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ScienceDirect
Clinical Biochemistry 43 (2010) 4–25
CLINICAL BIOCHEMISTRY
www.elsevier.com/locate/clinbiochem

Review

Impact of blood collection devices on clinical chemistry assays

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Received 8 May 2009; received in revised form 30 September 2009; accepted 2 October 2009
Available online 12 October 2009

Abstract

Blood collection devices interact with blood to alter blood composition, serum, or plasma fractions and in some cases adversely affect laboratory tests. Vascular access devices may release coating substances and exert shear forces that lyse cells. Blood-dissolving tube additives can affect blood constituent stability and analytical systems. Blood tube stoppers, stopper lubricants, tube walls, surfactants, clot activators, and separator gels may add materials, adsorb blood components, or interact with protein and cellular components. Thus, collection devices can be a major source of preanalytical error in laboratory testing. Device manufacturers, laboratory test vendors, and clinical laboratory personnel must understand these interactions as potential sources of error during preanalytical laboratory testing. Although the effects of endogenous blood substances have received attention, the effects of exogenous substances on assay results have not been well described. This review will identify sources of exogenous substances in blood specimens and propose methods to minimize their impact on clinical chemistry assays.

Keywords: Blood collection devices; Surfactant; Interference; Clinical assay; Tube; Clinical chemistry; Preanalytical; Phlebotomy.

Contents

Abbreviations: BD, Becton Dickinson; CLSI, Clinical Laboratory Standards Institute; EDTA, ethylenediamintetraacetic acid; OSCS, oversulfated chondroitin sulfate; OSHA, Occupational Safety and Health Agency; PP, polypropylene; PET, polyethylene terephthalate; PVP, polyvinylpyrrolidone; SST, serum separator tube; TBEP, tris (2-butoxyethyl) phosphate.

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doi:10.1016/j.clinbiochem.2009.10.001

Introduction

Blood collection and processing are two major steps in preanalytical laboratory testing. Proper blood collection and timely processing by well-trained staff using appropriate devices are needed to ensure test reliability. Blood collection devices have been typically regarded as inert specimen carriers. Therefore, laboratories have invested little effort to evaluate new blood collection devices and rarely monitor collection device performance. This review seeks to underscore the importance of blood collection devices by summarizing reports of blood collection devices that influence clinical chemistry assays, and by describing blood collection device components and their interactions with blood specimens for various analytic methods.

History of collection devices

The first hypodermic needle, created for local opiate injection in treating neuralgia [1], was made of steel and accompanied by a hard rubber hub. Initial improvement efforts resulted in a refined needle design and experimentation with syringe materials for the collection tube. The rubber was replaced with glass to allow syringes to be reused. The Luer-Lok syringe, which provided a convenient method of attaching and removing the hypodermic needle from the glass syringe, offered a safer and more reliable method of drug delivery. However, multiple hepatitis outbreaks necessitated the development of sterile disposable syringes to reduce disease transmission [2,3]. Glass syringes had several other disadvantages: (1) they were expensive because of the requirement for close tolerances to minimize leakage between barrels and plungers; (2) they could not be mass-produced because plungers were not interchangeable with other glass barrel syringes; and (3) they could break [4]. New sterilization techniques employing chemical agents (e.g., ethylene oxide gas) and radiation (e.g., cobalt 60) allowed the plastic syringe to emerge as the favored alternative.

Evacuated blood collection tubes have been developed in the 1940s and have provided a convenient alternative to syringe techniques and now these blood collection devices are widely used in clinical and research settings [5]. These tubes automatically draw a predetermined blood volume, and evacuated tubes can be switched more easily than syringes when multiple samples are needed [5]. Hence, the risk of spilling and contaminating specimens is greatly reduced. This improvement also minimizes phlebotomist exposure to blood and needle-stick injuries during blood transfer [6].

Glass evacuated blood collection tubes containing limited additives (e.g., anticoagulants) have been the standard blood collection devices since their introduction in the 1950s [7]. Recently, however, manufacturers have modified collection tubes through the substitution of plastic as the primary tube component, and the addition of polymer gel or clot activator [8]. The four major evacuated tube manufacturers in the United States (i.e., Becton Dickinson (Franklin Lakes, NJ); Greiner Bio-One (Baltimore, MD); Kendall, Sherwood, Davis, and Geck (St. Louis, MO); and Sarstedt (Newton, NC)) [9] produce tubes from a variety of materials and additives that can impact laboratory assays [9].

Because blood collection tubes function well for most clinical assays, many laboratorians are unaware of the complexities of blood collection tube components. Recent contamination of blood specimens with surfactant revealed how devices can have widespread adverse effects on laboratory test results [10,11] and emphasized the importance of being well-informed about potential problems associated with devices. The major blood collection tube components and their effects on clinical blood specimens are shown in Table 1.

Blood collection device components

Alcohol and other disinfectants

Before blood specimen collection, the skin is cleaned and disinfected with 70% isopropyl alcohol. If the alcohol does not dry completely before venipuncture, it may be inadvertently introduced into the blood sample. This contamination can cause hemolysis or interfere with blood ethanol level measurements [12,13]. To minimize the interference of antiseptics, the skin should be completely dry before obtaining blood specimens [12]. Stronger antiseptics such as Betadine (povidone–iodine solution) are used when stringent infection control is needed, as with blood cultures or arterial punctures [12]. Betadine contamination can falsely elevate phosphorus, uric acid, and potassium levels [14]. Additionally, the oxidative effects of Betadine are responsible for false-positive results for hemoglobin in stool and glucose in urine when using gum guaiac or toluidine tests [15]. For patients with iodine allergies, chlorhexidine gluconate or benzalkonium chloride are available [12]; however, benzalkonium compounds have been observed to affect electrolyte results [16].

Needles

Needles used with evacuated tubes, syringes, catheters, and butterfly systems are composed of various materials, including stainless steel, aluminum, titanium, chromium, iron, manganese,

Table 1
Interferences from blood collection tube components.

Device / component(s)	Interferences	Key references
Disinfectants		
Alcohol	Hemolysis	Stankovic and Smith [12]
Povidone–iodine	Elevated phosphate, uric acid, potassium	Meites [14]
	Guaiac test	Blebea and McPherson [15]
Needles		
Internal diameter	Hemolysis	Lippi et al. [20] Verssen et al. [51]
Metal material	Metal analysis	Sunderman et al. [18] Vesieck and Cornelis [42]
Lubricants	Immunoassays	Narayannan and Lin [33]
Syringes		
Suction/plunger	Hemolysis	Scott et al. [56] Caroll [81] Carraro et al. [31] Burns and Yoshikama [13]
Permeable plastic	Low PO_2	Rosenberg and Price [59] Winkler et al. [57] Smeenk et al. [58] Knowles et al. [70] Wiwanitkit [66]
Catheters		
Small lumen	Hemolysis	Kennedy et al. [78] Sharp and Mohammed [25] Tanable [83]
Povidone–iodine	Increased sodium, potassium	Koch and Cook [80] Gaylord et al. [79]
Plastic materials	Drug adsorption	Smith et al. [88] Grouzman et al. [89]
Blood collection tubes		
Surfactants	Immunoassays	Mckiel et al. [151] Bowen et al. [10]
	Ion-specific electrode	Sampson et al. [135]
	Mass spectroscopy	Drake et al. [155]
	Interaction with specimen	Bowen et al. [157]
Stopper	Drug assays	Borga et al. [167] Pike et al. [47] Shah et al. [162,163] JI and Evenson [207] Devine [168]
	Metal analysis	Williams [173] Cummings [175] van den Besslaar [171,172]
Stopper lubricant	Triglyceride, glycerol	Baum [177] Chowdry et al. [178]
	Gas-liquid chromatography	Chrzanowski et al. [170]

Table 1 (*continued*)

Device / component(s)	Interferences	Key references
	Metal analysis	Dimeski and Carter [174]
Separator gel	Drug adsorption	Gigliello and Kragle [185] Ji and Evenson [207] Quattrocchi et al. [166] Bergvist et al. [200] Koch and Platoff [201] Dasgupta et al. [198] Dasgupta et al. [199]
Clot activators	Fibrin clots	Beyne et al. [218]
	Increased lithium	Sampson et al. [135]
	Increased magnesium	Cao et al. [132]
	SELDI/TOF	Pilny et al. [223]
	Testosterone	Wang et al. [221]
	Metalloproteinases	Manello et al. [224,225]
Anticoagulants EDTA	Immunoassays	Butler [244]
	Ion binding	Tate and Ward [245] Jones and Honour [246] Banfi et al. [248]
Heparin	Dilution errors	Urban et al. [251]
	Decreased albumin	Meng and Krahn [262]
	Immunoassays	Zaninotto et al. [259]
	Ion binding effects	Urban et al. [251] Shek and Swaminathan [254] Sachs et al. [131] Landt et al. [255] Toffaletti and Wildermann [256] Yip et al. [253]
Fluoride	Enzyme inhibition	Feig et al. [271] Chan et al. [272] Astles et al. [273] Narayanan [249] Gambino [274] Mikesh and Bruns [277] Gambino et al. [275]
Iodoacetate	Electrolytes, glucose, and lactate dehydrogenase	Hall and Cook [279] Robertson et al. [280]

nickel, and alloys [17,18]. Typically, needles have a long sharp end (for puncturing the skin and blood vessel) covered by a protective sheath, and a shorter end for piercing the rubber stopper of the blood collection tube [17]. Needles are calibrated by gauge, which is inversely related to needle size [19,20]. The needles used with syringes range from 13-gauge (1.80 mm internal diameter) to 27-gauge (0.190 mm internal diameter) with lengths from 3.5 inches (8 cm) for the 13-gauge to 0.25 inches (0.6 cm) for the 27-gauge [21]. In clinical settings, venipuncture is usually performed with 19-gauge (0.686 mm internal diameter) to 25-gauge (0.241 mm internal diameter) needles, with the 21-gauge needle being standard for routine adult venipuncture [19,20,22].

One problem encountered with needles is hemolysis, which causes the release of hemoglobin and other intracellular analytes (e.g., potassium, lactate dehydrogenase, aspartate transaminase, alanine transaminase, inorganic phosphorus, and magnesium) into serum or plasma [19,20,23]. These analytes will be falsely increased in specimens, whereas albumin, alkaline phosphatase, and sodium will be falsely decreased by specimen dilution [20,24]. Free hemoglobin in serum or plasma can interfere with several clinical assays, leading to inaccurate results or

necessitating repeat blood draws [25]. Lippi et al. [20] found that small-bore needles (25-gauge or smaller) were associated with statistically significant increases in serum potassium and other analytes due to hemolysis [19,20]. Those authors recommended that small-bore needles be reserved for neonates and patients with poor venous access [20]. Slower flow rates in smaller bore needles are also associated with increased clotting, occlusion, and test result variations [20,25–30]. Large-bore needles (greater than 19-gauge) may cause hemolysis due to turbulence from increased non-laminar blood flow [20,25,31,32]. Therefore, it is important to match the needle to vein size; under most collection conditions, 21-gauge needles are preferred [12,33].

Lubricant coatings on needles reduce (1) penetration force (the force measured prior to needle puncture through tissue), (2) drag force (the force required to continue tissue penetration), and (3) pain associated with venipuncture [34,35]. The most widely used lubricants are silicones [34,35], specifically polydimethylsiloxane and curable amino-functional silicone dispersions [35,36]. Silicone lubricants impart hydrophobicity to the needle to minimize blood and metal contact [35,36]. Silicone lubricants may displace drugs from binding proteins and interfere with chemical reactions or antigen–antibody reaction in immunoassays [33]. Agents used to prevent release of lubricants into blood specimens include gelling agents [37]; polar lubricants, which strongly adsorb to surfaces [38]; plasma treatments [39]; graft polymerization [40]; and ultraviolet photopolymerization [41].

Similarly, metal needle components (e.g., chromium, iron, manganese, and nickel), can contaminate blood specimens and interfere with subsequent chemical reactions or falsely elevate blood metal levels [33,42]. Metals and alloys used in needles must be tested thoroughly to evaluate any effects on whole blood, serum, or plasma.

Butterfly collection devices

Butterfly needles are preferred to conventional venipuncture needles for pediatric patients and for accessing small or fragile veins because of their small size (21-gauge or 23-gauge). The butterfly collection set consists of a stainless steel needle with a protective shield and plastic wings, which are connected to plastic tubing on one end and a Luer adapter on the opposite end for insertion into the blood collection tube [43]. The design allows for ease of multiple tube collection, but the short needle length (0.5–0.75 inches) limits their utility to surface veins. US butterfly device manufacturers include BD (Vacutainer Safety-Lok), Kendall Co. (Angel Wing), and Wingfield (Shamrock Safety Winged Needle).

Problems arising from the use of butterfly collection devices include increased risks of hemolysis, exposure to blood-borne pathogens, needle-stick injuries, and incomplete filling of blood collection tubes [44]. No clinically significant differences have been found in test results obtained from specimens collected by butterfly devices versus straight needles [43]. Thus, butterfly devices may be good alternatives to straight needles for blood collection.

Syringes

Hypodermic syringes are preferred when obtaining venous blood specimens from small or fragile veins that may collapse under the forces associated with withdrawing blood into evacuated tubes [45,46]. This is often the case with elderly patients and neonates. Syringes are also used to collect arterial blood specimens for blood gas analysis because leaving a vacuum or air space in the collection device affects gas pressures [45,46]. Syringes may also be used to draw specimens from intravenous lines or catheters, often for transfer to collection tubes [45,46].

Syringes for blood collection are typically composed of polypropylene or polyethylene [33], with additives and modifiers (e.g., antioxidants, antistatic agents, heat stabilizers, ultraviolet stabilizers, lubricants, and plasticizers) to meet required physical properties and improve ease of plastic processing [33]. Materials used for stoppers on plastic syringe plungers (e.g., the plasticizer di(2-ethylhexyl)phthalate) have been shown to contaminate blood specimens and interfere with drug assays [33,47]. When present in syringe stoppers, 2-mercaptobenzothiazole can be transformed during sterilization to 2-(2-hydroxyethylmercapto) benzothiazole, which interferes with toxicological analysis [33,48]. Phthalates, including diethyl phthalate, can cause co-migration of gas chromatography peaks, thereby increasing peak areas for drugs with similar retention times [33]. Some syringe manufacturers have developed barrier films (e.g., fluoropolymer) to lubricate syringe components and prevent leaching of vulcanizing agents from the rubber stopper of the syringe plunger [49]. Medical grade silicone oil, which is applied to the plunger and the inside wall of the syringe barrel to smooth the stopper action, may affect co-oximetry measurements of different hemoglobin species [50]. To limit potential contamination by syringe lubricants, some manufacturers bake the silicone onto the inside wall of the syringe barrel [49].

Excessive suctioning and forceful plunger depression during blood collection or transfer creates shear forces and breakage of red blood cells [13,31,51]. Several studies have shown increased hemolysis when using syringes rather than evacuated tubes for collection [13,31]. In one study, 19% of syringe-collected specimens were hemolyzed compared to 3% of tube-collected specimens [12]. Recently, Ashavaid et al. [52] reported that the incidence of hemolysis was 200 times greater in specimens collected with needles and syringes compared to those collected with evacuated tubes. To minimize hemolysis, the syringe plunger should be moved gently to reduce stress on red blood cell membranes.

Although CLSI H3-A5 does not recommend their routine use due to increased risk of needle-stick injury and poorer blood specimen quality, a needle and syringe are still commonly used for arterial blood collection [53,54]. Arterial blood gas specimens were traditionally collected in glass syringes (which are impermeable to atmospheric gases) [55,56], then placed in ice slurry for transport to the clinical laboratory. High-density plastic syringes (usually polypropylene) have generally replaced glass syringes in clinical and research laboratories because of cost, convenience (single use, disposable, preheparinized), ease of plunger use, and resistance to breakage [57,58].

A major drawback to plastic syringe use for blood gas measurements is that oxygen (and to a lesser extent, carbon dioxide) can permeate the barrel walls and plunger tip [56,59]. Gas permeability is influenced by the type of plastic material, syringe size (surface-to-volume ratio), and barrel wall thickness [60–62]. Numerous studies report clinically significant changes in the partial pressure of oxygen (PO_2) in blood gas specimens obtained from glass compared to plastic syringes, especially when blood PO_2 is high [55,56,58,63–65]. Comparing pore size and density, it was determined that plastic syringes have 4 to 150 times the oxygen diffusion area compared to glass syringes [66]. Additional studies show that initial oxygen level, oxygen–hemoglobin dissociation, total hemoglobin, and length of time and temperature during storage may affect oxygen measurements in specimens from plastic syringes [58,61,65,67–70]. The CLSI currently recommends that blood gas specimens collected in plastic syringes be kept at room temperature and analyzed within 30 minutes, whereas glass syringes should be used when analyses will be delayed for longer than 30 minutes [71].

A SafePICO syringe, which has a safe tip cap for removing air bubbles and a soft magnetic steel ball to dissolve anticoagulants, was developed to standardize the mixing of whole-blood specimens for blood gas, electrolyte, metabolite, and hemoglobin measurements on an ABL FLEX blood gas analyzer (Radiometer America) [72]. Despite concerns that automatic magnetic mixing in the SafePICO syringes may hemolyze red blood cells and falsely elevate potassium concentrations measured by direct potentiometry, a recent study showed that results were comparable to those obtained with a hematology analyzer (LH 750) and chemistry analyzer (LX-20) [72].

Direct transfer of blood specimens from syringes to blood collection tubes via piercing of the rubber stopper of the tube should be avoided. This procedure may cause hemolysis when cells impact the tube wall with great force following plunger pressure; this is especially problematic with large-bore needles [25,12]. When a syringe must be used to transfer blood to a collection tube, the blood must be added to the indicated volume level to avoid an incorrect blood-to-anticoagulant ratio, which will generate unreliable assay results [43]. Other devices are now available to safely transfer blood from syringes to blood collection tubes [43].

Catheters

Catheters are manufactured from many polymers, including polytetrafluoroethyene (PTFE, Teflon™), polyethylene, polypropylene, polyurethane, silicone, polyether urethane, polyvinylchloride, polyimide, and fluoropolymer [73–76]. Catheters are used to administer fluids and medications and to withdraw blood and other body fluids [73–76]. Lubricants are used with catheters to minimize pain, facilitate insertion or removal of the catheter, and permit easy removal of the needle from the catheter [73–76]. Catheter lubricants include polydimethyl siloxanes, curable and non-curable silicones, silicone surfactant, and lecithin [34].

Blood flowing through catheters is exposed to shear forces, which modify cell shape, activate cells, damage cells, and cause the efflux of intracellular constituents into the serum [25]; these changes affect hematological, electrolyte, and enzymatic determinations [12,77–80]. Unequal diameters of the catheter, adapter device, and stopper–piercing needle cause varying levels of pressure on red blood cells, which leads to hemolysis during blood collection into conventional evacuated tubes [12]. Specimens obtained by intravenous catheter are up to three times more likely to hemolyze compared to those obtained by venipuncture [78,82,83], with hemolysis being most common in smaller 24-gauge to 20-gauge catheters [78]. Furthermore, air entering evacuated tubes from loose catheter connections or assemblies may also cause hemolysis [78,81]. If clinicians are unaware of the method of blood collection and the effects on laboratory results, patient care may be complicated by inconsistent values and difficulty determining true values.

Benzalkonium heparin, a catheter coating used to prevent thrombi and decrease infections, can be released into blood specimens and interfere with ion-sensitive electrodes, thereby falsely elevating sodium and potassium levels [79–80]. Falsely elevated potassium levels likely result from the interaction of benzalkonium (a monovalent cation) with electrodes [79–80]. Extensive flushing reduces and eventually eliminates this interference, but catheter coatings may leach into blood specimens, especially with initial blood draws after catheter placement. Under these circumstances, direct venipuncture should be used for accurate electrolyte measurements [12].

Many studies show that administered drugs may adsorb to catheter surfaces. This adsorption is of primary concern when blood specimens are drawn soon after a catheter is used for a drug infusion. Polyvinyl chloride catheters adsorb drugs such as glyceryl trinitrate, hydralazine hydrochloride, thiopental, warfarin [84], benzodiazepines [85–86], and phenothiazines [87], and polyurethane catheters adsorb a variety of drugs [88]. Tacrolimus infusion through polyurethane catheters can lead to falsely elevated tacrolimus levels (eight times higher than those drawn from a peripheral vein) when subsequently drawn through a saline-flushed catheter [89]. Cyclosporine binds to silicone, polyurethane, and silastic

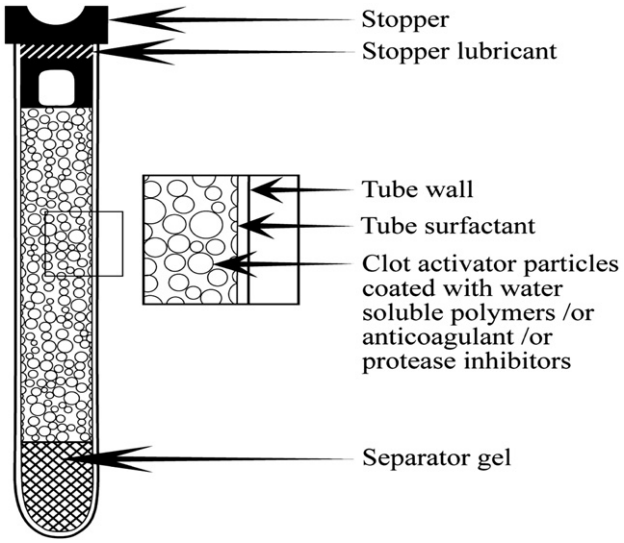

Fig. 1. Components of an evacuated blood collection tube.

material in catheters, even those lines not used for the infusion [73–76,90–94]. In general, specimens for therapeutic drug monitoring should not be obtained from a catheter or lumen previously used for drug infusion, even if the catheter has been flushed.

Blood collection tubes

Blood collection tubes are comprised of rubber stoppers, tube wall materials, surfactants, anticoagulants, separator gels, clot activators, anticoagulants, and surfactants, all of which may interfere with analytical assays (Fig. 1).

Tube wall

Evacuated blood collection tubes are generally cylindrical, with a length of 50 mm to 150 mm and a diameter of 10 mm to 20 mm [95,96]. Most measure 75 mm to 100 mm in length and 13 mm in diameter, and hold 2 to 10 mL of whole blood [95–97]. Microcollection tubes for pediatric blood specimens are typically 40 mm to 50 mm in length and 5 mm to 10 mm in diameter [95,96,98].

Historically, evacuated blood tubes were made from soda-lime or borosilicate glass, but soda-lime was later found to release trace elements, particularly calcium and magnesium, into blood specimens [33]. Because glass evacuated tubes are airproof, waterproof, and thermally resistant, they maintain vacuums over 200 days [99,100,101]. In glass tubes, the blood clotting cascade is activated when factor XII in blood contacts the hydrophilic glass surface; the clot does not adhere to the glass, so it is easy to separate from blood plasma by centrifugation [102]. This non-adherence also permits clot re-suspension into plasma during handling or transportation and can affect test results from resultant hemolysis [102].

To comply with Occupational Safety and Health Administration (OSHA) guidelines to minimize risks from shattering tubes, plastics have replaced glass in blood collection tubes [103]. Plastic blood collection tubes are manufactured by injection-molding processes using materials such as: polyethylene terephthalate (PET), polyolefins (polyethylene and polypropylene (PP)), polyesters, polyacrylic, polytetrafluoroethylene, polysiloxane, polyvinyl chloride, polyacrylonitrile, and polystyrene [95-97,99,100]. Plastic offers advantages by minimizing exposure to biohazardous material from breakage, increasing shock resistance, increasing centrifugation speed tolerance, decreasing shipping weights, facilitating disposal by incineration, and decreasing biohazard waste disposal costs [7,104-107]. Plastic tubes can be manufactured more economically and with excellent dimensional precision. However, plastic tubes are limited by increased gas permeability compared to glass tubes [100,104, 108]. PP and PET are the two most commonly used plastics in blood collection tubes [100,109]. PET is virtually unbreakable and maintains a vacuum for an extended shelf-life [100,108,110]. PP has lower water permeability than PET, which aids in retention of appropriate liquid anticoagulant volume and concentration in blood specimens [100]. Because anticoagulants in PET tubes tend to lose water, manufacturers have developed double-walled blood collection tubes to minimize anticoagulant evaporation, especially for coagulation studies [100,109]. Double-walled tubes have an internal PP layer, which protects against water evaporation from citrate solutions, and a PET external layer, which provides transparency to visualize tube fill levels [99,100,109]. The combined use of PP and PET helps retain anticoagulant solution volume and increase tube shelf-life [99,100,109].

Blood does not flow as smoothly over hydrophobic surfaces of most plastics, and blood components such as platelets, fibrin, and clotted blood adhere to plastic tube walls [111,112]. This prevents clean separation of serum from clot in conventional centrifuges and is particularly problematic during collection with microcollection tubes and in vacuum tubes during centrifugation. One approach to make the blood collection tubes less adherent to blood components is to make the surface glass-like, which presents a relatively hydrophilic surface to the blood [112,113]; this occurs when gas plasma is used to alter surface chemistry with heteroatoms [112]. Another approach is to coat the plastic interior with surfactants, water-soluble polymers, or water-insoluble polymers carrying hydrophilic–hydrophobic copolymers [111,114]; however, surfactant may be removed from the tube wall by blood. Moreover, surfactants in the plasma, serum, or clot may interfere with diagnostic tests [11]. To avoid these problems, manufacturers developed tubes with surfactant directly incorporated into the plastic [95,97]. Ideally, materials for blood collection tubes should promote clot formation, permit clean separation of clot from serum, and enhance strong adherence of the clot to minimize clot remixing.

Several studies have compared glass and plastic tubes with respect to clinical chemistry analyses [7,115,116], endocrinology [115,117], molecular testing [118], serology [119,120], and coagulation [97,112–115,121–124]. Although small statistically significant differences were found for some analytes, none were considered clinically significant. Therefore, it was concluded that switching from glass to plastic would not lead to major changes in test result interpretation.

Surfactants

Surfactants are commonly used in immunoassays to decrease nonspecific adsorption [125]. Inclusion of surfactants requires careful selection and optimization, as high concentrations may lead to direct loss of passively adsorbed antibody from the solid phase, among other nonspecific effects [125-128]. Commercially available blood collection tubes may contain many different surfactants [10,11,97,129] which are added as coatings or moldings to improve blood flow, better distribute clot activator along the tube wall, and decrease the tendency of proteins, red blood cells, and platelets to adsorb to tube walls [97,129,130]. Otherwise, cellular material may adhere to tube walls, contaminating plasma or sera and affecting results. There is little information available about the types and concentrations of surfactants used to coat inner surfaces and rubber stoppers of plastic tubes. More studies and further testing are needed to provide more information about the effects of surfactant coating.

Although researchers have used silicone surfactant to minimize adsorption of blood to tube walls [97], silicone may affect many test results. Reports show that silicone coating can

interact with ion-specific electrode membranes to increase voltage, thereby falsely elevating ionized magnesium and lithium concentrations [131-137]. Silicone may interfere with avidin–biotin binding in immunoradiometric assays for thyrotropin, prolactin, and human chorionic gonadotropin by physically masking antibodies [138-141]. Some silicones have been shown to activate platelets [99]. Researchers have also shown that surfactants may falsely elevate triidothyronine [10], affect competitive and non-competitive immunoassays like vitamin B_{12} and cancer antigen 15-3 [138,140,141], form complexes with C-reactive protein to falsely elevate results [152], and increase rates of false-positive hepatitis B surface antigens [153].

Bowen et al. [10] identified a common tube organosilane surfactant (Silwet™ L-720) in Becton Dickinson SST™ blood collection tubes that caused a falsely elevated triiodothyronine (T_3) and other analytes in a dose-dependant manner. Silwet L-720, the silicone surfactant used by Becton Dickinson for coating the interior of their blood collection tubes [95,142,143], is a member of a family of nonionic silicone surfactants that contain hydrophilic polyoxyalkylene chains. Typically, they exist as homopolymers or copolymers of polyoxyethylene and polyoxypropylene and are attached to a hydrophobic polydimethylsiloxane backbone [144–147]. The molecular structure of Silwet L-720 can be either comb-like, with the polyoxyalkylene chain side-grafted on a polydimethylsiloxane backbone, or linear, arranged with either the AB- or ABA-type configuration, with A representing a polyoxyalkylene hydrophile and B a polydimethylsiloxane hydrophobe [144–147]. The polydimethylsiloxane moiety of Silwet L-720 adsorbs to hydrophobic surfaces such as the plastic (i.e., polyethylene terephthalate) in blood collection tube walls, whereas the hydrophilic, polyalkylene oxide moiety faces outward toward the specimen and prevents erythrocyte adherence [144–148]. This surfactant, when present in excess amounts in blood collection tubes, causes interferences by desorbing the capture antibody from the solid phase used in the Immulite™ 2000/2500 triiodothyronine immunoassay, and has a similar effect on immunoassays from other manufacturers [10,11]. Interestingly, in the same study, the T_3 concentration did not increase in the presence of the surfactant when specimens were measured on an AxSYM™ analyzer. There are several possible explanations for this instrument-specific difference. It is conceivable that the anti-T_3 antibodies on the surface of the AxSYM microparticles are more resistant to desorption by the surfactant because of differences in solid support and/or conjugation. Differences in the competitive immunoassay format between the two analyzers could also explain the different responses of the two assays to the surfactant [10,11]. The Immulite 2000/2500 immunoassay for TT_3 is a simultaneous one-step assay, whereas the AxSYM uses a sequential two-step assay. The additional washing step with the AxSYM immunoassay format may more effectively remove the surfactant and prevent its binding to the microparticles or antibodies on the surface of the microparticle. The incubation time of the serum with surfactant from blood collection tubes and the microparticles coated with anti-T_3 antibodies from the AxSYM assay is considerably shorter than the 30-minute incubation in the Immulite 2500 TT_3 assay, thus providing less opportunity for the surfactant to interfere with the microparticle and/or the antibodies on the surface of the microparticle. Finally, differences in the amounts and types of antibodies used for the TT_3 assays could account for the differences in the two assays.

Some competitive and non-competitive immunoassays like vitamin B_{12} and cancer antigen 15-3, respectively, performed on the Advia Centaur™, were also affected by Silwet L-720, but their interference cannot be explained simply by the release of antibodies from the solid phase and must occur by a different mechanism. Therefore, further studies are needed to fully elucidate the mechanism of surfactant interference on these assays. In response to the immunoassay problems with the BD Vacutainer SST, SST II, and microtainer tubes, in 2005 Becton Dickinson reformulated their blood collection tubes to reduce the amount of surfactant in the tubes to decrease the assay interferences. Morovat et al. [149] have shown a bias in some immunoassays with these reformulated tubes; however, the difference was determined not to be clinically significant [149]. In that study, the reference blood collection tubes used were coated with silicone surfactant, the source of the immunoassay interference [10,11,125]; however, a plain glass blood collection tube with no surfactant would have been a better choice for the control tube. Wang et al. [150] investigated the effects of reformulated Vacutainer and Microtainer tubes on 16 widely used immunoassays performed on the Immulite 2000 analyzer. It was found that the gold-top SST Vacutainer and Microtainer compared to glass control tubes produced a significant bias for free triiodothyronine (12.2% and 39.1%, respectively) and free thyroxine (16.7% and 23.6%, respectively), exceeding the maximum desirable bias of 3.6% for both thyroid hormones. A previous study by McKiel et al. [151] also demonstrated increased free thyroxine levels when blood was collected in siliconized evacuated blood collection tubes. Hence, the reformulated Vacutainer and Microtainer tubes with reduced surfactant still showed a significant bias for certain analytes measured on the Immulite 2000 analyzer.

Other studies have also been published on the effects of surfactants in blood collection tubes on clinical assays. One study showed that silicone from blood collection tubes formed a complex with C-reactive protein that enhanced the antigen–antibody reaction in the Vitros C-reactive protein assay and falsely elevated results [152]. In another study, Sheffield et al. [153] reported a significant increase in false-positive hepatitis B surface antigen results in women (19 out of 24 women) for the AUSZYME™ monoclonal test (Abbott Diagnostics) using blood collected in BD Vacutainer SST Plus tubes over a 3-month period. The authors determined that the elevated false-positive rate was a result of higher absorbance readings from increased turbidity of the serum specimen due to higher surfactant and clot activator concentrations in these tube types (unpublished observations). The reformulated SST blood collection tubes that contain less surfactant significantly reduced the absorbance values and turbidity of the serum specimens, which led to fewer false-positive specimens (unpublished observations). Stankovic and Parmar [125] have also discussed

the impact of surfactant from blood collection tubes on clinical assays.

Specimens recently analyzed from reformulated SST tubes with decreased surfactant concentrations had significantly higher serum potassium levels [154]. It was thought that lower concentrations of surfactant in blood collection tubes increases the possibility of red blood cell, protein, and platelet adherence to tube walls with subsequent release of intracellular potassium [111].

Recent studies showed that some blood collection tube constituents interfere with peaks produced by mass spectrometry. Drake et al. [155] showed that 7 of 11 tubes tested added polymeric components such as surfactant or polyvinylpyrrolidone, which were detected as multiple signals by mass spectrometry in the *m*/*z* range of 1000 to 3000. These tube additive peaks complicate the interpretation of mass spectra in the low-molecular mass range, especially when using matrix-assisted laser desorption ionization or surface-enhanced laser desorption ionization, wherein a broad spectrum of components is measured in a single analysis [155,156].

Surfactants have detergent properties that may interact with blood components to influence cellular integrity or distributions of non-cellular particles in blood to alter serum plasma composition. For example, a recent study showed that blood collection tubes altered the concentration of free fatty acids in specimens rather than interfering with analytical methods [157].

Stopper

Rubber stoppers are sized to fit collection tubes and are color-coded by type of anticoagulant or presence of separator gels. Stoppers should be readily penetrated by needles, become self-sealing when the needle is removed [111,157], and maintain a vacuum [111,158]. Suitable materials for rubber stoppers include silicone, isobutylene–isopropene, styrene butadiene, chlorinated isobutylene–isoprene rubber, ethylene–propylene copolymers, polychloroprene, butyl rubber, and halogenated butyl rubber [111,147,148,159,160]. It is possible that components of rubber stoppers will contaminate blood specimens and cause assay errors. Numerous studies show discrepancies in bioavailability and bioequivalence of drugs when rubber stoppers containing the plasticizer tris (2-butoxyethyl) phosphate (TBEP) are used [161,162]. TBEP is used to increase softness and flexibility of the stopper, but it can displace certain drugs from plasma protein binding sites (e.g., α_1-acid glycoprotein [163–168]), thereby increasing drug uptake by red blood cells and lowering measured serum or plasma levels. Drugs with altered distribution from TBEP include quinidine, propanolol, lidocaine, tricyclic antidepressants, and phenothiazine drugs (e.g., fluphenazine and chlorpromazine) [161,163–168]. Janknegt et al. [169] demonstrated that rubber stoppers lacking TBEP showed no interference with several assays used for therapeutic drug monitoring. These findings have prompted tube manufacturers to decrease production of rubber stoppers containing TBEP [161,162].

Chrzanowski [170] found that other substances leached from butyl rubber stoppers to cause spuriously high theophylline results on gas liquid chromatography analysis (GLC). Certain metals such as calcium, aluminum, magnesium, and zinc are used in rubber stopper manufacturing and must not be extracted into blood specimens, as this could affect results [171-174]. Specially formulated rubber stoppers prevent divalent cation leaching [175]. Other potential contaminants found in rubber stoppers include sulfur, sulfur-containing vulcanization accelerators, fatty acids, and peroxides. Most manufacturers have reformulated their rubber stoppers with low extractable rubber or added substances to minimize leaching of contaminants into the blood specimen [163,157,192]. Despite these safeguards, it is good practice to fill the tubes to their designated volume and store in the upright position to minimize leaching from the stopper and not concentrate potential contaminants in low specimen volumes. It is also advisable to request that the manufacturer supply data from clinical trials and consult references on the specific type of tube and stopper used. Some collection tubes have elastomeric closures covered with polypropylene, polyvinylchloride, or polyethylene (e.g., Hemoguard™) to minimize contamination of blood specimens when the stopper is removed [176].

Stopper lubricant

The application of silicone or glycerol lubricants to stoppers facilitates insertion and removal of stoppers from blood collection tubes. The lubricants also minimize adherence of red blood cells and clots to the stoppers so that they do not contaminate the serum or plasma layer. Glycerol should not be used when blood concentrations of glycerol or triglycerides are measured, as glycerol is a component of both assays [177,178]. Siliconized stoppers are preferred because silicone causes less interference with analytical assays. However, silicone on rubber stoppers may falsely elevate ionized magnesium and total triiodothyronine [10,133,134]. Silicone lubricant may also leach from the stopper and confound mass spectroscopy results [155]. Thus, stopper lubricant should be considered a potential source of error in clinical chemistry assays.

Separator gel

Blood collection tubes commonly contain separator gels that form a barrier between packed cells and serum during centrifugation [179,184,185]. Separator gels markedly improve serum and plasma analyte stability, removing the need for aliquoting serum, and facilitating storage and transport [180–183]. The gel position is influenced by manufacturer-controlled variables (specific gravity, yield stress, viscosity, density, and tube material), laboratory conditions (centrifugation speed, temperature, acceleration and deceleration conditions, and storage conditions), and patient factors (heparin therapy, low hematocrit, elevated plasma protein, specific gravity) [184,186]. Advantages of separator tubes are (1) ease of use, (2) shorter processing time through clot activation, (3) higher serum or plasma yield, (4) reduced aerosolization of hazardous substances, (5) a single centrifugation step, (6) primary tube sampling, and (7) a single label.

Separator tube polymeric gels are made from viscous liquid, organic and inorganic fillers, and natural or synthetic tackifiers [111,144,148,187,189] to achieve proper viscosity, density, and

other physical properties. Viscous liquid components include silicone oil, chlorinated polybutadiene and polybutene, poly (meth)acrylate, polyisobutene, and copolymers obtained from alpha-olefin or styrene and maleic acid diester [111,144,148, 187,188]. Inorganic fillers include silica, alumina, talc, and kaolin, whereas organic fillers include styrene polymers and copolymers, acrylic resins, and polyvinyl chloride. Natural tackifiers include rosin and rosin derivatives, whereas synthetic tackifiers include olefin and diolefin polymers and pheonolic resins [111,144,148,187].

Because serum and plasma specific gravities range from 1.026 g/cm^3 to 1.031 g/cm^3, and clot specific gravities range from 1.092 g/cm^3 to 1.095 g/cm^3, the specific gravity of the separator gel should be between 1.03 g/cm^3 and 1.09 g/cm^3 (preferably 1.04 g/cm^3) [190,191]. Rarely, hyperproteinemia or high concentrations of radio-contrast dye cause high specimen-specific gravities and the serum or plasma may not float above the gel [186,192]. Hydrophobic coating may be applied to tube walls to improve adherence of the gel and form a barrier between red blood cells and the serum or plasma.

Ideally, laboratory results should not be affected by interaction with separator gels; however, several reports show effects on analyte concentrations. Specimen volume, storage time, temperature, and gel type may influence drug adsorption to the gel [181,193–197]. Hydrophobic drugs such as phenytoin, phenobarbital, carbamazepine, quinidine, and lidocaine may adsorb to hydrophobic separator gels. This adsorption can decrease serum drug concentration by 20% to 50% after 24 hours at 4 °C [166,198–201]. The organochlorine 1,1-dicholoro-2,2-bis(*p*-cholorophenyl)ethylene and polychlorinated biphenyls also adsorb to separator gels [202]. Progesterone concentrations undergo time-dependent reduction of up to 50% when stored over a separator gel for 6 days. [203]. Recently, Daves et al. [8] showed a statistically, but not clinically, significant difference in myoglobin and CK-MB concentrations in tubes containing separator gels; however, the mechanism is unknown. Tube manufacturers have developed new separator gel formulations to minimize drug and analyte adsorption [204].

Separator gels may also release materials that interfere with analytical assays [155,185,203,205,206]. Pieces of gel or silicone oil droplets may be present at the top or within serum and plasma of tubes containing separator gels [185,203]. The gel and oil droplets can interfere with the sample probe, coat tubes, and cuvettes and physically interfere with binding in solid-phase immunoassay systems [185,203,206]. Oil globules may coat and insulate electrodes, thereby changing the electrical potential and reported analyte concentrations. Some gel components dissolve in blood and affect solvent extraction characteristics of certain drugs [207]. Relatively high concentrations (20 mg/L or more) of ethylbenzene and the xylenes have been detected in blood collected with gel tubes [208]. Degradation of separator gel materials accelerates with improper storage orientation, temperature, and inappropriate centrifugation speeds [203].

Clot activator and water-soluble substances

Blood collected for serum testing should clot as rapidly and completely as possible to facilitate clot separation during centrifugation. Although glass surfaces activate clotting in less than 30 minutes, plastic tubes require clot activators to achieve this. Contact clot activators function through the intrinsic pathway, which is surface area-dependent [143,148]. Glass, silica, kaolin, bentonite, or diatomaceous earth are used as rapid contact activators [111,144], whereas particulate clot activators like inorganic silicates are relatively slow (30–60 minutes) [97,208]. Amounts of clot activators on plastic tube walls vary substantially (e.g., 0.1% to 1% by weight of silica) [111,210]. However, 40% to 80% of tube walls are typically covered by silica clot activator [210-212]. Silica clot activators are usually spherical and range from 0.01 μm to 100 μm in diameter (preferably 0.4 μm to 20 μm) [148]. Clot activators have the added benefit of decreasing latent fibrin formation in separated serum [203].

A second type of clot activator activates the extrinsic pathway and is biochemical and concentration-dependent [97,148,209]. Although these clot activators work rapidly (10–20 minutes), clots are gelatinous and do not separate cleanly; thus, the resultant serum is often of poorer quality [97,148,209]. Biochemical clot activators such as ellagic acid, thrombin, snake venoms, and thromboplastin [111,97,213,215] are added to small beads or paper discs, or sprayed onto tube surfaces with a carrier such as polyvinylpyrrolidone (PVP), carboxymethyl cellulose, polyvinyl alcohol, or water-soluble surfactants like polyethylene oxide [97,111,210,215]. The carriers allow for rapid suspension of the clot activator, increased clot formation [111,210,215], and reduced need for mixing [111,215]. However, the carriers become dissolved in both the serum and the clot [111,148]. Some clot activators degrade when exposed to high humidity [111,215], and silicone polymer vapors can condense and form liquid films that inhibit surface activation [209–215,216].

Some clot activators must be mixed by inversion and may not pellet completely with the clot, thereby contaminating the serum and interfering with analytical assays [111]. The suspended particles may also damage instrument sample probes. If small fibrin clots form, they can interfere with pipette accuracy or solid-phase binding efficiency in immunoassay systems [217–220]. To avoid these problems, tube walls can be treated with a plasma gas to introduce heteroatoms so that clotting is accelerated but no particulates, soluble clotting activators, or binders contaminate the serum or the clot [113].

Several studies have reported the effects of clot activators on laboratory tests. Sampson et al. [135] demonstrated that silica or silicone surfactant falsely elevate lithium concentrations determined by Lytening 2Z ion-specific electrode analyzer. The clot activator or the silicone surfactant apparently interacts with the analyzer's ion-specific membrane, thereby increasing the measured voltage and the serum lithium ion concentration. The exact mechanism by which this occurs is unknown. Testosterone concentrations have been measured at fourfold higher concentrations when performed on specimens in clot activator-containing tubes [221]. Clot activators interfere with testosterone measurements with the ion pair at the *m*/*z* ratio of 289.3/97.1, the selected transition for testosterone monitoring [221]. Changing the ion pair to an *m*/*z* ratio of 289.2/109.0 eliminates this interference [221]. Protein profiles obtained by mass spectroscopy can be altered by clot activators in tubes

Table 2
Some common evacuated blood collection tube stopper color and additives.

Stopper color[a]	Additive(s)	Amount / concentration
Red	Clot activator Uncoated interior	
Gold Red/black Red/gray	Clot activator with separator gel	
Light blue	Citrate, trisodium (liquid additive) (1 part additive to 9 parts of blood)	0.105 M (3.2%) or 0.129 M (3.8%)
Green	Heparin, sodium (dry additive) Heparin, lithium (dry additive)	10–30 USP units/mL blood 10–30 USP units/mL blood
Light green (mint)	Heparin, lithium (dry additive) with separator gel	10–30 USP units/mL blood
Lavender	EDTA, dipotassium (dry additive) EDTA, tripotassium (liquid additive) EDTA, disodium (dry additive)	1.5–2.2 mg/mL blood 1.5–2.2 mg/mL blood 1.4–2.0 mg/mL blood
Gray	Sodium fluoride/Potassium oxalate (dry additive) Sodium fluoride/disodium EDTA (dry additive) Lithium iodoacetate Sodium fluoride	Sodium fluoride: 2.5 mg/mL blood / potassium oxalate:2.0 mg/mL blood Sodium fluoride: 2.5 mg/mL blood / disodium EDTA: 1.5 mg/mL blood Iodoacetate: ~2 mg/mL blood Sodium fluoride: ~4.3 mg/mL blood
Yellow	Acid Citrate Dextrose (ACD)— solution A (1 part additive to 5.67 parts of blood) Acid Citrate Dextrose (ACD) — solution B (1 part additive to 3 parts of blood)	Citrate, disodium, 22.0 g/L; citric acid, 8.0 g/L; dextrose, 24.5 g/L Citrate, disodium, 13.2 g/L; citric acid, 4.8 g/L; dextrose, 14.7 g/L
Royal blue (with red band on label)	None	~1.8 mg/mL blood
Royal blue (with lavender band on label)	EDTA, dipotassium (dry additive)	

Table modified from the Clinical Laboratory Standards Institute: Evacuated Tubes and Additives for blood specimen collection: Approved standard H1-A5 [239] H3-A4 [240] and information from Young et al. [241] and at the BD website [242].
[a] Single or multiple stopper color combinations may vary from different tube manufacturers.

[222,223]. Silica and silicate clot activators can induce in vivo and in vitro release of pro, active, and complexed forms of matrix metalloproteinase-9 (gelatinase B) [224,225]. Increased matrix metalloproteinase-9 concentrations and clot activation may occur when red blood cells release matrix metalloproteinase-9 in the presence of silica and zinc ions [223,224]. To avoid this problem, citrate plasma is now recommended to measure matrix metalloproteinase-9 [226].

Anticoagulants

Plasma differs from serum in several important respects. Plasma has a higher viscosity and total protein content (approximately 4 g/L higher than serum) because plasma contains fibrinogen and other clotting factors [227-230]. Plasma contains slightly lower potassium and lactate dehydrogenase concentrations and much lower concentrations of coagulation factor activation peptides, platelet factor 4, thromboglobulins, and other platelet components released by platelet activation. Elevated platelet and white and red blood cell counts in patients with various hematologic malignancies are a well-recognized source of falsely high serum potassium concentrations [231,232]; plasma potassium measurements give more accurate results.

When plasma is used for diagnostic assays, care must be taken to select the appropriate anticoagulant. The most commonly used anticoagulants in blood collection tubes are ethylenediaminetetraacetic acid (EDTA), heparin, and citrate. Anticoagulants can be in liquid or solid (powdered, crystallized, or lyophilized) [233] and should be added in appropriate concentrations to preserve analytes to prevent interference with binding or precipitation of antigen–antibody complexes [234–238].

Potassium EDTA (K_2EDTA; Table 2) is a commonly used chelating agent that binds calcium and prevents clot formation [239,243]. It is the anticoagulant of choice for performing the complete blood cell (CBC) count. EDTA can bind metallic ions such as europium, which is present in some immunoassay reagents, or zinc and magnesium, which are common co-factors for enzymes (e.g., alkaline phosphatase) used as immunoassay reagents [244–246]. Thus, the blood-to-EDTA ratio is critical for optimal test results. Elevated EDTA levels in partially filled tubes may chelate magnesium and zinc, which in turn alters alkaline phosphatase activity in chemiluminescence assays (e.g., intact parathyroid hormone and ACTH) [245–247]. Also, proteins that contain divalent cation-binding sites (e.g., calcium and magnesium) may undergo conformational change when the

ions are not present, thereby affecting antibody test results [245,246]. EDTA also draws water from cells and dilutes plasma by 3% to 5% [239,243], which can change red blood cell indices and hematocrit. Therefore, EDTA tubes should be filled to the proper volume to avoid chelation and concentration changes [248]. An excellent review about the role of EDTA in diagnostic testing has been authored by Banfi et al. [248].

Heparin has been used in conjunction with lithium, sodium, and ammonium salts as an anticoagulant. Heparin acts primarily through an antithrombin III complex that prevents thrombin activation by inhibiting thrombin and factor Xa, which in turn prevents fibrinogen formation from fibrin [245,246]. The nominal amount of heparin issued in blood collection tubes is 14.3 U/mL of blood, although a range of 10 to 30 U/mL of blood is acceptable [249–252] (Table 2). Heparin solutions dilute samples, so dry heparin salts are typically used in blood tubes [253].

Heparin binds to electrolytes to change concentrations of bound and free ions [251,254,256]. To minimize calcium binding in heparinized syringes, electrolyte-balanced heparin formulations have been developed [256]. Heparin may interfere with chloride measurements because chloride ion electrodes select for ions like heparin that have hydration energies greater than chloride [257]. Interestingly, we observed positive interference with a chloride electrode (2–10 mmol/L) when specimens from heparin-treated blood tubes were assayed on the Dimension™ Vista 1500 analyzers (Siemens Healthcare Diagnostic, Newark, DE) compared to the Dimension RxL analyzers (unpublished observation). A large number of specimens showed negative anion gaps on the Vista analyzers, possibly because heparin interfered with the chloride membrane electrode.

Heparin may also interfere with antibody–antigen reactions [258,259]. Although heparin decreases the rate of reaction of some antibodies (particularly at the precipitation step in second-antibody systems), use of solid-phase systems has minimized this problem [203]. Heparin should not be used in cryoglobulin testing because cryoprecipitation may occur due to the complex formation between heparin and fibronectin and the cold-precipitable complexes of fibrin and fibrinogen [203,245,246,260,261]. The influence of administered heparin on serum thyroid hormone levels and other analytes has also been investigated [203,245,246]. Recently, falsely low albumin levels were found in hemodialysis patients whose blood was collected with heparinized blood collection tubes [262]. It was speculated that the falsely decreased albumin levels were caused by heparin preventing binding of bromocresol green (but not bromocresol purple) to albumin, which reduced colorimetric complex formation [262]. Heparin binds nonspecifically to proteins, affecting separation and mass spectrometric detection of peptides [263-265].

Recently, heparin-containing intravenous products were contaminated with oversulfated chondroitin sulfate (OSCS), which was associated with adverse reactions in at least 12 countries [266]. In response, the US Food and Drug Administration (FDA) requested that heparin manufacturers investigate OSCS contamination by capillary electrophoresis or nuclear magnetic resonance [267]. Some lots from a major North American tube manufacturer contained up to 0.91% OSCS [267]. However, extensive evaluation of lithium heparin blood collection tubes with and without OSCS showed that those containing OSCS produced clinically acceptable chemistry results [267] and that heparin concentrations were appropriate [267]. In contrast, Bosworth et al. [266] separately showed that OSCS (5% to 20% by weight) contamination of blood specimens produced statistically significantly different results for lactate dehydrogenase, total triiodothyronine, potassium, total protein, chloride, and uric acid [266]. However, no clinically significant differences were found between blood collected in lithium heparin tubes with OSCS and those without OSCS [266]. Although the mechanism of OSCS interference is unknown, polyanionic substances can interact with many clinical chemistry assay reagents [266]. Bosworth et al. [266] also showed that OSCS adversely affected anticoagulation in plasma specimens with OSCS. These two studies highlight the impact of anticoagulants on clinical assays.

Trisodium citrate, a calcium chelating agent, is used as an anticoagulant for coagulation testing [239,249] (Table 2). It inhibits aspartate aminotransferase and alkaline phosphatase by chelating required cation cofactors [239,249]. Sodium citrate is a component of acid citrate dextrose (ACD) and citrate theophylline adenosine dipyrridamole (CTAD) anticoagulants [249,268–270]. CTAD prevents platelet activation during specimen collection and is important for measuring plasma levels of platelet-derived components.

Potassium oxalate is an anticoagulant used to chelate calcium [239] (Table 2). However, it shrinks erythrocytes by drawing water out of cells, thus reducing hematocrit levels by as much as 10% [249]. Oxalate also inhibits enzymes such as acid and alkaline phosphatase, amylase, and lactate dehydrogenase [249]. Oxalate is often used in combination with antiglycolytic agents such as sodium fluoride and sodium iodoacetate. Sodium fluoride (2 to 3 mg/mL of blood; Table 2) inhibits enzymes so that glucose and alcohol are preserved [271–275]. Recently, sodium fluoride has been considered for antiglycolytic use because it inhibits enolase [271–275]. However, the antiglycolytic effects of fluoride may be delayed up to four hours after blood specimen collection [272–276], allowing glucose to be metabolized at 5% to 7% per hour at room temperature before glycolysis inhibition begins. This delay occurs because upstream enzymes continue to metabolize glucose to glucose 6-phosphate [276–278]. Thus, fluoride anticoagulants may be non-ideal when glucose levels must be preserved in non-separated blood samples. For example, fixed glucose cut points for diabetes are based on studies with blood that was immediately iced, which extends the time to clinically significant glycolysis [275,277,278].

Sodium fluoride may inhibit enzyme activity in some immunoassays and interfere with electrolyte measurements by altering cell membrane permeability or causing potassium efflux secondary to adenosine triphosphate depletion-induced hemolysis [249]. Similarly, iodoacetate inhibits glyceraldehyde-3-phosphosphate dehydrogenase, promotes hemolysis, and interferes with glucose, sodium, potassium, chloride, and lactate dehydrogenase measurements [249,279,280].

Certain anticoagulants and antiglycolytics may be inappropriate for certain assays. Because assay manufacturers do not always specify the source of plasma used to validate their tests, the clinical laboratorian should verify plasma tube performance with particular assays and instrument platforms. It is important to adhere to manufacturer recommendations for appropriate tube volume and order of draw to ensure proper additive-to-blood ratios. These efforts can save time and prevent laboratory errors.

Order of draw

The CLSI guidelines standardize the sequence of tubes and syringes during blood collection to minimize carryover of tube additives, which may affect assay results [20,282]. For example, blood draws beginning with potassium–EDTA tubes cause falsely low calcium and falsely high potassium values in subsequent blood tubes that do not contain anticoagulants [281]. The current CLSI guidelines suggest the following order of draw: blood culture tubes, sodium citrate tubes, serum tubes with or without clot activator and with or without gel separator, heparin tubes with or without gel separator, EDTA tubes, acid citrate dextrose-containing tubes, and glycolytic inhibitor (fluoride, iodoacetate) tubes [20,282]. Microcollection tubes have a different order of draw: blood gases, slides/smears, EDTA tubes, other additive tubes, and serum tubes [282]. This revised order prevents small clot formation and platelet clumping, which significantly affect test results [283,284,282]. Tube manufacturers use different colored closures to facilitate identification of tube additives.

Protease inhibitors

Blood contains a wide variety of protease inhibitors [285], with inhibitors outnumbering active proteases. Chelating agents (e.g., EDTA and citrate) do not inhibit serine proteases, but do slow coagulation protease activation by interfering with calcium-mediated binding. Thrombin and factor Xa inhibitors are anticoagulants offering protein stability and allowing chemistry and hematology tests on single specimens; however, they are costly and are not widely used [286,287]. Small peptides often have better stability in plasma, but parathyroid hormone has been noted to have better recovery in serum than EDTA plasma [288,289]; EDTA may interfere with some immunoassay detection systems. Stability of some peptides, like brain-type natriuretic peptide, is increased by aprotinin addition [290]; therefore, some reference laboratories recommend using aprotinin or other protease inhibitors in tubes used to collect specimens for bioactive peptide testing. Peptide stability is highly variable in plasma. Peptides like glucagon-like peptide 1 are rapidly cleaved by dipeptidyl peptidase IV [291]; collection tubes should include peptidase inhibitor for high recovery of the intact peptide. EDTA tubes are generally recommended for proteomic analyses [292]. Small peptides rapidly degrade in serum specimens, and protease inhibitors increase peptide stability in plasma [293]. Small peptides may be more susceptible to degradation because small peptides: (1) undergo peptidolysis by sterically-hindered proteases complexed with alpha 2-macroglobulin [296], (2) lack a globular structure, and (3) have greater accessibility to exopeptidase action. Some inhibitors such as sulfonyl halides may chemically modify proteins [294]. An alternative protein stabilization strategy is to inhibit proteases by decreasing specimen pH [295]. High-molecular weight endogenous protease inhibitors are abundant in plasma and are directed primarily against serine proteases, with little activity versus exopeptidases. Adding low-molecular weight exogenous inhibitors or small synthetic compounds may quantitatively augment inhibitor balance and provide access to sterically hindered proteases to expand antiproteolytic activity.

Protease activity may be augmented by protease secretion from white blood cells or release during red blood cell lysis. For example, insulin has substantially decreased stability in hemolyzed specimens due to release of a thiol protease from red blood cells [297]. Protease inhibitor addition has limited effects on recovery of chemokines and cytokines from plasma; processing time is the most critical factor [298].

Because protein and peptide stability varies widely, addition of exogenous protease inhibitors depends on intended specimen use. Thus, the specimen components of interest should be analyzed for stability to determine whether protease inhibitors are indicated.

Microcollection devices

Analytical instrumentation advancements allow many diagnostic tests to be performed on small quantities of blood (i.e., those obtained by spring-loaded puncture of the finger, heel, or earlobe). Microcollection with capillary tubes and microcollection tubes is typically used for infants, geriatric patients, or those with veins not amenable to venipuncture [299,300]. Various sizes, volumes, and shapes of capillary tubes are commercially available with or without heparin, EDTA, and citrate [300]. To minimize breakage, shattering, and exposure to blood-borne pathogens, and to provide flexibility, a Mylar™ film is added to glass or plastic tubes, although plastic capillary tubes are recommended [45]. Microcollection tubes have virtually replaced Caraway/Natelson tubes, which cannot be individually labeled, must be cut open to separate the serum from the red blood cells, and produce lower serum yields [301]. Microcollection tubes may be designed to protect neonatal specimens from visible light degradation of bilirubin (amber-colored tubes) and may include an integrated collection scoop to improve capillary blood collection [302]. Several types of capillary and microcollection tubes are available from BD (Franklin Lakes, NJ), Kendall Co. (Mansfield, MA), Sarstedt Inc (Newton, NC), and Greiner (Monroe, NC) [9,303,304,305]. Compared to larger evacuated blood collection tubes, the collection, handling, and processing of blood specimens from microcollection devices is more time-consuming [304,305].

Plastic microcollection devices are recommended to reduce the risk of injury and blood exposure [306]. The tube wall is usually made from clear thermoplastics like polypropylene (preferred), polyethylene, and polyvinylchloride so that the blood is easily visualized by the health care professional [129]. The statistically significant but clinically insignificant

differences in analyte levels collected by microcollection versus evacuated tubes may be attributable to tube wall material [304]. Disadvantages of microcollection include increased hemolysis from capillary collection and clot activation during collection by tissue fluid and lower serum or plasma yields [307].

As with venous blood specimens, platelets, fibrin, and clots in capillary blood may adhere to plastic tube walls [129,308]. This may be enhanced in microcollection because of smaller tube diameters [129,308]. Therefore, microcollection tubes may be coated with surfactants to enhance blood flow into the tube and minimize protein and cell adhesion to the tube wall [129,308]. The same immunoassay interference from surfactants in SST tubes that occurs with venous blood may also occur with capillary specimens in microcollection tubes [150]. Separator gels in microcollection tubes are the same as those used in venous blood collection tubes, with studies showing that microcollection tubes with or without separator gel are suitable for specimens intended for clinical assays, including therapeutic drug levels [309,301,304,305]. Although plastic screw caps are commonly used to cover microcollection tubes for transport, centrifugation, and storage, there is no indication that these materials interfere with clinical chemistry assays.

The effect of anticoagulants in microcollection devices has not been well described [253]. Two recent neonatal cases showed that blood collection tubes containing lithium heparin resulted in elevated serum lithium concentrations [310,311]. Underfilling microcollection devices can lead to erroneously high lithium levels to the toxic range [311]. Thus, health care personnel should be aware of the importance of proper filling, mixing, and additive use with microcollection devices. Manufacturers and laboratorians must be aware of all components of microcollection devices and understand potential effects on clinical assays.

Point-of-care testing

Point-of-care (POC) testing may assess conventionally collected specimens (e.g., operating room or intensive care unit testing) or, more commonly, capillary blood obtained by skin puncture (e.g., office, bedside, or home testing). For skin punctures, the site must be cleaned, then punctured by a lancet. The first blood drop is wiped off, and subsequent drops are collected by microdevices. Microcollection tubes are filled by gentle contact, and capillary tubes are filled by capillary action. Rapid filling helps prevent clotting and air bubbles. Both glass and plastic microcollection tubes are available with or without anticoagulants (e.g., heparin). Brown glass microcollection tubes are used to test light-sensitive analytes such as bilirubin.

A novel blood-conserving POC system uses a modified i-STAT™ cartridge, which permits blood to flow directly from the sampling port into the cartridge [312]. Clinically acceptable performance has been demonstrated for 12 tests, including blood gases, electrolytes, hematocrit, and glucose. Whereas typical testing requires a blood volume up to 10-fold higher than needed for testing, i-STAT only requires the exact sample volume (95 μL of whole blood) indicated for the test [312]. In addition to being blood-conserving, this technique can be used without heparinization [312]. Collection of blood specimens on filter paper for neonatal screening and genetic testing is a approach to on-site microsampling in which filter paper is touched directly against a drop of blood produced by skin puncture, air-dried, and transported to a laboratory for testing.

Cryoprotein testing

Cryoproteins are plasma proteins (immunoglobulins, fibrin/fibrinogen, and fibronectin) that reversibly precipitate at temperatures below 37 °C. Cryoglobulins, which consist of immunoglobulins and immunoglobulin–fibronectin complexes, are traditionally tested from serum specimens. Cryofibrinogens consist of fibrinogen–fibrin complexes and precipitate only from plasma. Because cryoglobulins also precipitate from plasma, parallel testing of serum and plasma is needed to detect cryofibrinogenemia.

Proper collection and processing of specimens is critical for cryoprotein testing [261,313]. It is recommended that blood be drawn into a prewarmed plain red top tube or syringe, transported in a thermos filled with prewarmed sand, allowed to clot in a 37 °C water bath, and separated from serum in a warm centrifuge (37 °C) [260]. For cryofibrinogen testing, blood should be collected into an EDTA tube and the same procedure followed [261]. For reasons outlined earlier, heparin tubes should not be used for cryoprotein/cryofibrinogen testing [260,261]. However, a recent cryoglobulin practice survey showed that 1 out of 137 laboratories from the UK National External Quality Assessment Service quality control program used heparin tubes for cryoglobulin testing [313].

Recommendations to minimize interference with clinical assays

Detection and prevention of errors associated with blood collection tube additives remain a problem for diagnostic assay manufacturers and clinical laboratories. Before marketing a new collection device, manufacturers must demonstrate safety and efficacy through analytical and clinical studies. Although it is impractical for manufacturers to test their products on all assay platforms, they should ensure process consistency in the quantity and quality of tube components and additives. Manufacturers should also evaluate new or substantially modified tubes under conditions of maximal interference (e.g., reduced specimen volumes and extended contact time with the tube components). Analysis of tube stability is needed to determine appropriate storage and lifetime of the collection device. Ideally, tube manufacturers should implement Design for Six Sigma, Six Sigma, and similar methodologies to reduce variation among blood collection device components [314,315]. In addition, the impact of blood collection tube components on clinical assays should be considered in the context of the total allowable error; hence, tube components should not increase the total allowable error for a clinical assay; thus, invalidating the usefulness of the assay [314,315].

Similarly, when releasing a new assay or instrument platform, manufacturers should verify performance of blood collection tubes with their diagnostic assay or instrument. Reference interval studies performed with outdated collection devices should be repeated with currently used devices.

Blood collection device problems are difficult for laboratorians to recognize in a timely manner because routine quality control testing may not use the problematic collection devices [10,11,316]. Furthermore, proficiency testing programs, which do not require collection of specimens with routinely used blood collection devices, will also fail to detect these types of problems [10,11,316]. Comparison of results for control sera exposed and unexposed to blood collection tubes will reveal adverse effects from tube additives [10,11,316], but this testing is uncommon in most clinical laboratories. This is also impractical for most clinical laboratories because of the diversity of tubes used and because of frequent changes in tube lots. It may, therefore, be more appropriate for manufacturers to expose quality control sera to blood collection tubes on a lot-by-lot basis. When the clinical laboratory changes the tubes it uses, a well-planned tube verification protocol should be implemented. The protocol should describe the procedure, with predefined acceptance criteria and statistical methods, and adhere to institutional review board or ethics committee policy and procedures for testing human subjects. Blood specimens from healthy persons and patients should be used to assess the entire blood collection system (needles, holders, tubing, etc.) rather than a particular device.

To determine assay result accuracy for new or substantially modified blood collection tubes, a tube comparison study similar to that described in the CLSI EP 9-A guideline should be conducted. The clinical laboratory should obtain specimens covering the clinically reportable range for each analyte and provide sufficient power to conduct statistical analyses of the data. Linear regression analysis or similar type of regression method and Bland–Altman type plots should be used to analyze the tube comparison data.

To assess imprecision of assay results, laboratorians should compare the variability of results obtained for new and current devices. This can be achieved by replicate testing of quality control materials or patient specimens as described in the CLSI EP5-A guideline or by duplicate testing in the tube comparison study described above.

For analytes typically at undetectable or low concentrations in healthy individuals, analytes of interest should be added to specimens. The total number of assays performed for verification studies will vary by intended use of the blood collection device. Laboratories may select representative assays from different testing methodologies (e.g., ion-specific electrode, immunoassay, spectrophotometry). The goal of this study was to demonstrate comparable levels of bias and imprecision in diagnostic assay results for new and currently used devices. When results are discordant, laboratorians should contact manufacturers to further investigate. Clinical laboratories should monitor reference intervals and population trends and report any deviations or inconsistencies to device manufacturers. These problems should also be reported immediately to regulatory agencies like the US FDA via the MedWatch program. Proficiency testing providers should ask clinical laboratories to include tube type as part of the proficiency survey, as the collection tube is part of the total testing system [317].

For clinical trials or research studies, the rationale for the chosen blood collection tube is important because of possible interactions of tube materials and additives with specimens. The same tubes from the same manufacturer should be used throughout multi-center clinical trials or research studies to minimize variations due to tube-related interferences. This is especially relevant for emerging technologies in genomics and proteomics where greater sensitivities and lower concentrations of analytes are measured; even small amounts of interferents from blood collection tubes can affect results.

Recently, the Becton Dickinson Diagnostic Preanalytical Division created an Instrument Company Liaison to work with diagnostic assay manufacturers to address potential tube assay-related interference before market release of these products [317]. This group may serve as a model for other manufacturers and diagnostic companies to collaborate and address interference issues.

A forthcoming CLSI guideline will help tube manufacturers, in vitro diagnostic manufacturers, and clinical laboratories validate and verify venous and capillary collection tube use to ensure reliability of chemistry, immunochemistry, hematology, and coagulation test results.

Conclusions

Modern blood collection tube development has greatly expedited the collection of blood specimens, but many laboratorians remain unaware of the complexities of tube components and their potential adverse effects on test results. As medical devices, blood collection tubes should achieve the intended performance levels during defined conditions of use [318]. Known and foreseeable risks as well as undesirable effects should be eliminated or minimized.

In this review, we have discussed how blood collection devices such as needles, syringes, and catheters, as well as collection tube components can alter laboratory test results. Additionally, we have recommended that when interference is suspected, laboratory personnel should: (1) test the same analyte with an alternative assay, (2) contact the collection device and assay manufacturer, (3) incubate the sample with the different parts of the collection device to identify the source of the interference, (4) if applicable, file a medical device alert to the appropriate regulatory organization such as the US FDA, and (5) if possible, change collection device manufacturers. Because test quality depends on the integrity of obtained specimens, laboratorians should be vigilant for potential interference from blood collection device components and work closely with manufacturers and diagnostic companies to minimize, or preferably, prevent these tube-related problems.

Acknowledgment

The authors thank Ms. Kathryn Hargis for designing Fig. 1.

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