columns, calibrators and controls, most tests offered on LC-MS/MS remain "home brew" assays and standardization remains a critical issue to address. To confound

the issue, the lack of national guidelines and general agreement on what constitutes acceptable validation criteria for LC-MS/MS assays, renders these assays susceptible to failure, especially if the common issue of matrix effects is not thoroughly evaluated and addressed. Another major hurdle is the large initial cost required to purchase the instrument (\$200,000 to \$400,000), which can be a deterring factor for smaller laboratories. The lack of appropriate field service support that meets the needs of a clinical lab is another limitation to the wide adoption of LC-MS/MS. Finally, there has been little to no effort interfacing LC-MS/MS with LIS, which is crucial in eliminating specimen mis-identification and post-analytical transcription errors, especially in high volume laboratories.

LC-MS/MS offers great potential for the diagnostic laboratory in spite of all of the associated challenges. In the US, the Clinical and Laboratory Standards Institute (CLSI) has recognized the need for a uniform set of guidelines for validation of LC-MS/MS methods, and has gathered the experts in the field to create one. Its release is expected imminent and represents a significant step forward in ensuring high quality methods to be used for patient care. Moving forward, communication with manufacturers is also crucial to making sure the needs of the clinical laboratory are met in terms of field service, affordability, automation, and LIS interfacing.

References

1. Vogeser M, Parhofer KG (2007) Liquid chromatography tandem-mass spectrometry (lc-ms/ms)--technique and applications in endocrinology. *Exp Clin Endocrinol Diabetes* 115: 559-70.
2. Carbone E, Mesquita C, Bille E, Day N, Dauphin B, et al. (2011) Maldi-tof mass spectrometry tools for bacterial identification in clinical microbiology laboratory. *Clin Biochem* 44: 104-109.
3. Griffiths WJ, Wang Y (2009) Mass spectrometry: From proteomics to metabolomics and lipidomics. *Chem Soc Rev* 38: 1882-1896.
4. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H (2007) Position statement: Utility, limitations, and pitfalls in measuring testosterone: An endocrine society position statement. *J Clin Endocrinol Metab* 92: 405-413.

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