QUESTIONS

1. What substance could cause the unusual appearance of the serum?
2. How would you confirm your suspicions?

The answers are below.

ANSWER

Significant intravascular hemolysis can complicate dialysis (e.g., because of a kink in a dialysis line) and may result in the formation of methemalbumin (1). This gives serum a brown appearance, quite distinct from the typical reddish color associated with extravascular hemolysis. In this case, spectrophotometry performed before and after the addition of a reducing agent (sodium dithionite) (2) revealed an increase in absorbance at a wavelength of 569 nm, confirming the presence of methemalbumin.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

References


News & Views

N-of-1 Clinical Trials: Removing the Hay to Find the Needle

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Selection of a proper sample size is an important concept in statistics. Typically, the larger the number of included subjects, the better the ability to make an accurate inference about the population. Numerous methods exist for determining the proper sample size to help balance the desired statistical power with the need to be realistic in how many subjects can be recruited. But the recognition of individual variability, with the well-known limitations of classic clinical trials to predict patient outcomes, has shed light on the growing need to refocus on single-person studies.

N-of-1 or single-subject clinical trials use observations from a single patient to establish efficacy or side-effect profiles (1). The renewed interest in N-of-1 clinical trials stems from an observed lack of universality in response to interventions and a greater focus on the individual with the emergence of precision medicine. A strong focus on the uniqueness of each individual has led to many discoveries in cancer diagnostics and drug efficacy and has prompted the US Food and Drug Administration to relabel numerous approved drugs to include pharmacogenomics information.

The need for a greater reliance on N-of-1 clinical trials as an avenue to replace “imprecision medicine” with precision medicine is the subject of a Comment by Dr. Nicholas Schork in a recent issue of Nature (2). Among his arguments for the use of N-of-1 trials is that for every
single person helped by 1 of the top 10 grossing drugs in the US, an eye-opening 3 to 24 people fail to improve. The bias toward the use of classic clinical trials has contributed to the recognized shortcomings of medical interventions despite the use of thousands of subjects, blinded patients and researchers, and control interventions. But these same techniques, coupled with frequent measurements and crossover designs inherent to N-of-1 clinical trials, provide a mechanism to better manage an individual’s response or lack thereof to a medical intervention. By aggregating results of similar N-of-1 studies, a high-resolution picture of treatment efficacy can be efficiently realized for subpopulations sharing key characteristics.

N-of-1 clinical trials are not possible or appropriate in all situations. In diseases in which progression is rapid or for which population-wide interventions are planned, the impracticality of multiple measurements dictates the need to refrain from abandoning classic clinical trials entirely. Biostatistical approaches, ethical implications, standardization of measurement frequency, and availability of practical methods for obtaining repeat measurements will continue to be hot topics in the journey toward true precision medicine.

Transforming routine patient care into massively parallel N-of-1 clinical trials requires a shift in the mindset of regulatory agencies, researchers, physicians, and pharmaceutical companies. Clear benefits have been and will continue to be realized as approaches to N-of-1 clinical trial design and result aggregation mature. The highly advanced technologies available in the clinical laboratory are opening up new and exciting opportunities to truly make precision medicine a reality, with nearly every area of laboratory diagnostics feeling the impact. From genetics to chemistry, the technological advances available to the laboratory will make highly effective, multiplexed investigations into a patient’s genome, metabolome, proteome, or cellular antigenic phenotype a personal reality.

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References

Unexpected Challenges in Noninvasive Prenatal Testing
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The clinical paradigm for prenatal screening for fetal chromosome aneuploidies has been transformed by the introduction of noninvasive prenatal testing (NIPT). NIPT sequences cell-free DNA from maternal plasma, which contains a mixture of small maternal DNA fragments as well as placental DNA fragments that serve as a fetal surrogate. The relative proportion of cell-free fetal DNA increases with gestational age and can reliably be detected by 9–10 weeks of gestation. As sequencing technologies have improved and become less expensive, there has been a rapid adoption of NIPT since its commercial launch in late 2011.

NIPT is a screening test, similar to traditional prenatal screening approaches that combine maternal serum screening plus ultrasound. A principal advantage of NIPT is that the false-positive rate is <0.2% compared to an average of 5% for traditional screening methods. Confirmatory testing for aneuploidies requires an invasive procedure such as chorionic villus sampling or amniocentesis; therefore, the reduced false-positive screening rate has a significant clinical