Detection of autoantibodies in a point-of-care rheumatology setting

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Abstract Autoimmune rheumatic diseases are common and confront society with serious medical, social, and financial burdens imposed by their debilitating nature. Many autoimmune diseases are associated with a particular set of autoantibodies, which have emerged as highly useful to define and classify disease, predict flares, or monitor efficacy of therapy. However, current practice for monitoring autoantibodies is protracted, labor-intensive, and expensive. This review provides an overview on the value of point-of-care (POC) biosensor technology in the diagnosis and management of patients with autoimmune rheumatic diseases. Real-time measurement of autoantibodies will clearly benefit the rheumatology practice in emergency and urgent care settings, where definitive diagnosis is essential for initiation of correct critical care therapy. Immediate serological information in clinic will provide considerable value for long-term patient care and an opportunity for an instant, result-deduced therapeutic action, avoiding delays and improving compliance, especially in field-based and remote areas. We describe the particular autoantibodies that are useful disease and activity markers and would, therefore, be attractive to POC applications. Already existing biosensors and platforms that show promise for autoantibody testing are summarized and comparatively evaluated. As POC assessment is gaining momentum in several areas of patient care, we propose that rheumatology is poised to benefit from this innovative and affordable technology.

Keywords Point-of-care (POC) testing · Autoantibodies · Autoimmunity · Rheumatic diseases

Abbreviations

ADAMTS13 A desintegrin and metalloproteinase with a trombospondin type 1 motif, member 13
ANCA Anti-neutrophil cytoplasmic antibodies
APL Anti-phospholipid
CCP Cyclic citrullinated peptide
CRP C-reactive protein
DFS70 Dense fine speckles 70 kDa
DVT Deep venous thrombosis
GBM Glomerular basement membrane
MCV Mutated citrullinated vimentin
MPO Myeloperoxidase
NMDA-R N-methyl-D-aspartate receptor
NPSLE Neuropsychiatric systemic lupus erythematosus
POC Point-of-care
PR3 Proteinase 3
RA Rheumatoid arthritis
RF Rheumatoid factor
SLE Systemic lupus erythematosus
Autoimmune rheumatic diseases afflict 2–3% of the population [1] and create enormous burden on individuals and society due to poor quality of life and lower productivity [2]. This heterogeneous group of clinical conditions are typically linked by the presence of autoantibodies directed against self-constituents. Often, serum autoantibodies are the only objective serological markers for an underlying rheumatic disease and as such, are part of classification criteria developed to provide a common language for diagnosis, monitoring, therapeutic trials, and international publications. While patient history and physical examination are the cornerstone of the differential diagnosis, current practice analysis shows that most clinicians readily act only after receiving confirmatory or exclusionary laboratory test results [3, 4].

Traditionally, the consultative and diagnostic services in rheumatology are not considered clinical emergencies that would require same-day diagnostic or clinical decisions. While this may hold true for chronic and non-inflammatory conditions, it should also be recognized that most inflammatory and autoimmune conditions that constitute a major part of academic or private rheumatology practice have to be diagnosed and acted upon quickly to curb irreversible immune-mediated damage and mortality. This is especially true for patients whose management includes critical care and aggressive therapy after diagnosis. Currently, it is necessary to use the services of centralized laboratories to obtain this information, which can delay diagnosis and appropriate treatment.

It has been estimated that 10–25% of all patients with rheumatologic disorders visiting the emergency departments require hospital admission, and up to one-third of the hospitalized patients need intensive care [5, 6]. These emergencies may present as a rapidly evolving and confusing multisystem organ failure, can mimic other conditions or initially mislead with deceptively benign clinical signs. High level of suspicion, clinical knowledge, and detection of circulating autoantibody markers contribute significantly to a timely diagnosis. Table 1 summarizes the use of specific autoantibody testing for the diagnostic process in acute clinical settings. Test selection and interpretation of results is often dependent on the observed clinical complexity, but a characteristic combination of particular clinical and timely laboratory features help to refine the pretest assessment of disease probability. Both positive and negative predictive values of a test result may be useful. For example, a patient visiting the ER with extensive palpable purpura may trigger suspicion of systemic vasculitis, which could be directly supported by a positive ANCA test. Unfortunately, laboratory tests for autoimmune disorders require significant processing time; most autoimmune serology tests performed in reference laboratories take at least several days. Turnaround times for tests ordered by practices in remote or outreach clinics are longer, as much as 7 days.

The outpatient rheumatology practice of dealing with autoimmune conditions collides with a different problem: assessing active disease resulting in progressive organ damage and early mortality. Establishing reliable biomarkers that accurately predict disease activity is a major challenge faced by practicing physicians. Such tests should be clinically meaningful, affordable, and easy, and should distinguish cross-sectional differences between patients with active and inactive disease as well as longitudinal changes in disease expression or activity in individual patients [7].

Quantitative measures of autoimmune activity, in contrast to critical care analytes, are generally not considered important in the biomarker field, as changes in autoantibody concentration are believed to be slow and of minor importance to the patient outcome. This misconception is particularly apparent in the rapid humoral immune response observed in autoimmune loop conditions like SLE and antiphospholipid syndrome [8, 9]. However, serial and routine testing in a cost-effective and readily accessible way requires technology and assays that currently do not exist.

Previous research suggests that some of the autoantibodies listed in Table 1 as diagnostic aids behave like parameters that wax and wane with disease activity, thus holding promise to provide prognostic clinical information and, when at their best, to guide therapy. When target organ involvement is considered, autoantibodies may correlate with important clinical outcomes. Current candidate autoantibody disease activity markers are summarized in Table 2. The more recently described value of regular autoantibody “profiling” in patients with Wegener’s granulomatosis due to change in epitope specificity of PR3-ANCA during active disease [10] and the association of high and low anti-NMDA-R autoantibody titers with unique CNS symptoms in neuropsychiatric SLE [11] underscores the importance of autoantibody assays for optimal management.

It is beyond the scope of this paper to discuss discrepancies observed among studies that characterize autoantibodies as disease activity markers. Many believe that lack of prospective or longitudinal studies, clearly defined methodology, patient selection bias, use of inconsistent definitions for disease activity, frequency of testing, and effects of therapy contribute to conflicting results [12, 13]. It should also be noted that disease activity, disease severity, and the ensuing irreversible damage should be conceptually differentiated, and measurement tools for these parameters may be different [14]. Despite these potential problems in interpreting laboratory results, the need of clinicians to judge disease activity has made the
| Symptom                                      | Positive test result                                                                 | Disease                                                                 |
|----------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| **Airway problems**                          | Have a positive test result for Anti-dsDNA, other lupus serologies and Anti-CCP, RF  | Alveolar hemorrhage in SLE, Cricoarytenoid arthritis in rheumatoid arthritis (RA) |
| Hemoptysis                                   | Anti-dsDNA, other lupus serologies                                                   | Alveolar hemorrhage in SLE                                             |
| Airflow obstruction                          | Anti-CCP, RF                                                                          | Cricoarytenoid arthritis in rheumatoid arthritis (RA)                 |
| Mucopurulent rhinorrhea; subglottic stenosis; hyopharyngeal ulcerations | Anti-neutrophil cytoplasmic antibodies (ANCA, MPO or PR3) | Wegener’s granulomatosis                                               |
| Stridor, laryngotracheal strictures          | Anti-type II collagen                                                                 | Relapsing polychondritis                                               |
| Acute pneumonitis                            | Anti-dsDNA, other lupus serologies                                                   | SLE                                                                    |
| **Pulmonary–renal problems**                 | **Anti-GBM, MPO-ANCA, PR3-ANCA**                                                      | **Goodpasture’s syndrome; systemic vasculitis**                        |
| Pulmonary hemorrhage and acute renal failure | Anti-GBM, MPO-ANCA, PR3-ANCA                                                          | Goodpasture’s syndrome; systemic vasculitis                            |
| Encephalopathy, psychosis, focal central nervous system disease | Anti-N-methyl-D-aspartate receptor (NMDA-R), antiribosomal P antibodies, antiphospholipid antibodies | Neuropsychiatric SLE, antiphospholipid syndrome                         |
| Weakness, paralysis, bilateral sensory deficit, impaired sphincter control | Lupus serologies                                                                     | Transverse myelitis in SLE                                             |
| Seizures                                     | Anti-dsDNA, other lupus serologies                                                   | Lupus cerebritis                                                       |
| **Thromboembolic problems**                  | Anti-phospholipid antibodies                                                          | Antiphospholipid syndrome                                              |
| DVT, pulmonary thromboembolism, fetal loss, retinal artery occlusion | Anti-phospholipid antibodies                                                          | Antiphospholipid syndrome                                              |
| **Neuromuscular problems**                   | Anti-Jo-1, other myositis-specific autoantibodies                                     | Dermatomyositis, polymyositis                                         |
| Progressive symmetric muscle weakness; dysphagia; dysphonia | Anti-Ro/SSA; anti-La/SSB                                                             | Sjogren’s syndrome hypokalemic paralysis                               |
| Unusual weakness and hypokalemia            | Anti-Ro/SSA; anti-La/SSB                                                             | Sjogren’s syndrome hypokalemic paralysis                               |
| **Cardiac problems**                         | Anti-dsDNA, other lupus serologies, Anti-phospholipid antibodies                     | SLE pleuro-pericarditis, pericardial tamponade                         |
| Pleuritic or positional chest pain, dyspnea, tachycardia | Anti-dsDNA, other lupus serologies, Anti-phospholipid antibodies                     | SLE pleuro-pericarditis, pericardial tamponade                         |
| Congenital heart block; neonatal carotis     | Anti-Ro/SSA; anti-La/SSB                                                             | Neonatal SLE                                                           |
| **Renal problems**                           | MPO-ANCA, PR3-ANCA, anti-dsDNA and other lupus serologies, anti-phospholipid antibodies | Microscopic polyangiitis, WG, lupus nephritis, catastrophic antiphospholipid syndrome |
| Rapidly progressive renal failure           | MPO-ANCA, PR3-ANCA, anti-dsDNA and other lupus serologies, anti-phospholipid antibodies | Microscopic polyangiitis, WG, lupus nephritis, catastrophic antiphospholipid syndrome |
| **Accelerated hypertension**                 | Anti-Scl-70; anti-centromeres, anti-RNA-Polymerase III                              | Renal crisis in systemic sclerosis                                     |
| **Joint problems**                           | Anti-CCP, RF and lupus serologies                                                   | RA, SLE                                                                |
| Pain, stiffness, swelling with symptoms of systemic disease | Anti-CCP, RF and lupus serologies                                                   | RA, SLE                                                                |
| **Ocular problems**                          | RF, anti-CCP, lupus serologies                                                       | RA, Behcet’s, juvenile RA, SLE                                         |
| Red, painful, photophobic eye                | RF, anti-CCP, lupus serologies                                                       | RA, Behcet’s, juvenile RA, SLE                                         |
| **Gastrointestinal problems**                | Lupus serologies                                                                     | SLE mesenteric arteritis                                               |
| Colicky abdominal pain                       | Lupus serologies                                                                     | SLE mesenteric arteritis                                               |
| **Skin problems**                            | Lupus serologies                                                                     | SLE mesenteric arteritis                                               |
| Petechiae, palpable purpura, hemorrhagic blisters, ulcerations and gangrene | Lupus serologies                                                                     | SLE mesenteric arteritis                                               |
| Neonatal skin rash                           | Anti-Ro/SSA, anti-La/SSB                                                             | Neonatal lupus                                                         |
| **Hematological problems**                  | Anti-DNA and lupus serologies; anti-erythrocyte, anti-platelet antibodies              | SLE, autoimmune hemolytic anemia                                       |
| Anemia, thrombocytopenia, leukopenia         | Anti-DNA and lupus serologies; anti-erythrocyte, anti-platelet antibodies              | SLE, autoimmune hemolytic anemia                                       |
| Thrombocytopenia                              | Anti-phospholipid antibodies                                                         | Antiphospholipid syndrome                                              |
practice of ordering autoantibodies widespread and frequent, with 92% of US rheumatologists using serial anti-dsDNA autoantibody titers to monitor disease activity in SLE [4].

New technologies, that deliver quantitative information in a simple, fast, and low-cost fashion when combined with frequent visits and blood sampling may provide for the first time a tool to definitively establish the predictive value of autoantibody fluctuations in disease flares. Point-of-care (POC) testing, otherwise referred as near patient, bedside or extra-laboratory testing for clinically important analytes, has gathered strength in diverse medical specialties. By virtue of its near real-time data collection capability, POC testing has the potential to change the paradigm in the practice of medicine, and we anticipate that rheumatology will not be an exception.

Devising a reliable assay for measuring a specific antibody in human serum is more difficult than measuring most non-antibody analytes in biological fluids, because any one antibody specificity is usually a tiny fraction of total serum immunoglobulin. Non-specific binding of immunoglobulin may have impeded the development of a reliable antibody biosensor. However, recent and evolving advances in the field of immunosensor technologies have provided high accuracy in quantification and low detection limit in testing for some autoantibodies used in clinical practice.

Current POC immunoassay technologies come in various configurations and complexities. Table 3 provides a partial list of new biosensors and their platforms that have the potential to measure autoantibodies in “real” clinical samples. Surface plasmon resonance-based sensors are the most rapid method, but will require adaptation to inexpensive miniaturized devices. Lateral flow based methods will probably be restricted to non-quantitative readouts. Devices that required specialized antigen tags may have limited practical potential. Electrochemical amplification methods using readily available autoantigens are especially promising. Autoantibody biosensors have generally equaled or surpassed traditional central laboratory methods in performance metrics, such as sensitivity, specificity, and especially time to result. Advances in the development and application of portable, antibody-based immunosensors are presented in several recent review papers [52–56].

The American College of Rheumatology (ACR) has recognized the value of decentralized laboratory testing in their position statement on the issue [57] in which not only patient convenience (a single site for physician contact and serology testing), but also cost savings associated with return visits just to implement treatment options would be benefited. According to the ACR, rheumatologists, in directing their office laboratories, are the most qualified for determining the utility of specific tests, analyzing their results and applying these results to therapeutic situations. Immediate autoantibody diagnostics can also help to establish autoimmune disease units in hospitals, as recently suggested [58, 59].

| Disease/condition | Autoantibody | Change | Clinical prediction |
|-------------------|--------------|--------|---------------------|
| Systemic lupus erythematosus | Anti-dsDNA | ↑ | Active flare [15–17] |
| | Anti-dsDNA | ↓ | Active flare [18] |
| | Anti-nucleosome | ↑ | Active disease/lupus nephritis [19–21] |
| | Anti-C1q | ↑ | Lupus nephritis [22–24]/active disease [25] |
| | Anti-NMDA-R | ↑ | Permanent CNS impairment [26, 27] |
| | Anti-NMDA-R | ↓ | Transient CNS symptoms [26, 27] |
| | Anti-CRP | ↑ | Lupus nephritis/response to therapy [28] |
| | Anti-interferon-α | ↓ | Inactive disease [29] |
| Systemic vasculitis | Anti-PR3 | ↑ | Active disease/disease relapse [30–32] |
| | Anti-MPO | ↑ | Active disease/disease relapse [33, 34] |
| | Anti-GBM | ↑ | Active disease/disease relapse [35, 36] |
| Scleroderma | Anti-topoisomerase I | ↑ | Active scleroderma [37–39] |
| Rheumatoid arthritis | Anti-drug (adalimumab) | ↑ | Treatment failure [40] |
| Antiphospholipid syndrome/SLE | Anti-phospholipid | ↑ | Procoagulant state, thrombosis [41–43] |
| Necrotizing myopathy | Anti-signal recognition particle | ↑ | Decreased muscle strength, increased creatine kinase activity [44] |
| Thrombotic thrombocytopenic purpura | Anti-ADAMTS13 antibodies | ↑ | Disease relapse [45, 46] |
| Pregnancy in SLE | Anti-Ro(SSA)/anti-Ro52 | ↑ | Congenital heart block [47, 48] |
| | Anti-La(SSB) | ↑ | Neonatal lupus [49] |
| Autoantibody serum screening | Anti-DFS70 | ↑ | ANA-positive healthy individuals [50, 51] |
Table 3 Devices with potential to measure autoantibodies (Ab) at point-of-care

| Autoantibody | Detection technology/assay platform | Assay duration | References |
|--------------|------------------------------------|---------------|------------|
| Anti-dsDNA   | Electrochemical reduction of redox-tagged probe/Ab inhibition in single-step cell | ~45 min | [60] |
|              | Decreased resonance frequency/piezoelectric quartz crystal microbalance | <60 min | [61] |
|              | Refractive index change/surface plasmon resonance sensor chip | ~5 min | [62] |
| Anti-CCP     | Formation of visual line by colored nanoparticles/lateral flow chromatography | 10 min | [66] |
| Anti-chromatin | Refractive index change/surface plasmon resonance sensor chip | ~5 min | [67] |
| Anti-IgG (RF) | Peroxidase-mediated electrochemical amplification/flow-through cell | 20 min | [64] |
| Anti-MCV     | Formation of visual line by colored nanoparticles/lateral flow chromatography | 15 min | [65] |
| Anti-Ro/SSA, Anti-Ro52, Anti-La/SSB | Luminescence by luciferase-tagged probe/bead immobilized Ab in two-step cells | 25 min | [63] |
| Anti-β2-glyco-protein I | Refractive index change/surface plasmon resonance sensor chip | ~5 min | [68] |

Sites for POC serology testing could include outpatient rheumatology clinics, intensive care units, and emergency or urgent care facilities, as well as hospital infusion centers. Another attractive possibility is the use of POC serology testing in field-based, remote or rudimentary clinical settings, thereby bringing laboratory-based medicine to low-resource areas. In all these environments, POC devices would be of value to rheumatology physicians, who can immediately act on the information. In the outpatient clinic, a rapid test result could affect physician evaluation of the patient, thereby facilitating action and likely improving the usefulness of the office visit. POC methods should enhance patient compliance for laboratory testing and decrease the number of return visits. The efficiency and quality of health care from both the physician and the patient perspective is likely to improve as a result.

At this point it is unlikely that POC testing will replace the traditional central clinical laboratory model in all situations. Establishing rigid quality control of POC testing that satisfies regulatory requirements and oversight could be challenging. Handling and disposal of potentially bio-hazardous and chemical fluids may need to be addressed. Physical records, transfer of test results into a patient chart, and reimbursement issues will also play a major role in acceptance of POC technology.

POC serology testing is truly a work in progress, and its successful deployment requires a long-term commitment. The anti-CCP assay has recently been commercialized, but general acceptance of POC autoantibody testing in rheumatology has yet to happen. The optimum technology should be reliable, fast, inexpensive, quantitative, and easy to put in place and use. The latter features will make POC testing attractive to clinical rheumatology staff whose primary focus is patient care. Analyses of health care in the future predict that medicine will be more decentralized, and realization of POC testing has the promise to accelerate this paradigm shift for patient management.

Conflict of interest Konstantin N. Konstantinov, Antonios Tzamaloukas, Robert L. Rubin declare that they have no conflict of interest.

Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2005. Informed consent was obtained from all patients for being included in the study.

Animal studies No animal studies were carried out by the authors for this article.

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