Societal expectations, coupled with the physician Antimicrobial agent overuse

Introduction

The discovery of antimicrobial agents was one of the major events of the twentieth century. However, with the ‘antibiotic era’ barely five decades old, we are now faced with the global problem of emerging resistance in virtually all pathogens. Guidelines and admonishments to improve prescribing have had little effect. At this point, in the twenty-first century, we are on the threshold of another era of discovery—that of molecular diagnostics. We postulate that the development and use of new molecular microbiological testing, coupled with an ever-improving understanding of how best to use these precious drugs in the treatment of infection, offers the greatest hope yet for physician prescribing that can retard, or perhaps even reduce, the development of drug resistance in many microbial species. This diagnostic advance could preserve the utility of antimicrobial agents well into the future for the benefit of all people.

Keywords: molecular diagnostics, infectious disease diagnosis, antibiotic prescribing, empirical therapy

Antimicrobial agent overuse

Societal expectations, coupled with the physician’s intrinsic desire to help, have contributed to widespread overuse of antibacterial agents in most countries. Highlighting this is a report from Spain that found that while only 22% of patients seeking medical care were clinically diagnosed as having an infection, 67% were actually given antibiotics as a result of their physician visit. More recently, Cars et al.4 demonstrated the considerable variation of antibiotic consumption within countries of the European Union, which suggests considerable opportunity for improvement in prescribing practices in many areas. Such studies are starting to look at outpatient use of antimicrobial treatment, an area critical to deal with since at least 85% of usage is in the non-hospital setting. All antibiotic overuse exposes microbes—the infecting pathogen or the resident flora—to antimicrobial agents when this is not needed. It is only recently that we have begun to appreciate the complexity whereby resistance develops when humans are either treated unnecessarily or given inappropriate regimens, and either the resident flora or the invading pathogens or even both can subsequently develop or acquire resistance-coding DNA. While clinical practice as well as environmental conditions may help to enhance or select bacteria with newly acquired resistance genes, it is clear that the pressure generated from exposure to antimicrobial agents is the critical opportunity for microbes to develop and to disseminate resistance.

Guidelines have been produced for managing resistance by improving antibiotic prescribing,5,6 and pharmacodynamic concepts have been developed to maximize therapeutic response, prevent emergence of resistance and minimize adverse events.7 However, most interventions to date have been vague and eventually arrive at the concept of ‘using antibiotics wisely’ to solve the problem.8 Apart from the general concepts of appropriate use there are more precise and predictive tools available to identify patient- and institution-
specific variables that may place an individual patient at risk and which may foster resistance development. Based on either antimicrobial surveillance systems or individual susceptibility testing, computer-based modelling methods have recently been developed to identify profiles of either institutions facing resistance problems or an individual patient infected with a resistant strain, or to assist infection monitoring and treatment at the bedside. Importantly, all this effort has led to little practical implementation or improved drug use by most of the prescribing physicians.

**Advent of improved diagnostics**

In 1998 we were admonished to improve rational antimicrobial agent use, with the reminder that 50% of prescribing in Canada was done without any microbiological diagnostics. This observation highlights a possible solution to our dilemma. Therapy of infection is optimized when aetiological organisms and their susceptibilities are known. Such practice depends on accurate laboratory testing and timely reporting of results. In hospitals these critical results often occur in the sensing of which microbes are present. New diagnostics will also need to sense those settings where infection is actually occurring. A first step in the reasoning was that the blood was reported by Gibot et al., who measured receptor expression as a reliable way of detecting pulmonary infection from bacteria or fungi. We believe that full development of molecular diagnostic testing as envisaged in some ‘science fiction’ can be achieved in the near future, and is likely to be the long-missing key to lowering antibiotic overuse. To avoid unnecessary prescribing of antimicrobial agents, rapid tests will be particularly useful when they can indicate what type of antibacterial, antiviral or symptomatic therapy is most beneficial.

Perhaps the first molecular test that was successful in reducing antibiotic use because a specific diagnosis of viral aetiology could be rapidly made was the application of PCR to the detection of enteroviral meningoencephalitis. In 2003, several reports appeared assessing the impact of early detection of infectious agents, and the potential for use of molecular diagnostics in the rapid and accurate detection of infectious pathogens. There was a general acceptance that laboratories were the ‘front line’ for detecting emerging antimicrobial resistance, and discussion began regarding the potential widening role of molecular testing in pathogen detection as well as resistance determination for individual patients.

The newest and most exciting possibility for specific outpatient diagnosis is that based upon amplification technology such as PCR. Rapidity of testing and cost are always key issues. With the advent of real-time PCR we finally have as a reality access to a reliable diagnostic test with same-day results. Our recent experience with the detection of vancomycin-resistant enterococci (VRE) and S. aureus, both tested directly from perianal and nasal swabs, respectively, and having better recovery than culture, demonstrates that these tests can be sufficiently sensitive for clinical diagnostic requirements.

**Promise of molecular testing**

In the community setting, where most antimicrobial prescribing occurs, laboratory diagnosis using current technology is problematic. In addition to the usual delay of 2–4 days before microbial identification and susceptibility testing are available, another practical problem is the fact that key microbes like pneumococci and *Haemophilus* do not survive very long in an expectorated sputum specimen. Thus, with most physician outpatient practices not close to a diagnostic laboratory, routine culture of sputum from patients with suspected pneumonia is not even currently recommended. This unfavourable situation is worsened by the perception that drug resistance is not associated with reduced clinical efficacy in non-meningeal pneumococcal infections. Optimizing diagnostic testing could differentiate true infection with pathogenic microbes, amenable to specific antimicrobial agent treatment, and a clinical symptom complex that does not require antimicrobial agent therapy. In order to achieve this new diagnostic plateau, testing needs to do more than simply signal which microbes are present. New diagnostics will also need to provide sufficient information to permit specific application or antimicrobial chemotherapy. The newer applications of molecular diagnostics known as gene ‘chip’ and ‘microarray’ and ‘nanoparticle’ technology offer the potential to solve many remaining impediments to rapid detection of important infectious agents in health care. Since these technologies do not require organism viability, and thus avoid any adverse effect of longer specimen transport, they can be successfully applied to both the in- and outpatient settings. Also, the resulting test rapidity theoretically will provide relevant information within a few hours, which would limit any necessary empirical treatment to one or two doses. Several companies currently possess the technical expertise and laboratory research infrastructure to bring a useful diagnostic testing approach to the clinical trial stage very shortly. One example is the new technology company Nanosphere, Inc. (Northbrook, IL, USA), which is developing gold nanoparticle technology to detect molecular DNA, RNA and protein biomarker targets using automated instrumentation, without the need for prior amplification. This testing could detect likely pathogens responsible for important clinical scenarios, such as respiratory disease symptom complexes, implicating the key bacterial, viral or atypical
microbial pathogens responsible. Simplified automation opens the potential for testing to be done near the patient at a peripheral site. If the testing were widely applied, it could be done at a very manageable cost and would have a significant impact on lowering unnecessary antibiotic prescribing.

Regulatory challenges

However, some additional hurdles remain other than the technological issues. For example, in the United States the estimated cost of regulatory requirements for approval and ongoing modification of multi-targeted molecular tests, added to the expense of first developing them (in excess of $100 million) are considered prohibitive by the industry. This is due primarily to the fact that regulations have not changed to encompass test platforms having the capacity to detect a variety of genetic targets from multiple microbial species, with the aim of providing a unified diagnosis based on interpretation of a complex pattern using multiple results. Because of what is at stake—managing antimicrobial agent resistance—it clearly appears in the best interest of all to develop a modernized set of regulations that facilitate development and application of this testing.

Conclusions

To date there has been little evidence of improvement in antimicrobial agent prescribing, with 50% of use even in hospitals still considered inappropriate.26 Isenberg’s recent review27 on the past, present and future of clinical microbiology suggested that molecular biology techniques, while now in their infancy, have the potential to revolutionize the diagnosis (and treatment) of infectious diseases, and we wholeheartedly agree. The hurdles to be faced are not insignificant. New pathogens will continue to emerge, and as soon as they are recognized will need to be incorporated into existing diagnostic test menus. Mixed viral and bacterial infections can also be daunting for diagnosis and therapy, but if the molecular tests developed not only delineate all that is present (signals) but also differentiate what is responsible for illness in the host (sensors), then we will be at a true crossroads in the treatment of infectious diseases. Dunne et al.28 described a future scenario where this testing develops as we envisage here, and postulated that by the year 2025 sophisticated samplers will painlessly obtain the necessary material, followed by automated analysers to process simultaneously DNA, RNA, protein, glycopeptides and exoplysaccharides to detect any of a possible 168 pathogenic microbes as well as toxins and resistance genotypes—all completed and yielding a diagnosis within 15 min. We believe this future is attainable even earlier, and that bringing these advances to fruition is critical for mastering antimicrobial agent prescribing in order to manage their use in a rational way and finally reverse the increasing resistance that threatens these precious agents we have as necessary aids to all our health. The technology and vision are here—we just need the will to do it.

References


