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文献导读

本期的文献导读是一篇关于《分离胶促凝管对药物浓度监测（TDM）的影响》综述，分离胶分离血清/血块的机理、采血管的材质与采血管壁粘附性和分离胶对 TDM 检测的影响，有助于临床在进行真空采血管的性能验证时，综合考虑可能影响的因素，充分验证其性能满足本实验室的质量管理要求。

分离胶促凝管对药物浓度监测（TDM）的影响

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临床血清学检测过往通常应用干燥管（无添加剂管），随着临床检测标本量的增加，从采血到上机检测时间过长，血液中细胞代谢不断向血清中释放物质，干扰检测结果。分离胶的发明是数十年来真空采血管的一项重要改进，并在临床实验室中广泛应用。分离胶可将红细胞与血浆或血清快速分离，减少溶血，显著提高分析血清和血浆的稳定性，提高标本中血清的得率，方便储存和运输，可原管上机检测，从而减少等分标本的需求，并最大程度地减少分析前误差[1-5]。

尽管具有所有这些优点，但分离胶的使用仍存在争议，尤其是对于治疗药物监控（TDM）。自从分离管问世以来，已经发表了许多关于分离胶对分析结果的影响的研究[2-15]，不仅报告了分析物在分离胶上的吸附，而且还报道了分离胶干扰分析的物质[6,9]。除了分离胶，采血管的所有组分（图 1）包括管体、管壁、胶塞、表面活性剂和促凝剂等，都可能通过添加血液的成分、吸收血液组分、与蛋白质和细胞组分进行交换或改变血液样本中分析物的稳定性，使得血清或血浆成分发生变化，这些都可以影响标本的质量和实验室检测的准确性[1-19]。

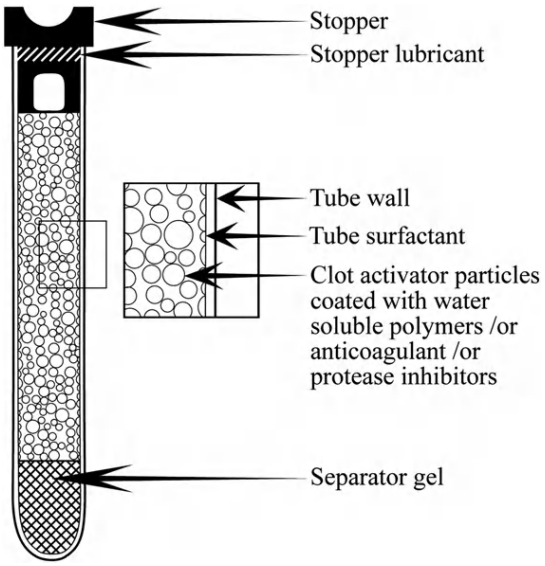

图 1. 真空采血管的组成

分离胶分离血清/血块的机理

血清分离胶通常由疏水有机化合物和硅石粉组成，是具有触变性的粘液胶体，其结构中含有大量氢键，由于氢键的缔合作用形成网状结构，在离心力的作用下因网状结构被破坏而变为粘度低的流体，当离心力消失之后又重新形成网状结构，这种性质被称为触变性（thizotropy）。即在温度不变的情况下，对这种粘液胶体施加一定的机械力，可从高粘度的凝胶状态变为低粘度的溶胶状态，如果机械力消失又恢复原来高粘度的凝胶状态。硅石表面具有硅羟基（SiOH），形成 Si0 分子凝聚体（初级粒子），在这种初级粒子间以氢键连结成链状结合粒子。这种链状硅石粒子与构成分离胶的疏水有机化合物的粒子间更进一步形成氢键而产生网状结构，构成具有触变性的凝胶状分子。

血清和血浆的比重范围为 1.026 ~ 1.031 g/cm^3，而凝块的比重范围是 1.092 ~ 1.095 g/cm^3，因此，分离胶的比重应该在 1.03 ~ 1.09 g/cm^3 之间（适宜值为 1.04 g/cm^3）[18,19]。

当分离胶与凝固后的血液在同一采血管中离心时，在离心力的作用下，高粘度的分离胶分子间氢键断开转化为低粘度状态，当外在离心力消失后，分子间的氢键重新缔合，由于比重的不同，分离胶便在血清和血块之间形成胶状的隔离层将血清和血块隔开（图 2）[20]。

少数情况下，高蛋白血症及高浓度放射性对照染料可导致标本特有的高比重血清或血浆不能漂浮在分离胶的上面[21]。

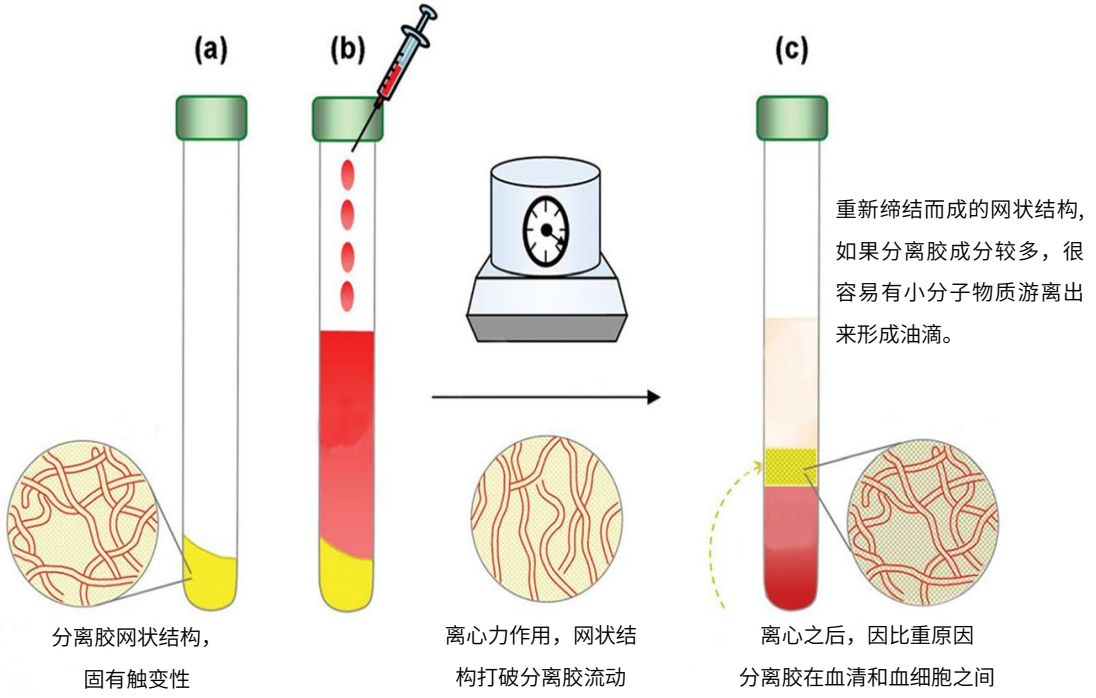

图 2. 分离胶分离原理

采血管的材质与采血管壁粘附性

分离胶采血管的管壁必须与分离胶之间具有牢固的粘附性，其粘附性与采血管的材质有关。玻璃试管的主要成分是亲水性的硅酸盐，采血后玻璃试管内壁可出现吸着水分子的吸水层，所以，分离胶不能直接粘附于玻璃试管的内壁。随着放置时间的延长，红细胞中的钾或者酶等物质，可以通过水分子吸水层向血清中扩散，所以，玻璃采血管在原状态下保存血清的期限以 2 ~ 3 天为宜。塑料采血管材质是疏水性质，其管壁不产生水分子层，分离胶可牢固地粘附着内壁上，红细胞中的钾不能扩散到血清中，因而冷藏保存 8 天血清钾含量不变。

分离胶对 TDM 检测的影响

塑料采血管已被广泛证明适用于常规临床化学分析物、激素分析和治疗药物监测，除了治疗药物的问题外，血清分离胶管对许多测定法的影响被认为不具有临床意义[13,22-24]。分离胶的类型、标本的体积、储存时间，以及储存温度都会影响药物被吸入胶里的速度[3, 8,13,23-26]。

分离胶通常被认为是疏水的，亲脂性分析物和药物具有吸附的危险[6,9,10,14,17]，会吸收疏水性化合物（例如某些药物）[25]。疏水性的药物如：苯妥英、苯巴比妥、卡马西平、奎尼丁和利多卡因等可能被吸收到疏水的分离胶中，在 4℃，这种

吸收能够在 24 小时后降低血清中药物浓度 20% ~ 50%[11,13,23,28]。一些研究表明，某些品牌采血管可能不适合存放含有苯妥英和利多卡因等药物的标本；其他一些研究也类似地描述了其他抗癫痫药和催眠镇静药（苯妥英、苯巴比妥、戊巴比妥和卡马西平）在 SST 管中的稳定性问题[17]，Dasgupta 等研究表明 VACUTTE 管中三环类抗抑郁药浓度显著下降，不适合用于三环抗抑郁药分析[28]。在 PST 分离胶管中受影响最大的药物是：（i）一些抗精神病药（包括阿利马嗪、氯氮平及其活性代谢物去氯氮平、阿马西嗪、氟苯那嗪、氟哌啶醇、左氧丙嗪、洛沙平和异丙嗪）；（ii）抗抑郁药、尤其是但不限于三环抗抑郁药（包括阿米替林及其活性代谢物去甲替林、丁螺环酮、西酞普兰、多苏平、多西平、丙米拉明、米安丝林、米氮平、帕罗西汀、舍曲林和三甲胺）[35]。Barricor 管不建议用于羟基-伊曲康唑，、泊沙康唑、环丙安定，、羟基安定、胺碘酮、THC、THC-COOH、THC-OH、格列本脲和格列美脲[35]。

分离胶对药物的吸附效果主要取决于其接触时间和采血量[1,6,9-11,14,17]。由于与分离胶的相互作用，长时间保存的标本中疏水性药物浓度可能人为地降低，因此其测量结果在临床上具有误导性[1,13]。分离胶（基于丙烯酸、有机硅或聚酯聚合物）采血管采集血液标本后快速上机检测，茶碱、地高辛、苯妥英、苯巴比妥、庆大霉素、乙醇和环孢菌素的浓度均无明显影响；标本保存 24 小时后，丙烯酸分离胶采血管中茶碱值平均增加 2.4%；聚酯基分离胶采血管中苯妥英平均下降 8.1%；聚酯基分离胶采血管中苯巴比妥平均降低 4.2%[10]。用 SST 管采集血液标本时，随时间和采血量的变化，苯妥英、苯巴比妥、利多卡因、奎尼丁和卡马西平的浓度显著下降（从 5.9%到 64.5%），当少量（200 ~ 500 μL）的血清长时间与分离胶接触（ > 2 ~ 6 小时）时，Vacutainer SST 管和 Corvac 管中治疗药物的血清浓度明显降低，这是由于分离胶对药物的吸收所致，用甲醇化学提取分离胶后回收的药物可以证明这一点[25]。

分离胶也可能会释放一些物质（如凝胶剂和硅油），这些物质会干扰被测物质的含量[29-31]，在含有分离胶的采血管里，血清或血浆的上面或者是里面可能会出现凝胶剂或者是硅油滴，凝胶剂和油滴会干扰取样探针、试管表面、比色皿和因与免疫复合物结合而影响固相免疫测定系统[30-31]。一些胶的成分可以溶到血液里面去，并且影响一些药物的溶解浓度[32]。在含有分离胶的采血管里，血液标本会检测到相对较高浓度（20 mg/L 或者更多）的苯乙烷和二甲苯，不适当的储存、温度、不恰当的离心速度会加速分离胶的降解[30]。

有报道建议勿使用血清分离胶管进行治疗性药物监测或毒理学分析，塑料血清分离胶材料会提取亲脂性物质（大多数药物），从而导致错误地降低药物浓度[33]，推荐用无添加剂管用于药物浓度监测[25,33]。Steuer 等使用 LC-MS/MS 研究了分离胶管对 15 种常用治疗药物的影响，并发现理化性质和稳定性之间的相关性，研究表明肝素锂采血管应该是治疗药物监测的首选[34]。

胶塞对 TDM 检测的影响

胶塞应易于被针刺穿，拔针后会自动密封[36]，并保持真空[37]。胶塞的合适材料包括硅树脂、异丁烯-异丙烯、苯乙烯丁二烯、氯化异丁烯-异戊二烯橡胶、乙烯-丙烯共聚物、聚氯丁二烯、丁基橡胶和卤化丁基橡胶[38]。胶塞的组件可能会污染血液样本并引起检测结果错误。大量研究表明，当使用含有增塑剂三（2-丁氧基乙基）磷酸酯（TBEP）的胶塞时，药物的生物利用度和生物等效性存在差异[39,40]。TBEP 用于增加胶塞的柔软性和弹性，但它同样能使某些蛋白从血浆蛋白结合位点（如 α1-酸性糖蛋白[41-44]）移除，从而增加了红细胞对药物的吸收和降低了待测血清或血浆中药物的水平。TBEP 中分布发生变化的药物包括奎尼丁、普萘洛尔、利多卡因、三环类抗抑郁药和吩噻嗪类药物（例如氟奋乃静和氯丙嗪）[39,41-45]。Janknegt 等[46]证明无 TBEP 的胶塞对用于治疗性药物监测的几种测定法没有干扰。这些发现促使管材生产商减少了含 TBEP 的胶塞的生产[39,40]。

总结

以上研究表明，应特别谨慎地使用血清分离胶采血管进行治疗药物监测，尤其是在可能需要减少采血量或延长标本贮存时间的情况下。在用于治疗药物分析之前，应对任何品牌的血清分离胶采血管进行彻底评估，建议考虑采血量、延长标本贮存时间、某些药物与血清蛋白结合（药物）减少的潜在影响，以及分离胶在吸收各种治疗药物方面的选择性。

《ISO15189：2012 医学实验室质量和能力认可准则》第 5.3.2.3“试剂和耗材-验收试验”明确规定：影响检验质量的耗材应在使用前进行性能验证[47]。美国临床和实验室标准协会 CLSI《GP34 Valiation and verification of Tubes for venous and capillary blood specimen collection》指南要求临床实验室将任何新的或显著改良过的采血管引入到本实验室时，应该制定一个详细的验证方案，由有资质的人进行科学性的审核[48,49]。我国于 2018 年 11 月 1 日发布《WS/T 224-2018 真空采血管的性能验证》指导临床实验室应在本实验室对所选择的真空采血管进行性能验证，以确保真空采血管满足实验室检验项目的保证能力。

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Article Abstract Collection

文献摘要

本期的文献摘要，选取了综述中若干重要的引用文献，针对其摘要做了中文翻译。这些文献综述或研究了采血管的构成与材质、分离胶分离血清/血块的机理、分离胶对分析物浓度测定的影响、采血管胶塞对分析物浓度测定的影响，以及评估采集管组件对临床检测的干扰的方法和要求。

参考文献摘要翻译

1. **M.P. O'Keane, S.K. Cunningham. Evaluation of three different specimen types (serum, plasma lithium heparin and serum gel separator) for analysis of certain analytes: clinical significance of differences in results and efficiency in use. Clin. Chem. Lab. Med. 44 (2006) 662-668.**

摘要

背景：目前还缺乏关于用来分析多种生物化学分析物的最合适标本类型的共识。本研究的目的是比较普通血清管（S）、血清凝胶管（G）和血浆管（肝素锂，P）中的肾脏分析物和脂质分析物的特征及苯妥英值，并研究这些分析物在长时间与细胞和凝胶接触后的稳定性以及分离样品并保存在4℃下的稳定性。

方法：将原始样本离心一次，室温保存，并分别在 2 h 内 [T(0)]、24 h 后 [T(24)] 和 48 h 后 [T(48)] 进行分析。为了评估在 4℃下的稳定性，将两个无细胞分离样品与其原始试管分开，并于 4℃保存，然后在 T(24)和 T(48)进行分析。评估了试管在 T(0)时和随后的存储 [T(24)和 T(48)] 之间分析物浓度差异的统计学显著性和临床显著性。

结果：在 T(0)时，除钾离子外，所有分析物在血清管、凝胶管和血浆管之间均表现出等效性。凝胶管中的钾离子和肌酐比血清管/血浆管中的稳定。相反，室温下 T(48)时普通血清管和血浆管中苯妥英含量保持稳定，但在室温下 T(24)和 T(48)时凝胶管中的苯妥英浓度表现出临床显著的逐渐降低。分离样品储存在 4℃时，除 CO_2 以外的所有分析物均稳定在 T(48)保持稳定。

结论：我们得出的结论是：除了苯妥英以外，血清凝胶管在测量本研究中所分析的分析物方面比普通血清管和血浆管更具优势。在实践中，凝胶管显示出增强的分析物稳定性，且减少了分离样品的需要，并提供了更多的保护以防止可能的污染。需要进一步研究以评估更广泛的分析物。

2. **Boyanton Jr BL, Blick KE. Stability studies of twenty-four analytes in human plasma and serum. Clin Chem 2002;48:2242-2247.**

摘要

背景：研究了在未离心的 Vacutainer 管中长时间与血细胞接触后血浆和血清中分析物的稳定性和化学计量变化。

方法：我们同时调查了（a）血浆和血清与血细胞长时间接触以及（b）立即分离血浆和血清（2000 g 离心 5 分钟两次）这两种情况下 24 种分析物的稳定性。我们通过同时测量 pH、PCO_2 和 PO_2 验证了观察到的分析物变化的生化机制。对溶血进行了定性和半定量评估。将所有样品保存在室温（25℃）下，并在采集后 0.5 h、4 h、8 h、16 h、24 h、32 h、40 h、48 h 和 56 h 重复分析。使用重复测量方差分析确定从 0.5 小时平均值开始的统计学显著变化。应用显著变化极限来确定所测分析物的临床显著变化。

结果：与细胞接触的血浆和血清中的 24 种分析物中有 15 种表现出与临床相关的变化，这种变化的程度在大多数血浆标本中更为明显。收集后立即与细胞分离的血浆和血清中的所有分析物均稳定。

结论：未离心标本的储存超过 24 小时会导致大多数被分析物发生显著变化，原因是：（a）葡萄糖耗竭以及 Na^+，K^+-ATPase 泵失效；（b）水进入细胞，引起血液浓缩；（c）细胞内成分和代谢产物泄漏。立即从细胞中分离血浆或血清可以提供室温下最佳的分析物稳定性。当血浆或血清与细胞长时间接触不可避免时，建议使用血清，因为血浆分析物的不稳定性更高。

3. Landt M, Smith CH, Hortin GL. Evaluation of evacuated blood-collection tubes: effects of three types of polymeric separators on therapeutic drug-monitoring specimens. Clin Chem 1993;39:1712-1717

摘要

评估了在传统采血管中发现的三种分离胶材料对治疗药物测量产生干扰的潜力。分离胶（基于丙烯酸、有机硅或聚酯聚合物）对经过迅速处理和分析的血液样本中的七种药物（茶碱、地高辛、苯妥英、苯巴比妥、庆大霉素、乙醇和环孢菌素）的浓度均无明显影响。标本保存 24 小时后，用丙烯酸分离胶管收集的标本中茶碱值平均增加 2.4%（$p = 0.024$）；用基于聚酯的分离胶管收集的标本中苯妥英平均下降 8.1%（$p < 0.001$）；用基于聚酯的分离胶管收集的标本中苯巴比妥平均降低 4.2%（$p = 0.02$）。其他药物浓度均未受到明显影响。当将 7 mL 基于聚酯的分离胶管中的标本体积减少至 1.0 mL 时，苯妥英含量略有下降（7.9%；$p < 0.01$）。其他药物浓度均不受试管部分填充的影响。在无添加剂管和含有丙烯酸分离胶的试管收集儿科患者的成对血液标本时，两种采血管中茶碱、地高辛、妥布霉素、苯妥英及苯巴比妥的浓度无明显差异。三种市售的分离胶对治疗药物的浓度影响很小，并且新开发的基于丙烯酸树脂的分离胶是适当惰性的。

4. Heins M, Heil W, Withold W. Storage of serum or whole blood samples? Effects of time and temperature on 22 serum analytes. Eur J Clin Chem Clin Biochem 1995;33:231-238.

摘要

在血清或全血样品存储过程中有关血清分析物稳定性的信息通常不完整，有时还会相互矛盾。因此，通过广泛使用的分析仪（Hitachi 737/Boehringer），我们确定了存储时间和温度对以下血清分析物的测量浓度的影响：钠、钾、钙、氯、无机磷酸盐、镁、肌酐、尿素、尿酸酸、胆红素、胆固醇、HDL 和 LDL-胆固醇、三酰基甘油、肌酸激酶、天冬氨酸氨基转移酶、丙氨酸氨基转移酶、γ-谷氨酰转移酶、碱性磷酸酶、α-淀粉酶、乳酸脱氢酶和胆碱酯酶。根据德国联邦医学委员会的指南，当分离的血清在+9℃下储存 7 天时，无机磷酸盐和乳酸脱氢酶的平均变化明显（分别为 $p < 0.05$ 或 0.001）超过了最大允许误差；其他分析物浓度都非常稳定。在室温下储存时，储存期间血清中的无机磷酸盐、尿酸、HDL-胆固醇和三酰甘油持续增加，而胆红素、LDL-胆固醇、肌酸激酶和天冬氨酸转氨酶的降低幅度超过了指南的规定（天冬氨酸转氨酶 $p < 0.05$，对于提到的其他分析物 $p < 0.001$）。在+9℃下存储 7 天的全血中，只有以下血清分析物满足指南的稳定性要求：钙、尿素、胆固醇、HDL-胆固醇、LDL-胆固醇、三酰基甘油、肌酸激酶、γ-谷氨酰转移酶和胆碱酯酶。在室温下储存的全血中，仅钠、尿酸、胆红素、胆固醇、三酰基甘油、天冬氨酸转氨酶、丙氨酸转氨酶、碱性磷酸酶、α-淀粉酶和胆碱酯酶在 3 天后仍保持稳定。收集的数据表明，在+9℃储存的

分离血清中，所有检测的分析物浓度都能在 4 天内保持稳定。

5. **Dousmas BT, Hause LL, Simuncak DM, Breitenfeld D. Differences between values for plasma and serum in tests performed in the Ektachem 700 XR analyzer, and evaluation of "plasma separator tubes. Clin Chem 1989; 35: 151-153.**

摘要

我们使用 Kodak Ektachem 700 XR 分析仪测量了同一血液标本的血浆和血清中的 25 种分析物。对于其中的 22 种分析物，血浆值与血清值实质等同；对于其余 3 种分析物，血浆和血清中的浓度无论在统计学上还是医学上差异都很大。常规肝素管与血浆分离胶管（PST）收集的血浆中同一分析物的值基本没有区别。

6. **Bowen RA, Hortin GL, Csako G, Otañez OH, Remaley AT. Impact of blood collection devices on clinical chemistry assays. Clin Biochem 2010; 43: 4-25.**

摘要

采血装置与血液相互作用会改变血液成分、血清或血浆分率，在某些情况下还会对实验室检测产生不利影响。血管进入装置可能释放涂层物质并施加剪切力使细胞破裂。溶解在血液中的采血管添加剂会影响血液成分的稳定性和分析系统。采血管胶塞、胶塞润滑剂、管壁、表面活性剂、促凝剂和分离胶可能会增加物质、吸收血液成分或与蛋白质和细胞成分发生相互作用。因此，采集装置可能是实验室测试中分析前误差的主要来源。采集装置制造商，实验室测试供应商和临床实验室人员必须将这些相互作用理解为实验室测试分析前期潜在的误差来源。尽管内源性血液物质的影响已引起关注，但尚未很好地描述外源性物质对测定结果的影响。本综述将确定血液样本中外源性物质的来源，并提出将其对临床化学分析影响最小化的方法。

7. **Daves M, Trevisan D, Cemin R. Different collection tubes in cardiac biomarkers detection. J Clin Lab Anal 2008;22:391-394.**

摘要

不同采血管所起的作用是最常被遗忘的影响实验结果质量的参数之一。我们旨在确定采血管中抗凝剂和分离胶的存在对肌红蛋白、心肌肌钙蛋白 I 和 CK-MB 的测定是否存在显著差异。采集 40 例急性冠状动脉综合征患者的血液样本。同时使用三种不同的采血管采集样本（分离胶无抗凝管、分离胶肝素管和无分离胶肝素管；Venosafe，Terumo Europe，Leuven Belgium）。采用双面（夹心）化学发光免疫酶法（Access Myoglobin，Access CK-MB，Access acutni）测定肌红蛋白、CK-MB 和心肌肌钙蛋白 I。心肌肌钙蛋白 I 不受采血管类型的影响。相反，肌红蛋白和 CK-MB 则因采血管而异。分离胶无抗凝管与无分离胶肝素管之间存在尤其显著的差异。

8. **Bush V, Blennerhasset J, Wells A, Dasgupta A. Stability of therapeutic drugs in serum collected in vacutainer serum separator tubes containing a new gel (SST II). Ther Drug Monit 2001;23:259-262.**

摘要

本文研究了 Becton-Dickinson Vacutainer SST 血清分离采血管采集的血清中治疗药物的稳定性。虽然大多数治疗药物是稳定的，但某些药物，如苯妥英钠、卡马西平和苯巴比妥，在较长的储存时间内浓度会降低。为了避免这个问题，Becton-Dickinson 设计了一种新的分离胶配方。作者研究了 14 种常用监测药物在新 SST-II 分离胶管中的稳定性，并比较了普通管（无凝胶）、旧 SST 管和含有新血清分离胶的 SST-II 管中的药物浓度。大多数药物在 SST-II 试管中即使储存 24 小时，浓度也没有下降。在 SST-II 管中贮存 7 d 后，卡马西平浓度下降 10%，苯妥英钠浓度下降 4%。现有管储存的几种药物浓度随着时间的延长而下降，因而新型采血管是对现有采血管的显著改进。作者认为，新型 SST-II 管是一种有效的监测治疗药物的采血方法。

9. **Bergqvist Y, Eckerbom S, Funding L. Effect of use of gel-barrier sampling tubes on determination of some antiepileptic drugs in serum. Clin Chem 1984;30:465-466.**

摘要

我们评估了样本在三种不同的采血管中的储存时间对药物浓度的影响：SST（Becton Dickinson）、AutoSep（Terumo）和 Microvette（Sarstedt），所有这些采血管都含有惰性屏障（例如，分离胶），用于在离心过程中将血清从凝血标本中分离出来。我们用两个试管（SST 和 AutoSep）检查了接受苯巴比妥、苯妥英钠和卡马西平治疗的患者的样本。我们发现药物浓度在 24 小时后显著下降，SST 管血清中的苯巴比妥、SST 管和 AutoSep 管血清中的卡马西平都越过了分离胶屏障。在三种类型的采血管中补充加入上述药物浓度的水性药物溶液或血清样品，可使 SST 管和 Auto-Sep 管中的浓度比 Microvette 管中的浓度降低得更显著。

10. **Karppi J, Akerman KK, Parviainen M. Suitability of collection tubes with separator gels for collecting and storing blood samples for therapeutic drug monitoring (TDM). Clin Chem Lab Med 2000;38:313-320.**

摘要

在这项研究中，我们提出一个观点：在使用含有分离胶的血液采集管时，血清药物浓度会发生显著变化。这份报告还包含了抗抑郁药物的结果，这些药物以前从未对人类样本进行过相关研究。采用高效液相色谱法（HPLC）和荧光偏振免疫法（FPIA）测定药物浓度。结果表明，分离胶管对癫痫、抗生素、哮喘和心脏活性药物的血药浓度测定是可行的，因为只有轻微的吸附（0% ~ 5%）。然而，所研究的采血管不适用于抗抑郁药和苯二氮卓类药物测定的血液样本采集，因为其吸附率可达 5% ~ 30%。分离胶管中样本在离心后 24 小时，样本的吸附率甚至更高（高达 40%）。当储存后再进行离心时，分离胶的吸附效果较低（仅为 0% ~ 13%）。使用所研究分离胶管采集并保存 3 小时后的患者样本中进行的抗抑郁药物测量显示，研究药物的吸附率小于 10%。储存 24 小时后，所有分析药物的浓度都出现更为显著的降低：药物的吸附量约为 5% ~ 20%。如果在血液凝固后 3 h 内进行离心分离操作，则所研究的分离胶管可用于抗抑郁药物的血液采集。加标样品对分离胶的吸附率较高，因此当药物与血清蛋白结合程度不高时，吸附速度似乎更快。

11. **Bowen RA, Vu C, Remaley AT, Hortin GL, Csako G. Differential effect of blood col- lection tubes on total free fatty acids (FFA) and total triiodothyronine (TT3) con- centration: a model for studying interference from tube constituents. Clin Chim Acta 2007;378:181-193.**

摘要

背景：血清分离管（SST）标本中的总三碘甲状腺原氨酸（TT3）的游离脂肪酸（FFA）含量明显高于 Vacuette 管。

方法：观察表面活性剂、胶塞、分离胶对 8 种不同管型健康志愿者血液中游离脂肪酸（FFA）、β-羟丁酸（beta-HB）和 TT3 的影响。

结果：与 Vacuette 管相比，SST 组血清 FFA 和 TT3 浓度明显高于玻璃管组。改进的 SST 消除了 TT3 的增加，但未消除 FFA 的增加。不同管型间 β-HB 浓度无显著差异。不同管型的表面活性剂和胶塞能显著增加了 TT3 浓度，但不增加 FFA 和 β-HB 的浓度。用 SST 和改良 SST 的分离胶以及血浆制备管（PPT）对全血（而非血清或血浆标本）进行搅拌，与 Vacuette 管相比，可获得较高的 FFA，但 β-HB 水平不高。

结论：SST、改良 SST 和 PPT 管分离胶中成分不明，导致 FFA 浓度假性升高。与 TT3 相比，FFA 假性升高的结果是由全血而不是血清暴露于试管成分造成的。本文所采用的方法可作为评估管组分干扰的模型。

12. **Quattrochi F, Karnes HT, Robinson JD, Hendeles L. Effect of serum separator blood collection tubes on drug concentrations. Ther Drug Monit 1983; 5:359-362.**

摘要

采用 EMIT 法，对使用 12 种常用药物的患者临床样本进行检测，以评价血清分离采血管（SST）（Becton-Dickinson）中所含血清分离胶的效果。利多卡因、戊巴比妥和苯妥英钠的浓度显著降低。体外实验表明，苯妥英钠的这种作用依赖于暴露于凝胶的时间和全血的体积，而不依赖于红细胞的存在和初始浓度。在治疗范围的上限和下限，由于使用 SST 而产生的偏倚可能会干扰

临床结果的有用性。通过在 1 h 内对至少 2 mL 的样品进行处理，可以将此问题最小化。

13. **Smets EM, Dijkstra-Lagemaat JE, Blankenstein MA. Influence of blood collection in plastic vs glass evacuated serum-separator tubes on hormone and tumor marker levels. Clin Chem Lab Med 2004;42:435-439.**

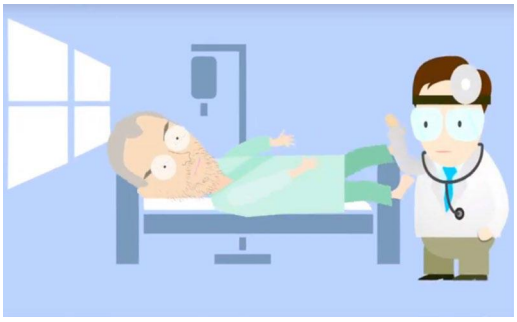
摘要

我们实验室分析前自动化的引入需要使用塑料采血管。由于成分吸附在塑料壁上可能造成干扰，而且几乎没有关于这方面的文献，我们研究了在塑料管采集的血清对几乎所有激素和肿瘤标记物免疫测定结果的影响。使用玻璃管和塑料管同时采集健康志愿者的血液，或者使用玻璃管采集血液后，制备血清后转装入正在研究的塑料管中。对这样获得的对比标本组进行激素和肿瘤标记物水平的测量。结果采用配对 t 检验或 Wilcoxon 符号秩检验进行分析。我们发现玻璃和塑料在游离三碘甲状腺原氨酸、孕酮、催乳素、前列腺特异性抗原和妊娠相关血浆蛋白 A 方面存在微小但有统计学意义的差异（$p < 0.05$）。α-胎儿蛋白、雄烯二酮、BR（糖基抗原 15.3 测定）、人绒毛膜促性腺激素和睾酮无显著趋势（$0.05 < p < 0.15$）。然而，Passing 和 Bablok 回归分析没有显示出临床相关的差异（孕酮的斜率为 0.89，妊娠相关血浆蛋白 A 的斜率为 1.07，截距均较小）。我们的结论是，在不影响结果解释的情况下，可以改用塑料采血管。

14. **Dasgupta A, Blackwell W, Bard D. Stability of therapeutic drug measurement in specimens collected in Vacutainer plastic blood collection tubes. Ther Drug Monit 1996;18:306 -309.**

摘要

最近，Becton-Dickinson 销售了一种塑料血清分离管，它使用与玻璃管相同的血清分离胶。通过与玻璃血清分离管和普通红色帽盖玻璃管中药物稳定性的比较，研究了塑料管中药物的稳定性。我们观察到无论是塑料或玻璃的血清分离管，咖啡因、苯扎溴铵、茶碱、妥布霉素、茶碱、妥布霉素、对乙酰氨基酚、丁胺卡那霉素、丙戊酸、氨甲喋呤、水杨酸盐和环孢菌素均不吸收。另一方面，利多卡因、奎尼丁、苯巴比妥和苯妥英钠在塑料和玻璃血清分离管中储存后浓度降低，特别是在储存时间延长和样品体积小的情况下。浓度降低是由于血清分离胶对这些药物的缓慢吸收所致。



15. **Boeynaems JM, DeLeener A, Dessars B, Villa-Lobos HR, Aubry JC, Cotton F, et al. Evaluation of a new generation of plastic evacuated blood-collection tubes in clinical chemistry, therapeutic drug monitoring, hormone and trace metal analysis. Clin Chem Lab Med 2004;42:67-71.**

摘要

聚对苯二甲酸乙二酯（PET）管比玻璃管具有多个优点：它们不易碎，更轻且更易于处理。尽管它们的使用稳步增长并，但很少有文献证实其使用。本文介绍了已进行的各种研究，并比较 VENOJECT 玻璃、PET 和 PET /肝素管在常规临床化学、免疫化学、激素和肿瘤标志物分析以及痕量金属测定应用。 这些研究表明，PET 管是玻璃管的合适替代品。

16. **Dasgupta A, Dean R, Saldana S, Kinnaman G, McLawhon RW. Absorption of therapeutic drugs by barrier gels in serum separator blood collection tubes: volume and time dependent reduction in total and free drug concentrations. Am J Clin Pathol 1994;101:456 -471.**

摘要

比较了 Vacutainer SST 和 Corvac 血清分离胶采血管中七种常用监测治疗药物在血清中的稳定性。Vacutainer SST 血清分离胶管中观察到苯妥英钠、苯巴比妥、利多卡因、奎尼丁和卡马西平的浓度随时间和样品量的变化显著下降（5.9% ~ 64.5%）。相反，在相同的标本贮存条件下，茶碱和水杨酸盐的测量浓度没有变化。Corvac 血清分离胶采血管中未观察到苯妥英钠、苯巴比妥、卡马西平、茶碱、奎尼丁和水杨酸盐的浓度有显著变化。在 Corvac 管中贮存 24 小时后，仅血清利多卡因浓度降低（从 31.5%降至 72.6%，具体取决于样品量）。当少量

（200 ~ 500 μL）血清长时间与分离胶接触（ > 2 ~ 6 小时）时，Vacutainer SST 和 Corvac 管中治疗药物血清浓度均明显降低。这些减少是由于分离胶对药物的吸收所致，用甲醇化学提取分离胶后回收的药物证明了这一点。对于苯妥英钠和苯巴比妥而言，总药物浓度的降低还导致游离药物浓度的成比例降低，并且取决于药物与蛋白质结合的程度。Vacutainer 红色管（无分离胶）延长标本保存时间，所有药物均未受到不利影响。数据表明，监测治疗药物应特别谨慎地使用血清分离胶采血管，尤其是在可能需要减少标本量或延长标本保存时间的情况下。

17. **Koch TR, Platoff G. Stability of collection tubes with separator gels for therapeutic drug monitoring. Ther Drug Monit 1990; 12:277-280.**

摘要

本研究的目的是确定四种分离胶管是否适合采集 15 种治疗药物的标本。 向采集志愿者（非毒品吸食者）血液标本的采血管中添加选择的药物，并在离心后 6 h、24 h 和 72 h 进行测量。我们发现，即使在立即分离血清的情况下，Becton Dickinson SST 管仍可提取苯妥英钠。为了延长保存时间，SST 管不适用于奎尼丁（大于 24 小时）和利多卡因（大于 6 小时）；Monoject Corvac 不适合利多卡因（任何保存方式）。采血量不足引起其他误差。保证准确采血量的 Terumo Autosep 管和 Monoject Corvac 管，如果迅速转装血清，所有测试的药物结果令人满意。

18. **Dasgupta A., Yared M.A., Wells A. Time-dependent absorption of therapeutic drugs by the gel of the Greiner Vacuette blood collection tube. TherDrugMonit. (2000)**

摘要

已经对 Becton-Dickinson VACUTAINER 血清分离胶 SST 管治疗药物在血清中的稳定性进行了深入研究。最近，Greiner Vacuette 血清分离胶管已可用于血液采集，但尚未见治疗药物在血清中的稳定性研究报道。作者研究了 15 种经常监测的药物在 Greiner 血清分离胶管中的稳定性。研究的药物为阿米卡星、庆大霉素、妥布霉素、万古霉素、地高辛、奎尼丁、茶碱、卡马西平、苯巴比妥、苯妥英钠、丙戊酸、三环抗抑郁药、水杨酸酯、对乙酰氨基酚和乙醇。作者比较了普通管（无分离胶）和含有血清分离胶的 Greiner 管中保存的血清药物浓度。他们发现，保存在 Greiner 管中的三环类抗抑郁药浓度显著下降。有趣的是，阿米替林的浓度下降幅度大于其代谢物去甲替林，而丙咪嗪的浓度下降幅度也大于其代谢产物地昔帕明。当血清保存在 Greiner 管中时，卡马西平的浓度也会随时间略有下降。尽管卡马西平浓度在 Greiner 管中长期保存后下降具有统计学意义，但该下降可能并不具有临床意义。作者得出的结论是 Greiner 采血管不适合用于三环抗抑郁药分析的血液采集。

19. **Ji SQ, Evenson MA. Effects of contaminants in blood-collection devices on measurement of therapeutic drugs. Clin Chem 1983;29:456-461.**

摘要

采血管中的物质会产生气相色谱峰，其保留时间与药物相似。通过质谱测定，除血清分离胶管外，所有测试的管均含有磷酸三（2-丁氧基乙基）酯。此外，根据药物和采血管的不同，某些药物在溶剂萃取步骤中的分配系数最多增加 40%，而对于其他药物，分配系数最多减少 30%。Becton Dickinson 血清分离胶管还包含几种其他化合物，这些化合物经质谱鉴定为在制备分离胶时使用的二元酯。康宁血清分离管和 Venoject 血清管还含有其他杂质。 Becton Dickinson 宝蓝色帽管中所含杂质最少。血浆池中 25 种常用测定药物的 CV：从玻璃管中样本的 5%增加到真空采血管中样本的 20%以上。显然，如果使用了不适当的采血装置，治疗药物的测量准确性和精确性将受到严重损害。

20. **C. Steuer, A.R. Huber, L. Bernasconi. Where clinical chemistry meets medicinal chemistry. Systematic analysis of physico-chemical properties predicts stability of common used drugs in gel separator serum tubes. Clin. Chim. Acta Int. J. Clin.Chem. 462 (2016) 23-27.**

摘要

背景：随着 LC-MS/MS 技术的普及，甚至在高度专业化的临床实验室之外，在实施治疗药物监测之前，应严格评估分析前问题，例如标本储存过程中的药物稳定性。我们的研究调查了不同药物的理化性质对它们与市售采血管中分离胶相互作用的影响。

方法：将加药的血液标本储存在不同的分离胶和非分离胶采血管中进行分析。基于 LC-ESI-MS/MS 的方法确定血清标本中的药物浓度。

结果：由 logP > 3 和相容性因子 > 20 定义的亲脂性化合物易于被亲脂性分离胶有效、快速地吸收，从而在短时间内降低药物浓度。我们的数据显示，当贮存在分离胶采血管中时，泊沙康唑、舍曲林和西酞普兰的浓度会相应下降。 logP、极性表面积和蛋白质结合等分子描述符似乎是识别分离胶相互作用药物的良好预测指标。

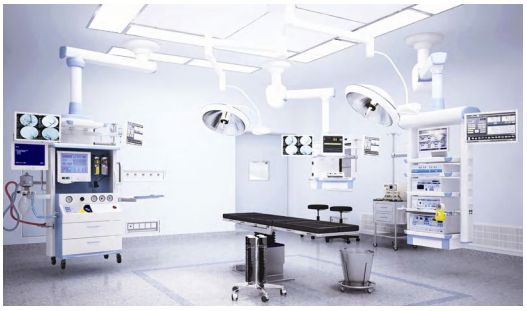
结论：为便于处理并最大程度地减少抽血时间，我们假设分离胶采血管可用于高亲水性药物的治疗性药物监测。相反，应该严格考虑显示 logP 高于 3 和/或 CF > 20 的亲脂性化合物，并通过广泛的稳定性研究对其进行验证。

缩写：logP，分配系数；PSA，极性表面积；TDM，治疗药物监测；ACN，乙腈；MeOH，甲醇；IVD，体外诊断；CF，相容性系数。

21. Aurelien Schrappa, Celine Mory, Thomas Duflot et al. The right blood collection tube for therapeutic drug monitoring and toxicology screening procedures: Standard tubes, gel or mechanical separator? Clinica Chimica Acta 488 (2019) 196-201.

摘要

缺乏基于分离胶或机械分离采血管的有毒物或药物稳定性数据，尤其是对于治疗药物监测和临床毒理学程序而言。根据 ISO 15189 认证标准，实验室需要掌握整个分析前过程，包括特定管中分析物的稳定性。在这里，我们使用 LC-MS/MS 探索了 PST II 和 Barricor 管对血浆样品中 167 种治疗化合物和常见滥用药物稳定性的影响。PST II 管显著影响了 40 种药物，包括抗抑郁药（11/26）、抗精神病药（9/13）、心血管药物（5/26）、抗焦虑药和催眠药（4/25）以及一些滥用药物（5/26）。Barrico 管显著影响了六种化合物。由于测定间差异，十种药物的回收率较低（ < 85%），但回收率不显著。此外，logP > 3.3 被确定为一个预测值，用于预测 PST™II 管中可能缺乏稳定性，灵敏度为 86.4%，特异性为 61.4%。因此，PST™II 管采集的血浆标本，应谨慎进行 logP > 3.3 的药物测定。研究表明非分离胶管对药物的干扰较小，因此推荐用于所研究的药物。



22. Bowen RAR, Vu C, Remaley AT, Hortin GL, Csako G. Differential effect of blood collection tubes on total free fatty acids (FFA) and total triiodothyronine (TT3) concentration: a model for studying interference from tube constituents. Clin Chem Acta 2007;378:181-193.

摘要

背景：除了总三碘甲状腺素（TT3）外，血清管（SST™）中的总游离脂肪酸（FFA）浓度也高于 Vacuett 管。

方法：用 8 种不同采血管采集健康的志愿者血液样本，研究不同采血管表面活性剂、胶塞和分离胶对 FFA、β-羟基丁酸酯（β-HB）和 TT3 的影响。

结果：与 Vacuette 管相比，SST 中的血清 FFA 和 TT3 浓度显著高于玻璃管。重新定制的 SST 消除了 TT3 的增加，但没有消除 FFA。不同试管中未观察到 β-HB 浓度的显著差异。来自不同管的表面活性剂和胶塞明显增加了 TT3 浓度，但没有增加 FFA 和 β-HB 的浓度。与 Vacuette 管相比，SST、重新定制的 SST 和血浆制备管（PPT 管）中 FFA 较高。

结论：SST、重新定制的 SST 和 PPT 管中分离胶的不确定成分会导致 FFA 浓度假性升高。与 TT3 相比，FFA 假高结果要求全血而不是血清暴露于采血管成分。这里采用的方法可以用作评估来自采血管成分干扰的模型。

23. Raffick Bowen. Blood Collection Tubes: Reducing Pre-Analytical Errors. https://www.aacc.org/publications/cln/articles/2014/december/bench-matters.

摘要

实验室自然会尽可能减少分析前误差，提高血液测试结果的质量，减少重新采集样本的次数，减少周转时间，改善患者的整个医疗管理。采血管（BCTs）通常被认为是惰性的标本载体，然而，研究表明，采血管也会引起分析前误差。

我们还不完全清楚这些采血管是如何影响血液标本的，但是它们对测试结果的影响可能卫生专业人员意识到的要更大。采血管的组成，包括管壁、橡胶塞子、润滑油、抗凝血剂、分离凝胶、促凝剂和表面活性剂，这些都可以影响标本的质量和实验室检测的准确性。这些组件和添加剂可能是通过添加全血的成分、吸收血液组分、与蛋白质和细胞组分进行交换或改变血液样本中分析物的稳定性使得血清或血浆的成分发生变化。

除了在检查实验室测试结果时提高警惕和提高临床实验室与临床医师之间的沟通外，如果不进行总体平均值（浮动均值）的分析，实验室工作人员很难发现采血管问题。定期追踪总体平均值周期性的变化可以提醒实验室人员潜在采血管问题的存在。

在评估采集管组件对临床检测的干扰时，实验室工作人员应该：1）用另一种实验方式检测同一分析物；2）用采集管不同的部分来孵育样本以鉴别潜在的干扰来源；3）同时联系采集管生产商和仪器制造商；4）如有需要可列入食品药品监督局的医疗器械警告；5）如果可以，更换一家新的采血管制造商。

将任何新的或显著改良过的采血管引入到实验室时，应该制定一个精密的验证方案，由有资质的人员进行科学性的审核。该方案应该详细描述验证过程，包括预先定义的可接受标准和统计方法，并遵循该机构审查委员会或伦理委员会所建立的与测试受试者相关的政策和程序。在采血管验证试验中，患者和健康人的血液标本都应该被采集。本研究还应包括整个血液收集系统(针头、采血人员、采血管，等等)而不是一个特定的采血管或组件。

对新的或改良的采血管分析结果的准确性进行评估，实验室应该进行如 CLSI EP9 -A (1992) 指南所描述的采血管比较研究。标本数量要足够，并测定标本中所包含的每一种分析物的可报告范围。这才能为数据统计提供足够的效能。数据应该采用线性回归分析或类似的回归方法和 Bland-Altma 进行采血管的比较分析。

在进行新的或改良的采血管采集的样本检测结果的不精密度进行评估时，实验室工作人员可以比较收集在新管中的样品分析结果与目前使用的收集管中的样品分析结果的可变性。另一个途径是根据 CLSI EP5-A(1992)的指南的规定，重复检测质控品和/或患者标本。如果分析物在健康个体中检测不到或处于较低浓度，或产生覆盖可报告范围的样本，可以在样本中加入被分析物。对采血管有效性研究所需要分析的总数将取决于采血设备的预期用途。实验室可以选择有代表性的但检测原理的分不同析方法来进行有效性分析评估，如离子特异性电极、免疫测定、分光光度法。CLSI GP-34A 包括了采血管的确认和验证程序。采血管所涉及的问题很难及时发现，因为常规质控可能不会使用有问题的采集装置。同样,性能测试也不会发现采血管问题，因为性能测试样本不要求使用同种采血管采血。

通过比较在采血管中加入或不加质控血清的检测结果，可以揭示管内添加剂对检测的不良影响，但是这些测试在大多数临床实验室是很少开展的。而且上述检测也是不切实际的，因为种类繁多的采血管同时在被使用，采血管的清洗剂也在频繁的更换。因此它可能更适合于采血管制造商逐批的将质量控制血清暴露于采血管中进行检测。实验室在改变他们使用的采血管时应该对采血管进行一个精心策划的验证协议。

展望未来，新兴技术的将带来更高分析敏感性和更低的标本量。然而，他们可能更容易出现分析干扰，甚至采血管组件的少量的干扰，就可能产生错误的测试结果。采血管制造商、研究人员和实验室工作人员都需要勤于挑战开发新产品，如对采血消除管壁进行化学修饰，消除表面活性剂对分析干扰。

有效的临床决策取决于准确和精确的实验室测试结果，因而采血管应该像其他的医疗设备一样，需要采用极高的标准来生产。已知的和可预见的风险以及不良影响应该被消除或最小化。采血管制造商，体外诊断企业和实验室工作人员都应该保持警惕，防止采血管的潜在不利影响。

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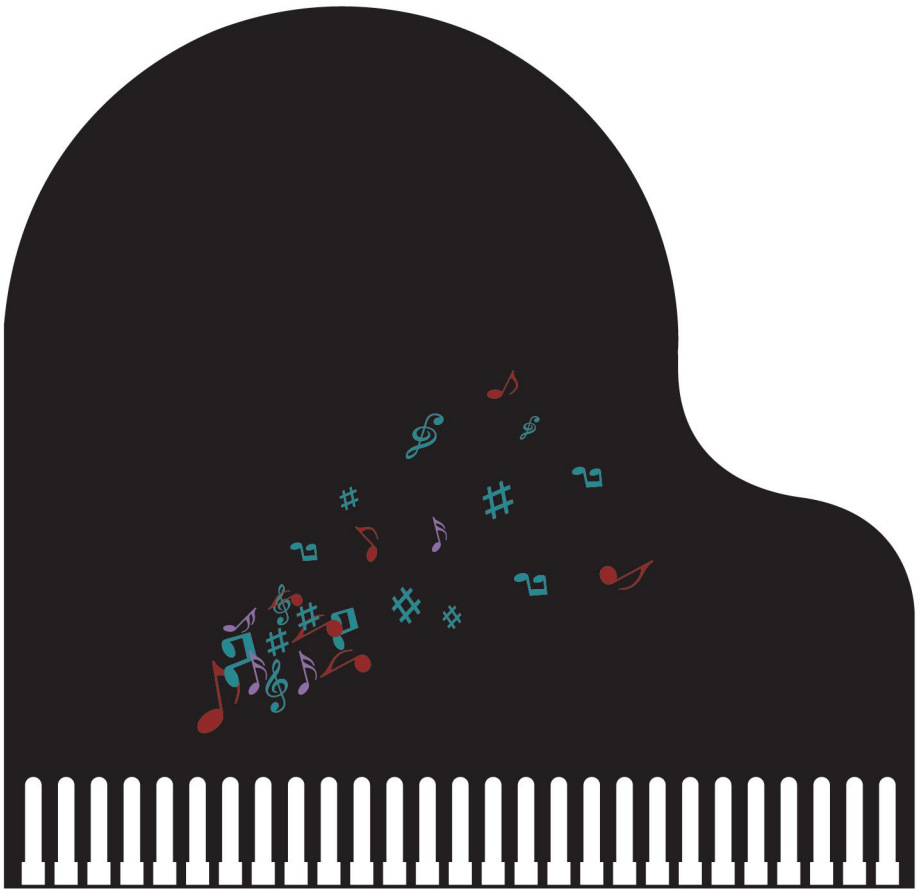

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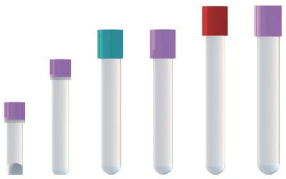

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Featured Article

文献精读

本期的文献精读是一篇综述《真空采血管对临床化学检测的影响》，原标题为《Impact of blood collection devices on clinical chemistry assays》。本文作者综述了采血装置历史、组成和尽量减少对临床检测干扰，重点介绍了真空采血管对临床化学检测的影响。因此，采血管制造商、实验室检测试剂和设备供应商，以及临床实验室人员有必要理解采血管与血液间的交互作用，并寻求将其对临床化学分析的影响降至最低的有效方法。

真空采血管对临床化学检测的影响

摘要

采血装置与血液相互作用改变血液成分、血清或血浆组成，在某些情况下会对实验室检测产生不利影响。采血装置可能释放涂层物质并施加剪切力裂解细胞。采血管内的添加剂会影响血液成分的稳定性和分析检测系统。采血管胶塞、胶塞润滑剂、管壁、表面活性剂、促凝剂和分离胶可能会增加血液中的物质、吸收血液成分或与蛋白质和细胞成分发生相互作用。因此，采血装置可能是实验室检测中分析前误差的主要来源。制造商、实验室检测系统供应商和临床实验室人员必须将这些相互作用理解为实验室分析前误差的潜在来源。尽管内源性血液物质的影响已引起关注，但尚未很好地描述外源性物质对检测结果的影响。本综述将确定血液样本中外源性物质的来源，并提出将其对临床化学分析影响最小化的方法。

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关键字：采血管；表面活性剂；干扰；临床检测；管；临床化学；分析前；采血

介绍

血液采集和处理是分析前实验室检测的两个主要步骤。为了确保检测的可靠性，需要由受过良好培训的人员使用适当的器械进行适当的采血和及时处理。采血装置通常被认为是惰性标本载体。因此，实验室投入很少的精力来评估新的采血装置，很少监视采血装置的性能。这篇综述试图通过总结影响临床化学分析的采血装置相关研究报道，并通过描述采血装置的部件及其与各种分析方法血液样本之间的相互作用，来强调采血装置的重要性。

采血装置历史

第一个皮下注射针头由钢制成，并配有坚硬的橡胶衬套，专门用于局部麻醉剂注射治疗神经痛[1]。最初的改进工作推动了精巧的针头设计，并对注射器材料进行了试验。用玻璃代替了橡胶，以便可以重复使用注射器。Luer-Lok 注射器提供了一种从玻璃注射器中安装和移除皮下注射针头的简便方法，提供了一种更安全、更可靠的药物递送方法。然而，多次肝炎暴发推动必须开发无菌一次性注射器以减少疾病传播[2,3]。玻璃注射器还有其他一些缺点：（1）它们很昂贵，需要紧密的公差以最小化针筒和柱塞之间的泄漏；（2）由于柱塞不能与其他玻璃桶注射器互换，无法大量生产；（3）玻璃易碎[4]。使用化学试剂（例如，环氧乙烷气体）和辐射（例如，钴 60）

的新灭菌技术使得塑料注射器成为首选的替代品。

自 19 世纪 40 年代真空采血管开发出来，提供了一种替代注射器采血技术的便捷选择，被广泛用于临床和研究环境[5]。真空采血管会自动抽取预定的血液量，在需采集多个样本时，真空采血管比注射器更容易切换[5]。因此，大大减少了标本溢出和污染的风险。这种改进还可以最大程度地减少采血医生在输血过程中对血液和针刺伤害的暴露[6]。。

自 19 世纪 50 年代以来，装有定量添加剂（例如抗凝剂）的玻璃真空采血管就成为标准的采血装置[7]。然而，最近，制造商采用塑料替代玻璃，通并添加了分离胶或促凝剂改进采血管[8]。美国四家主要的真空采血管制造商[9]用各种可能影响实验室分析的材料和添加剂生产采血管[9]。

由于采血管在大多数临床分析中表现良好，因此许多实验室工作人员并未意识到采血管的复杂性。近期表面活性剂对血液样本的污染揭示了采血管如何对实验室检测结果产生广泛的不利影响[10,11]，并强调充分了解与采血管相关的潜在问题的重要性。表 1 展示了采血管的主要组成及其对临床血液标本的影响。

采血装置组成

酒精和其他消毒剂

在采集血液样本之前，先用 70%异丙醇清洁皮肤并进行消毒。如果异丙醇在静脉穿刺前没有完全干燥，可能会无意中将其引入血液样本中。这种污染可能导致溶血或干扰血液中乙醇水平的检测[12,13]。为了最大程度地减少消毒剂的干扰，在获取血液样本之前，皮肤应完全干燥[12]。当需要严格的感染控制时，如血培养或动脉穿刺术，可使用更强的消毒剂，例如 Betadine（聚维酮-碘溶液）[12]。Betadine 污染会导致高磷、尿酸和钾的含量错误地提高[14]。此外，当使用愈创木脂或甲苯胺检测时，Betadine 会导致粪便中的血红蛋白和尿液中的葡萄糖假阳性[15]。对于碘过敏的患者，可使用葡萄糖酸氯己定或氯化苯扎氯铵[12]。然而，已经发现苯扎氯铵化合物会影响电解质的结果[16]。

表 1. 采血管组分的干扰

装置/组分	干扰	关键参考文献
消毒剂		
酒精	溶血	Stankovic and Smith [12]
聚维酮碘	磷酸盐，尿酸，钾升高	Meites [14]
	愈创木脂测试	Blebea and McPherson [15]
采血针		
内径	溶血	Lippi et al. [20] Verssen et al. [51]
金属材料	金属分析	Sunderman et al. [18] Vesieck and Cornelis [42]
润滑剂	免疫测定	Narayannan and Lin [33]
注射器		
柱塞	溶血	Scott et al. [56] Caroll [81] Carraro et al. [31] Burns and Yoshikama [13]
渗透性塑料	低 PO_2	Rosenberg and Price [59] Winkler et al. [57] Smeenk et al. [58] Knowles et al. [70] Wiwanitkit [66]
导管		
小管腔	溶血	Kennedy et al. [78] Sharp and Mohammed [25] Tanable [83]

表 1. 采血管组分的干扰（续）

装置/组分	干扰	关键参考文献
聚维酮碘	钠、钾升高	Koch and Cook [80] Gaylord et al. [79]
塑料材料	药物吸收	Smith et al. [88] Grouzman et al. [89]
采血管		
表面活性剂	免疫测定	Mckiel et al. [151] Bowen et al. [10]
	离子专用电极	Sampson et al. [135]
	质谱法	Drake et al. [155]
	与标本的相互作用	Bowen et al. [157]
胶塞	药物测定	Borga et al. [167] Pike et al. [47] Shah et al. [162,163] JI and Evenson [207] Devine [168]
	金属分析	Williams [173] Cummings [175] van den Besslaar [171,172]
胶塞润滑剂	甘油三酸酯，甘油	Baum [177] Chowdry et al. [178]
	气液色谱法	Chrzanowski et al. [170]
	金属分析	Dimeski and Carter [174]
分离胶	药物吸收	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]
促凝剂	纤维蛋白块	Beyne et al. [218]
	锂升高	Sampson et al. [135]
	镁升高	Cao et al. [132]
	SELDI/TOF	Pilny et al. [223]
	睾酮	Wang et al. [221]
	金属蛋白酶	Manello et al. [224,225]
抗凝剂		
EDTA	免疫测定	Butler [244]
	离子结合	Tate and Ward [245] Jones and Honour [246] Banfi et al. [248]
肝素	稀释误差	Urban et al. [251]
	白蛋白减少	Meng and Krahn [262]
	免疫测定	Zaninotto et al. [259]

表 1. 采血管组分的干扰（续）

装置/组分	干扰	关键参考文献
	离子结合效应	Urban et al. [251] Shek and Swaminathan [254] Sachs et al. [131] Landt et al. [255] Toffaletti and Wildermann [256] Yip et al. [253]
氟化物	酶抑制	Feig et al. [271] Chan et al. [272] Astles et al. [273] Narayanan [249] Gambino [274] Mikesh and Bruns [277] Gambino et al. [275]
碘乙酸盐	电解质、葡萄糖和乳酸脱氢酶	Hall and Cook [279] Robertson et al. [280]

采血针

与真空采血管、注射器、导管和蝶翼系统配套使用的采血针由多种材料组成，包括不锈钢、铝、钛、铬、铁、锰、镍和合金[17,18]。通常，针头有一个长的锋利末端（用于刺穿皮肤和血管），并被保护套覆盖，而另一个较短的末端则用于刺穿采血管的橡胶塞[17]。针头用量规校准，与量规成反比[19,20]。注射器使用的针头范围从 13 G（1.80 毫米内径）到 27 G（0.190 毫米内径），长度从 13 G 的 3.5 英寸（8 厘米）到 27 G 的 0.25 英寸（0.6 厘米）[21]。在临床环境中，通常采用 19 G（内径 0.686 毫米）到 25 G（内径 0.241 毫米）针进行静脉穿刺，而 21 G 针是常规成人静脉穿刺的标准针[19,20,22]。

针头遇到的一个问题是溶血，溶血会导致血红蛋白和其他细胞内分析物（例如钾、乳酸脱氢酶、天冬氨酸转氨酶、丙氨酸转氨酶、无机磷和镁）释放到血清或血浆中[19,20,23]。这些分析物在样本中会错误地升高，而白蛋白、碱性磷酸酶和钠会因样本稀释而错误地减少[20,24]。血清或血浆中游离的血红蛋白会干扰几种临床检测，导致结果不准确或需要重复抽血[25]。Lippi 等人[20]发现，小口径（25 G 或更小号）针头与溶血引起的血清钾和其他分析物的统计学显著升高有关[19,20]。这些作者建议新生儿和静脉通路不良的患者使用小口径针头[20]。小口径针的流速较慢还与凝血、阻塞和测试结果变化有关[20,25-30]。大口径的针头（大于 19 G）可能会由于非层状血流增加引起的湍流而引起溶血[20,25,31,32]。因此，重要的是使用与静脉大小相匹配的针头。在大多数采集条件下，最好使用 21 G 针头[12,33]。

针头上的润滑剂涂层可减少（1）穿透力（在针刺穿组织之前测得的力）；（2）拖曳力（继续穿透组织所需的力）和（3）与静脉穿刺有关的疼痛[34,35]。使用最广泛的润滑剂是有机硅[34,35]，特别是聚二甲基硅氧烷和可固化的氨基官能有机硅分散体[35,36]。有机硅润滑剂赋予针头疏水性，以最大程度地减少血液和金属的接触[35,36]。有机硅润滑剂可能会使药物脱离结合蛋白，并干扰免疫测定中的化学反应或抗原抗体反应[33]。防止润滑剂释放到血液样本中的试剂包括胶凝剂[37]；极性润滑剂，可强烈吸附到表面[38]；等离子处理[39]；接枝聚合[40]；和紫外光聚合[41]。

同样，金属针头成分（例如铬、铁、锰和镍）会污染血液样本并干扰随后的化学反应或导致血液中的金属水平假性升高[33,42]。针头中使用的金属和合金必须经过彻底测试，以评估对全血、血清或血浆的影响。

蝶翼采集装置

由于蝶翼针尺寸小（21 G 或 23 G），蝶翼针比传统静脉穿刺针更适于小儿患者、静脉脆弱或细小的患者。蝶翼针由带防护罩的不锈钢针和塑料翼组成，它们的一端连接到塑料管，另一端连接到鲁尔接头，用于插入采血管[43]。该设计可简化多管采集，但短针长（0.5 ~ 0.75 英寸）将其实用性限制在表面静脉。蝶翼针引起的问题包括溶血风险增加、暴露于血源性病原体、针刺受伤以及采血量不足[44]。从蝶翼针与直针采集的标本检测结果没有发现临床上的显著差异[43]。因此，蝶翼针可能是直针采血针的良好替代品。

当从细小或易碎的静脉中获取静脉血标本时，因为静脉可能会在真空采血管相关的力作用下塌陷，最好使用皮下注射注射器[45,46]。老年患者和新生儿通常是这种情况。注射器还用于采集动脉血样本以进行血气分析，因为在采集管中留有真空或空气空间会影响气体压力[45,46]。注射器也可用于从静脉管线或导管中采集标本，并转移至采血管中[45,46]。

采血针通常由聚丙烯或聚乙烯[33]以及添加剂和改性剂（例如抗氧化剂、抗静电剂、热稳定剂、紫外线稳定剂、润滑剂和增塑剂）组成，可满足所需的物理性能并提高塑料加工的难易程度[33]。已显示用于塑料注射器柱塞的塞子材料[例如，增塑剂邻苯二甲酸二（2-乙基己基）酯] 会污染血液样本并干扰药物分析[33,47]。注射器瓶塞中 2-巯基苯并噻唑可在灭菌过程中转化为 2-（2-羟乙基巯基）苯并噻唑，干扰毒理学分析[33,48]。邻苯二甲酸盐（包括邻苯二甲酸二乙酯）会引起气相色谱峰的共同迁移，从而增加保留时间相似的药物峰面积[33]。一些注射器制造商已经开发了隔离膜（例如，含氟聚合物）来润滑注射器组件并防止硫化剂从注射器柱塞的橡胶塞中浸出[49]。应用于柱塞和注射器针筒内壁的医用硅油可能会影响不同血红蛋白种类的共氧测定法[50]。为了限制注射器润滑剂的潜在污染，一些制造商将有机硅烘烤到注射器针筒内壁上[49]。

血液采集或转移过程中过度抽吸和强行压下柱塞会产生剪切力并破坏红细胞[13,31,51]。几项研究表明，使用注射器而不是真空采血管时溶血增加[13,31]。在一项研究中，19%的注射器采集标本溶血，而真空采血管采本溶血率是 3%[12]。最近，Ashavaid 等人[52]研究报道，用针头和注射器采集的标本溶血率是用真空采血管采集的 200 倍。为了最大程度地减少溶血，应轻轻移动注射器柱塞以减少对红细胞膜的压力。

尽管 CLSI H3-A5 由于针刺伤害的风险增加和血液样本质量较差而不建议常规使用，但针头和注射器仍普遍用于动脉血的采集[53,54]。传统上，用玻璃注射器（不渗透大气气体）采集动脉血气样本[55,56]，然后将其放入冰浆中，以运送至临床实验室。在临床和研究实验室中，高密度塑料注射器（通常是聚丙烯）已取代玻璃注射器，原因是成本低、方便（一次性使用、预肝素化）、易于使用柱塞和抗破裂性[57,58]。

塑料注射器用于血气测量的主要缺点是氧气（在较小程度上是二氧化碳）会渗透到针筒壁和柱塞头中[56,59]。气体渗透性受塑料材料类型、注射器尺寸（表面积与体积之比）和管壁厚度的影响[60-62]。大量研究表明，与塑料注射器相比，从玻璃注射器获得的血气样本中的氧气分压（PO_2）在临床上有显著变化，尤其是当血液中 PO_2 高时[55,56,58,63-65]。比较孔径和密度，可以确定塑料注射器的氧气扩散面积是玻璃注射器的 4 ~ 150 倍[66]。进一步研究表明，初始氧气水平、氧气-血红蛋白解离、总血红蛋白以及储存期间时间和温度可能会影响塑料注射器标本中的氧气测量[58,61,65,67-70]。CLSI 当前建议将塑料注射器中采集的血气样本保存在室温下并在 30 分钟内进行分析，而如果分析延迟超过 30 分钟，则应使用玻璃注射器[71]。

开发了一种 SafePICO 注射器，该注射器具有清除气泡的安全端盖和可溶解抗凝剂的软磁钢球，用于 ABL FLEX 血气分析仪（美国 Radioometer）标准化血样、血气、电解质、代谢产物和血红蛋白的全血样本混合[72]。尽管有人担心 SafePICO 注射器中的自动磁力混合会裂解红细胞，并通过直接电位计测得的钾浓度假性升高，但最近的一项研究表明，结果与使用血液分析仪（LH 750）和化学分析仪（LX-20）相当[72]。

应避免通过刺穿橡胶塞将血液样本从注射器直接转移到采血管。当细胞在柱塞压力下以很大的力撞击管壁时，可能会导致溶血；对于大口径针头，这尤其成问题[25,12]。当必须使用注射器将血液转移至于采血管时，必须按照规定的血量转移标本，以避免不正确的血液与抗凝剂比率，否则会产生不可靠的测定结果[43]。现在有其他设备可以安全地将血液从注射器转移至采血管[43]。

导管

导管是由许多聚合物制成的，包括聚四氟乙烯（PTFE，Teflon™）、聚乙烯、聚丙烯、聚氨酯、硅树脂、聚醚氨酯、聚氯乙烯、聚酰亚胺和含氟聚合物[73-76]。导管用于输注液体和药物，以及抽取血液和其他体液[73-76]。润滑剂与导管一起使用，以最大程度地减少疼痛，促进导管的插入或拔出，并易于从导管中拔出针头[73-76]。导管润滑剂包括聚二甲基硅氧烷，可固化和不可固化的有机硅、有机硅表面活性剂和卵磷脂[34]。

流过导管的血液会受到剪切力的作用，从而改变细胞的形状，激活细胞，破坏细胞，并导致细胞内成分向血清中外流[25]。这些变化影响血液学、电解质和酶学测定[12,77-80]。导管、适配器装置和穿刺针的直径不相等会导致红细胞上压力的变化，从而导致血液在常规真空采血管中的溶血[12]。与静脉穿刺法相比，通过静脉导管获得的标本溶血可能性高出三倍[78,82,83]，其中溶血最常见于较小的 24 G ~ 20 G 导管中[78]。此外，空气从松动的导管连接或组件进入真空采血管也可能引起溶血[78,81]。如果临床医生不了解采血方法及其对实验室结果的影响，则可能由于数值不一致和难以确定真实数值而使患者护理变得复杂。

苯扎氯铵肝素是一种用于预防血栓形成和减少感染的导管涂层，可释放到血液样本中并干扰离子敏感电极，使钠和钾的水平假性升高[79-80]。苯扎甲铵（单价阳离子）与电极的相互作用可能导致钾水平的假性升高[79-80]。大量冲洗可减少并最终消除这种干扰，但是导管涂层可能会浸入血液样本中，尤其是在放置导管后开始抽血时。在这种情况下，应采用直针穿刺来进行准确的电解质测量[12]。

许多研究表明，药物可能会吸附到导管表面。当导管用于药物输注后不久抽取血液样本时，这种吸附是主要关注的问题。聚氯乙烯导管可吸收药物，例如三硝酸甘油酯、盐酸胼屈嗪、硫喷妥钠、华法林[84]、苯并二氮杂[85-86]和吩噻嗪[87]，而聚氨酯导管可吸收多种药物[88]。通过聚氨酯导管输注他克莫司，随后通过盐水冲洗的导管抽取标本时，可能导致他克莫司水平假性升高（比从外周静脉采血高 8 倍）[89]。环孢菌素与导管中的硅树脂、聚氨酯和硅橡胶材料结合，即使是那些不用于输液的管线也是如此[73-76,90-94]。通常，即使已冲洗过导管，也不应从先前用于输液的导管或内腔中获得用于治疗药物监测的标本。

采血管

采血管由胶塞、管壁材料、表面活性剂、抗凝剂、分离胶、促凝剂和表面活性剂组成，所有这些都可能会干扰分析测定（图 1）。

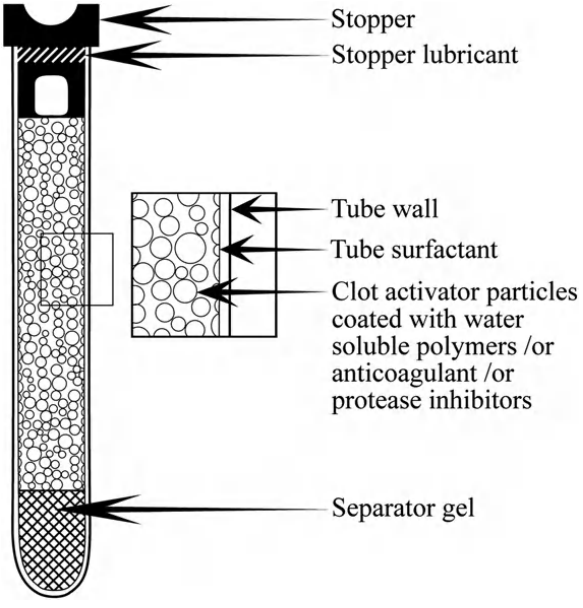


图 1. 真空采血管的组成

管壁

真空采血管通常是圆柱形的，长度为 50 ~ 150 mm，直径为 10 ~ 20 mm[95,96]。管长大多数为 75 ~ 100 mm，直径为 13 mm，并容纳 2 ~ 10 mL 全血[95-97]。用于小儿血液样本的微量采集管长度通常为 40 ~ 50 mm，直径为 5 ~ 10 mm[95,96,98]。

历史上，真空采血管由钠钙或硼硅酸盐玻璃制成，后来发现钠钙玻璃可将微量元素（尤其是钙和镁）释放到血液样本中[33]。由于玻璃真空采血管密封性强、防水和耐热，因此它们可以保持 200 天以上的真空度[99,100,101]。在玻璃管中，当血液中的 XII 因子接触亲水性玻璃表面时，血液凝结级联反应被激活。血块不粘附在玻璃上，因此很容易通过离心与血浆分离[102]。这种不粘附还会使血凝块在处理或运输过程中重新悬浮到血浆中，并可能影响溶血的检测结果[102]。

为了遵守职业安全与卫生管理局（OSHA）的指导原则，以最大程度地减少破碎管造成的风险，塑料采血管取代了玻璃采血管[103]。塑料采血管通过注模工艺使用以下材料制造：聚对苯二甲酸乙二酯（PET）、聚烯烃 [聚乙烯和聚丙烯（PP）]、聚酯、聚丙烯酸酯、聚四氟乙烯、聚硅氧烷、聚氯乙烯、聚丙烯腈和聚苯乙烯[95-97,99,100]。塑料具有以下优点：最大程度地减少破损对生物危害材料的暴露，提高抗冲击性，提高离心速度耐受性，减轻运输重量，促进焚化处置并降低生物危害废物的处置成本[7,104-107]。塑料管可以更经济地制造，并具有出色的尺寸精度。然而，与玻璃管相比，塑料管的透气性受到了限制[100,104,108]。PP 和 PET 是采血管中最常用的两种塑料[100,109]。PET 非常坚固，不易破损，可以保持真空以延长保质期[100,108,110]。PP 的渗透性低于 PET，这有助于保留适当的液体抗凝剂体积和血液样本中的浓度[100]。由于 PET 管中的抗凝剂往往会失水，因此制造商开发了双壁采血管，以最大程度地减少抗凝剂的蒸发，特别是用于凝血研究[100,109]。双壁管具有内部 PP 层（防止柠檬酸盐溶液蒸发水分）和 PET 外层（透明，可视化观察采血量）[99,100,109]。PP 和 PET 的组合使用有助于保留抗凝剂溶液的体积并延长管的保质期[99,100,109]。

血液在大多数塑料的疏水表面上流动不那么顺畅，并且血液成分（例如血小板、纤维蛋白和凝固的血液）粘附在塑料管壁上[111,112]。这阻止了常规离心机中血清与凝块的彻底分离（注：临床常见的血液挂壁现象），在微量采血管采血和离心过程真空采血管中尤其成问题。一种使采血管与血液成分粘附性降低的方法是使表面呈玻璃状，从而使血液呈现出相对亲水的表面[112,113]。当使用气体等离子体改变杂原子的表面化学时会发生这种情况[112]。另一种方法是用表面活性剂，水溶性聚合物或带有亲水性-疏水性共聚物的水不溶性聚合物覆盖塑料内部[111,114]。但是，表面活性剂可能会被血液从管壁上清除。此外，血浆、血清或凝块中的表面活性剂可能会干扰诊断测试[11]。为避免这些问题，制造商开发了将表面活性剂直接掺入

塑料中的管[95,97]。理想地，用于采血管的材料应促进血块形成，使血块与血清完全分离，并增强血块的牢固附着力，以最大程度地减少血块的再混合。

几项研究比较了玻璃管和塑料管的临床化学分析[7,115,116]、内分泌学[115,117]、分子检测[118]、血清学[119,120]和凝血[97,112-115,121-124]。尽管发现某些分析物的统计差异不大，但均无临床意义。因此，可以得出结论，从玻璃转换为塑料不会导致测试结果解释的重大变化。

表面活性剂

表面活性剂通常用于免疫测定，以减少非特异性吸附[125]。包含表面活性剂需要仔细选择和优化，因为高浓度可能导致固相中被动吸附抗体的直接损失，以及其他非特异性影响[125-128]。市售的采血管可能包含许多不同的表面活性剂[10,11,97,129]，这些表面活性剂可作为涂层或模制物添加，以改善血液流动、更好地将血凝块活化剂沿管壁分布，并减少蛋白质、红细胞和血小板吸附到管壁[97,129,130]。否则，细胞材料可能会粘附在管壁上，污染血浆或血清并影响结果。关于涂覆塑料管内表面和橡胶塞表面活性剂的类型和浓度信息很少。为了提供有关表面涂层效果的更多信息，需要进行更多的研究和进一步的测试。

尽管研究人员已使用有机硅表面活性剂来最大程度地减少血液对管壁的吸附[97]，但有机硅可能会影响许多测试结果。研究报告显示硅树脂表面活性剂能够与离子特异性电极膜发生相互作用，使电位差上升，从而使检测出的镁离子和锂离子浓度偏高[131-137]。在放射免疫法测定促甲状腺激素、催乳素和人绒毛膜促性腺激素过程中，硅树脂表面活性剂可能会完全地掩蔽抗体，从而干扰生物素与亲和素的结合[138-141]。某些有机硅已被证明可以激活血小板[99]。研究指出，表面活性剂可能会使三碘甲腺原氨酸的检测结果偏高，影响竞争性与非竞争性免疫法检测维生素 B12 和癌抗原 15-3[138,140,141]，与 C-反应蛋白形成复合物使检测结果偏高[152]，增加乙肝表面抗原的假阳性率[153]。

Bowen 等人[10]在 BD SST™采血管中发现了常见的有机硅烷表面活性剂（Silwet™L-720），其剂量依赖性地导致了三碘甲状腺素（T3）和其他分析物的假性升高。Silwet L-720 是 BD 用于涂覆其采血管内部的有机硅表面活性剂[95,142,143]，是包含亲水性聚氧化烯链的非离子有机硅表面活性剂家族成员。通常，它们以聚氧乙烯和聚氧丙烯的均聚物或共聚物形式存在，并连接到疏水性聚二甲基硅氧烷骨架上[144-147]。Silwet L-720 的分子结构可以是梳状的，聚氧亚烷基链侧接在聚二甲基硅氧烷主链上，也可以是线性的，呈 AB 型或 ABA 型构型排列，其中 A 是聚氧化烯亲水基，B 是聚二甲基硅氧烷疏水物[144-147]。Silwet L-720 的聚二甲基硅氧烷部分吸附在采血管管壁上的疏水表面，例如塑料（即聚对苯二甲酸乙二酯）上，而亲水的聚环氧烷部分则面向标本，防止红细胞粘附[144-148]。

当采血管中表面活性剂过量时，会通过从 Immulite™ 2000/2500 三碘甲甲状腺素免疫测定法中使用的固相上解吸捕获抗体而引起干扰，并且对其他制造商的免疫测定法具有类似的作用[10,11]。有趣的是，在同一研究中，当在 AxSYM™分析仪上测量样本时，在表面活性剂存在下 T3 浓度没有增加。对于此仪器特定的差异，有几种可能的解释。可以想象的是，由于固相支持和/或结合的差异，AxSYM 微粒表面的抗 T3 抗体对表面活性剂的脱附更具抵抗力。两种分析仪之间竞争性免疫测定形式的差异也可以解释两种测定对表面活性剂的不同反应[10,11]TT3 的 Immulite 2000/2500 免疫测定是同时进行的一步测定，而 AxSYM 使用连续的两步测定。使用 AxSYM 免疫测定法进行的额外洗涤步骤可以更有效地去除表面活性剂并防止其与微粒或微粒表面上的抗体结合。血清与采血管中表面活性剂的孵育时间以及 AxSYM 分析中涂有抗 T3 抗体的微粒孵育时间明显短于 Immulite 2500 TT3 分析中的 30 分钟孵育时间，因此它为表面活性剂提供了较少机会干扰微粒和/或微粒表面上的抗体。最后，用于 TT3 分析的抗体数量和类型的差异可以解释两种分析方法的差异。

Advia Centaur™某些竞争性和非竞争性免疫测定（例如维生素 B12 和癌症抗原 15-3）也受到 Silwet L-720 的影响，但其干扰不能简单地通过从固体阶段中释放抗体来解释，并且必须通过其他机制发生。因此，需要进一步的研究来充分阐明表面活性剂干扰这些测定的机理。为了应对 SST、SST II 和微量采血管的免疫分析问题，制造商于 2005 年重新设计了其血液采集管，以减少管中的表面活性剂含量，以减少分析干扰。Morovat 等[149]使用这些减少表面活性剂的采血管，某些免疫测定中仍然显示出偏差，但在临床上没有显著性[149]。在该研究中，所使用的参考采血管涂有有机硅表面活性剂，这是免疫测定干扰的来源[10,11,125]。但是，没有表面活性剂的无添加剂玻璃采血管将是对照管的更好选择。Wang 等[150]研究了新的 Vacutainer 和 Microtainer 管对在 Immulite 2000 分析仪上进行的 16 种免疫测定的影响。结果发现，与玻璃对照管相比，SST 真空采血管和微量采血管对游离三碘甲状腺素（分别为 12.2%和 39.1%）和游离甲状腺素（分别为 16.7%和 23.6%）产生了明显的偏差，超过了最大期望值。两种甲状腺激素的偏倚为 3.6%。McKiel 等人先前的研究[151]还表明，当用硅化的真空采血管采血时，游离甲状腺素水平升高。因此，表面活性剂含量降低的 Vacutainer 和 Microtainer 管采集的标本，在

Immulite 2000 分析仪上测得的某些分析物仍显示出明显的偏差。

一项研究表明，采血管中的有机硅与 C 反应蛋白形成复合物，从而增强了 Vitros C 反应蛋白测定中的抗原抗体反应，导致结果假性升高[152]。在另一项研究中，Sheffield 等[153]报道，使用了放置 3 个月以上的上述采血管，用 AUSZYM 酶免疫测定法检测乙肝表面抗原时，其假阳性在妇女中显著的升高（19/24）。他指出假阳性率的增加是由于该采血管中有高浓度的表面活性剂和促凝剂，使血清标本的浊度增加，从而导致吸光度增大（数据未发表）。表面活性剂含量较少的 SST 采血管将会显著降低血清标本的吸光度值和浊度，从而使假阳性率大大降低（数据未发表）。Stankovic 和 Parmar[125]也讨论了采血管表面活性剂对临床测定的影响。

含低浓度表面活性剂的 SST 采血管检测血清钾离子浓度，发现有显著的偏高[154]，其原因为采血管中低浓度的表面活性剂增加了红细胞、血小板和蛋白质粘附到管壁上的可能性，随后释放出细胞内的钾离子，从而使钾离子浓度升高[111]。

最近的研究表明，某些采血管中的成分干扰了质谱法测定中产生的峰。Drake 等[155]研究发现在 11 个添加了多种组分如表面活性剂或聚乙烯吡咯烷酮的采血管中，有 7 个通过质谱法测定时在 m/z 值为 1000 ~ 3000 范围内检测到多重信号。这些试管的加性峰使解释变得复杂。在低分子质量范围内进行质谱分析，尤其是在使用基质辅助激光解吸电离或表面增强激光解吸电离时，其中一次分析即可测定较宽范围的组分[155,156]。

胶塞

胶塞的尺寸适合采血管，并按抗凝剂类型或分离胶进行颜色编码。胶塞应易于被针刺穿，拔针后会自动密封[111,157]，并保持真空[111,158]。胶塞的合适材料包括硅树脂、异丁烯-异丙烯、苯乙烯丁二烯、氯化异丁烯-异戊二烯橡胶、乙烯-丙烯共聚物、聚氯丁二烯、丁基橡胶和卤化丁基橡胶[111,147,148,159,160]。胶塞的组件可能会污染血液样本并引起检测结果错误。大量研究表明，当使用含有增塑剂三（2-丁氧基乙基）磷酸酯（TBEP）的胶塞时，药物的生物利用度和生物等效性存在差异[161,162]。TBEP 用于增加胶塞的柔软性和弹性，但它同样能使某些蛋白从血浆蛋白结合位点（如 α1-酸性糖蛋白[163-167]）移除，从而增加了红细胞对药物的吸收和降低了待测血清或血浆中药物的水平。TBEP 中分布发生变化的药物包括奎尼丁、普萘洛尔、利多卡因、三环类抗抑郁药和吩噻嗪类药物（例如氟奋乃静和氯丙嗪）[161,163-168]。Janknegt 等[169]证明无 TBEP 的胶塞对用于治疗性药物监测的几种测定法没有干扰。这些发现促使管材生产商减少了含 TBEP 的胶塞的生产[161,162]。

Chrzanowski[170]发现，在用气液色谱法（GLC）测定茶碱时，从丁基橡胶浸出得到的几种物质，可使其结果假性增高。橡胶塞制造过程中带入的金属元素如钙、铝、镁和锌，不能从血样中移除，这些均可影响结果[171-174]。特殊配制的胶塞可防止二价阳离子浸出[175]。胶塞中发现的其他潜在污染物包括硫、含硫的硫化促进剂、脂肪酸和过氧化物。大多数制造商已经用低萃取性橡胶或添加的物质来重新配制其橡胶塞，以最大程度地减少污染物渗入血液样本中[163,157,192]。尽管有这些保护措施，还有一种好的做法，是将采血管采血至额定采血量并以直立的方式存放，以最大程度地减少从胶塞中浸出的现象，并且不要将潜在的污染物集中在小体积的样本中。采血管的弹性胶塞覆盖有聚丙烯、聚氯乙烯或聚乙烯，当胶塞拔掉时，可以使血样中的污染物降至最低[176]。

胶塞表面润滑剂

在胶塞表面覆盖硅酮和甘油润滑剂，使胶塞易于插入和拔出采血管，润滑剂也能减少胶塞对红细胞和血块的吸附，使它们不能污染血清或血浆层。当检测甘油和甘油三酯的血药浓度时不应该用甘油做润滑剂，因为甘油是两者的成分之一[177,178]，应优先选用硅化处理的胶塞，因为在分析测定时硅酮的干扰较小。但是，胶塞表上的硅树脂可使镁离子和总三碘甲腺原氨酸假性升高[10,133,134]。硅树脂润滑剂也可从塞子浸出，干扰质谱分析的结果[155]。因此，在临床生化分析中，塞子润滑剂应被考虑为潜在的误差来源。

分离胶

采血管通常包含分离凝胶，在离心过程中在分离的细胞和血清之间形成屏障[179,184,185]。分离胶可以显著提高分析血清和血浆的稳定性，提高标本中血清的得率，方便储存和运输[180-183]。分离胶位置受制造商控制的变量（比重、屈服应力、粘度、密度和试管材料）、实验室条件（离心速度、温度、加速和减速条件以及存储条件）和患者（肝素治疗、低血细胞比容、血浆蛋白升高、比重）的影响[184,186]。分离管的优点是（1）使用方便；（2）通过凝血活化缩短处理时间；（3）血清或血浆产率更高；（4）减少有害物质的雾化；（5）单个离心步骤；（6）原管取样，以及（7）单个标签。

分离胶由粘性液体，有机和无机填料以及天然或合成增粘剂[111,144,148,187,189]制成，以实现适当的粘度、密度和其他物理性质。粘性液体成分包括硅油、氯化聚丁二烯和聚丁烯、聚（甲基）丙烯酸酯、聚异丁烯，以及由 α-烯烃或苯乙烯与马来酸二酯制得的共聚物[111,144,148,187,188]。无机填料包括二氧化硅、氧

化铝、滑石和高岭土，而有机填料包括苯乙烯聚合物和共聚物、丙烯酸树脂和聚氯乙烯。天然增粘剂包括松香和松香衍生物，而合成增粘剂包括烯烃和二烯烃聚合物以及酚醛树脂[111,144,148,187]。

血清和血浆的比重范围为 1.026 ~ 1.031 g/cm^3，而血凝块的比重范围是 1.092 ~ 1.095 g/cm^3，因此，分离胶的比重应该在 1.03 ~ 1.09g/cm^3 之间（适宜值为 1.04 g/cm^3）[190,191]。少数情况下，高蛋白血症及高浓度放射性对照染料可导致标本特有的高比重血清或血浆不能漂浮在分离胶的上面[186,192]。疏水涂层可以涂在管壁上，以改善分离胶的附着力，并在红细胞与血清或血浆之间形成屏障。

理想情况下，实验室结果不应受到与分离家相互作用的影响；但是，一些报告显示了对分析物浓度的影响。标本的体积、储存时间、温度、以及胶的类型都会影响药物被吸入胶里的速度[181,193-197]。疏水性的药物如：苯妥英、苯巴比妥、卡马西平、奎尼丁和利多卡因等可能被吸收到疏水的分离胶中，在 4℃，这种吸收能够在 24 小时后降低血清中药物浓度 20% ~ 50%[166,198-201]。有机氯：1,1-二氯-2,2-双（4-氯苯基）乙烯和多氯联苯化合物也可以被分离胶吸收[202]。孕酮聚合物的浓度和时间有关，在分离胶里放置 6 天就会减少 50%以上[203]。Daves 等[8]的研究证明在统计学上而不是在临床上肌红蛋白和 CK-MB 的浓度在装有分离胶的试管里有很显著的差别，然而，机制还不知道。采血管制造商已经发现了新的分离胶的组成配方，这种组成可以减少药物和被测物质的吸收[204]。

分离胶也可能会释放一些物质，这些物质会干扰被测物质的含量[155,185,203,205,206]，在含有分离胶的试管里，血清或血浆的上面或者是里面可能会出现凝胶剂或者是硅油滴，凝胶剂和油滴会干扰取样探针、试管表面、比色皿和因与免疫复合物结合而影响固相免疫测定系统[185,203,206]。一些胶的成分可以溶到血液里面去，并且影响一些药物的溶解浓度[207]。在含有分离胶的采血管里，血液标本会检测到相对较高浓度（20 mg/L 或者更多）的苯乙烷和二甲苯。不适当的储存、温度、不恰当的离心速度会加速分离胶的降解[203]。

促凝管和水溶性物质

内源性的凝血途径被激活需要与体外物质接触而启动[143,148]。玻璃、硅石、白陶土、皂粘土或者是硅藻土都可以作为快速促凝剂[111,144]。而微小的促凝剂像无机硅酸盐类相对慢些（30 ~ 60 分钟）[97,208]。40% ~ 80%的管壁都会覆盖二氧化硅促凝剂[210-212]。二氧化硅促凝剂通常是球体的，直径范围是 0.01 ~ 100 μm（比较适合的是 0.4 ~ 20 μm）[148]。在分离的血清中，促凝剂还有一个优点就是减少潜在的纤维蛋白[203]。

第二种激活促凝因子的途径是外源性途径，是一种生物化学反应，并且和浓度有关[97,148,209]。尽管这些促凝剂可以快速工作（10 ~ 20 分钟），但是凝块是凝胶状的，不能干净地分离。因此，所得血清通常质量较差[97,148,209]。生化促凝剂像鞣花酸、凝血酶、蛇毒液及促凝血酶原激酶等[111,97,213,215]被加工成小颗粒或者是纸盘或者是喷到试管的表面，试管的表面含有像聚维酮、羧甲基纤维素、聚乙烯醇或者是聚氧化乙烯一样的水溶性物质作为载体。载体使促凝剂快速悬浮，增加了凝块形成[111,210,215]，并减少了摇匀需求[111,215]。但是，载体溶解在血清和血块中[111,148]。某些促凝剂在高湿度下会降解[111,215]，而有机硅聚合物蒸气会凝结并形成抑制表面活化的液膜[209-215,216]。

一些促凝剂必须通过颠倒混匀，并且可能无法与凝块完全沉淀，从而污染血清并干扰分析[111]。悬浮的颗粒也可能损坏仪器的探针。如果形成小的纤维蛋白凝块，则它们会干扰移液器的准确性或免疫测定系统中的固相结合效率[217-220]。为避免这些问题，可使用等离子气体处理管壁以引入杂原子，从而加速凝固，但不会有颗粒、可溶性促凝剂或粘合剂污染血清或凝块[113]。几项研究报告了促凝剂对实验室检测的影响。Sampson 等[135]通过 Lytening 2Z 离子选择电极分析仪，发现二氧化硅或是聚硅酮表面活化剂可导致锂离子浓度假性升高。促凝剂或有机硅表面活性剂显然与分析仪的离子特异性膜相互作用，从而增加了测得的电位差和血清锂离子浓度。发生这种情况的确切机制尚不清楚。含有促凝因子的采血管里检测的睾酮浓度高于正常检测的四倍[221]。对所选的标本进行监测，促凝剂干扰睾酮检测的方法中离子对 m/z 的比率是 289.3/97.1[221]。改变离子对 m/z 的比率为 289.2/109.0 就可以消除这种干扰[221]。在含有促凝剂的采血管里通过质谱法获得蛋白质的含量会有所改变[222,223]。二氧化硅和硅酸盐促凝剂可以诱导体内和体外的蛋白质释放、激活、形成基质金属蛋白酶-9 复合物（明胶酶-B）[224,225]。存在二氧化硅和锌离子情况下，红细胞释放基质金属蛋白酶-9 时可导致基质金属蛋白酶-9 浓度升高、血块激活[223,224]。为避免这个问题，现推荐采用柠檬酸盐抗凝血浆检测基质金属蛋白复合物-9[226]。

抗凝剂

血浆的粘度较高，并且总蛋白含量也比较高（比血清高约 4 g/L），这是因为血浆中含有纤维蛋白原和其他的促凝因子[227,228,229,230]，血浆中钾离子和乳酸脱氢酶的含量较低，而肽类促凝因子激活物、血小板因子-4、血小板球蛋白的含量及其他因血小板被激活而释放出来的成分却很低。血小板、红细胞、白细胞升高的恶性血液病患者很容易与假性高血钾区分[231,232]，血钾测定可获取更准确的结果。

当血浆用于诊断测定时，必须注意选择合适的抗凝剂。采血管中最常用的抗凝剂是乙二胺四乙酸（EDTA），肝素和柠檬酸盐。抗凝剂可以是液体或固体（粉状、结晶或冻干的）[233]，应以适当的浓度添加以保存分析物，防止干扰抗原-抗体复合物的结合或沉淀[234-238]。

乙二胺四乙酸二钾（EDTA.K2，表 2）是一种常用的金属螯合剂，它可以和钙离子结合来阻止血块的形成[239,243]。它是血细胞计数实验常用的抗凝剂。EDTA 可以结合金属离子，例如某些免疫分析试剂中的锌和镁，它们是免疫分析试剂中酶（例如碱性磷酸酶）的常见辅因子[244-246]。因此，血液与 EDTA 的比例对于最佳检测结果至关重要。采血量不足可能导致 EDTA 浓度相对升高，螯合在化学发光反应中可以改变磷酸酶活性的镁离子和锌离子，从而改变化学发光法（例如，完整的甲状旁腺激素和 ACTH）中碱性磷酸酶活性[245-247]。同样，当不存在离子时，包含二价阳离子结合位点（例如钙和镁）的蛋白质可能会发生构象变化，从而影响抗体检测结果[245,246]。EDTA 可以使血细胞失水，导致血浆稀释 3% ~ 5%[239,243]，这样就会改变红细胞指数和血细胞比容。因此，EDTA 管应确保采血量准确，这样才能避免阳离子螯合及浓度变化[248]。Banfi 等人撰写了一篇出色的关于 EDTA 在诊断测试中作用的综述[248]。

表 2. 常规真空采血管帽盖颜色和附加剂

胶塞颜色 [a]	添加剂（s）	含量/浓度
红色	促凝剂 内壁未制膜	
金黄色	促凝剂 + 分离胶	
红色/黑色		
红色/棕色		
浅蓝色	柠檬酸三钠（液体添加剂） （1 体积添加剂：9 体积血液）	0.105 M（3.2%）或 0.129 M（3.8%）
绿色	肝素钠（干燥添加剂）	10 ~ 30 USP 单位/mL 血
	肝素锂（干燥添加剂）	10 ~ 30 USP 单位/mL 血
浅绿色（薄荷绿）	肝素锂（干燥添加剂）+分离胶	10 ~ 30 USP 单位/mL 血
紫色	EDTA.K2（干燥添加剂）	1.5 ~ 2.2 mg/mL
	EDTA.K3（液体添加剂）	1.5 ~ 2.2 mg/mL
	EDTA.Na2（干燥添加剂）	1.4 ~ 2.0 mg/mL
灰色	氟化钠/草酸钾（干燥添加剂）	氟化钠：2.5 mg/mL 血/草酸钾：2.0 mg/mL 血
	氟化钠/EDTA.K2（干燥添加剂）	氟化钠：2.5 mg/mL 血/EDTA.K2：1.5 mg/mL 血
	碘乙酸锂	碘乙酸盐：~2 mg/mL 血
	氟化钠	氟化钠：~4.3 mg/mL 血
黄色	柠檬酸葡萄糖（ACD）——配方 A （1 体积添加剂：5.67 体积血液）	柠檬酸二钠，22.0 g/L；柠檬酸，8.0 g/L；葡萄糖，24.5 g/L
	柠檬酸葡萄糖（ACD）——配方 B （1 体积添加剂：3 体积血液）	柠檬酸二钠，13.2 g/L；柠檬酸，4.8 g/L；葡萄糖，14.7 g/L
宝蓝色 （标签上有红色带）	无	~1.8 mg/mL 血
宝蓝色 （标签上有紫色带）	EDTA.K2（干燥添加剂）	

本表参考《CLSI：真空采血管和血液样本添加剂：获批标准 H1-A5[239]、H3-A4[240]》以及 Young 等提供的信息[241]和 BD 网站上的信息[242]修改而来。

a 单个或多个帽盖的颜色组合可能因不同的制造商而异。

肝素常和锂、钠、铵盐等联合使用作为抗凝剂。肝素主要通过抗凝血酶 III 复合物阻止纤维蛋白原的形成，抗凝血酶 III 复合物通过抑制凝血酶和八因子从而阻止凝血酶的激活[245,246]。采血管中肝素可接受的血液范围为 10 ~ 30 U/mL [249-252]（表 2）。肝素溶液会稀释样本，因此采血管内肝素通常为干燥状态[253]。

肝素可以和电解质结合从而会改变这些结合和游离型离子的浓度[251,254,256]，为了尽量减少肝素化注射器中钙的结合，已经开发出电解质平衡的肝素制剂[256]。肝素可能会干扰氯的测定，因为氯离子电极会优先选择肝素这类水化能量比氯高的离子[257]。有趣的是，与 Dimension RxL 分析仪相比，在 Dimension™Vista 1500 分析仪上对肝素管内标本进行分析，我们观察到氯化物电极（2 ~ 10 mmol/L）受到正干扰（未发布观察结果）。大量样本在 Vista 分析仪上显示出负的阴离子间隙，可能是因为肝素干扰了氯化物膜电极。

肝素也可能干扰抗体-抗原反应[258,259]。尽管肝素降低了某些抗体的反应速率（特别是在第二抗体系统中的沉淀步骤），但固相系统的使用已使该问题最小化[203]。由于肝素和纤维连接蛋白形成复合物及纤维蛋白和纤维蛋白原复合物的冷沉淀，球沉淀会发生，因此肝素不能用于冷球蛋白试验[203,245,246,260,261]。肝素对血清甲状腺激素水平和其他分析物的影响也有研究[203,245,246]。最近，用肝素抗凝的采血管收集血液透析患者时发现，发现虚假的低白蛋白水平[262]。据推测，虚假的白蛋白水平降低与肝素干扰溴甲酚绿（非溴甲酚紫）与白蛋白结合有关，从而减少了比色复合物的形成[262]。肝素能够非特异性地与蛋白结合，影响多肽的分离和质谱检测[263-265]。

含有肝素的静脉产品污染了硫酸软骨素（OSCS），至少在 12 个国家都引起了不良反应[266]。因此，美国食品和药物管理局（FDA）要求肝素生产商通过毛细管电泳或核磁共振检查是否污染了 OSCS[267]。北美一家主要管材制造商的一些批次 OSCS 含量高达 0.91%[267]。通过对含有和不含 OSCS 的肝素锂抗凝的采血管进行广泛评估，表明那些含 OSCS 的采血管的临床化学结果是可接受的，肝素浓度适当。但是 Bosworth 等发现污染 OSCS（5% ~ 20%）的血标本对于乳酸脱氢酶、总甲状腺素、钾、总蛋白、氯化物和尿酸等的测定结果都有显著差异[267]。尽管 OSCS 干扰的机制尚不清楚，但聚阴离子物质可与许多临床化学分析试剂相互作用[266]。Bosworth 等[266]研究还显示 OSCS 会对 OSCS 血浆标本中的抗凝产生不利影响。这两项研究突出了抗凝剂对临床检测的影响。

柠檬酸三钠是一种钙的螯合剂，在凝血实验中被用作抗凝剂[239,249]（表 2）。它可以抑制需要螯合阳离子辅因子的谷草转氨酶和碱性磷酸酶[239,249]。柠檬酸钠是酸性柠檬酸葡萄糖（ACD）和柠檬酸茶碱腺苷（CTAD）抗凝剂的一种成分[249,268,269,270]。CTAD 可以防止在标本采集过程中血小板的活化，对测量血浆血小板衍生物很重要。

草酸钾是用于螯合钙的一种抗凝剂[239]（表 2）。但是它会使红细胞脱水而收缩，从而减少多达 10%的血细胞比容水平[249]。草酸也抑制一些酶的活性，如酸、碱性磷酸酶，淀粉酶和乳酸脱氢酶[249]。草酸经常同氟化钠和碘醋酸钠等抗凝剂联合使用。氟化钠（2 ~ 3 mg/mL 血液；表 2）抑制酶，使葡萄糖和酒精得以保存[271-275]。氟化钠一直被用作抗酵解使用，因为它抑制烯醇化酶[271-275]。在血液标本采集后，氟化钠的抗酵解效果可能延迟四个小时[272-276]。因此，在糖酵解受到抑制之前，葡萄糖代谢在室温下以 5% ~ 7%的速率进行。这种延迟是因为上游酶继续使葡萄糖代谢为 6-磷酸葡萄糖[276-278]。因此，对于非分离的血液标本血糖水平必须保持时，氟化物抗凝血剂可能是不理想的。

在某些免疫测定中，氟化钠可能会抑制某些酶的活性，并通过改变细胞膜的通透性或者三磷酸腺苷耗竭引起溶血后造成钾离子外流而干扰电解质的测定[249]。类似地，碘醋酸可以抑制三磷酸甘油醛脱氢酶，促进溶血，干扰葡萄糖、钠、钾、氯及乳酸脱氢酶的测定[249,279,280]。

某些抗凝血剂和抗酵解剂可能不适合某些测定。由于生产商不一定会详细说明用来验证测试结果的血浆来源，临床实验员应该通过特殊的检测分析和仪器平台来验证他们所使用的血浆采集管的性能。为了保证适当的添加剂/血样的比例，遵循制造商的建议而采取恰当的采样体积和排管顺序，这一点是非常重要的。这些努力可以节省时间并防止实验室误差。

采血顺序

CLSI 指导方针把血液采集过程中使用导管和注射器的顺序标准化，使导管添加剂的携带污染降到最低，而这种污染可能会对检测结果造成影响[20,282]。采血时先使用 EDTA-钾抗凝

的导管会引起后续使用的不含抗凝剂的导管所采集的血液检测出不符实的低血钙和高血钾[281]。CLSI 指导方针建议真空采血管的使用顺序如下：血培养瓶、枸橼酸钠抗凝管、有或无促凝剂和有或无分离胶的血清采血管、有或无分离胶的肝素钠抗凝管、EDTA 抗凝管、含枸橼酸盐葡萄糖的管和含糖酵解抑制剂（氟化物，碘醋酸盐）的管[20,282]。微量采血管的使用顺序则不相同：血气分析、载玻片或者涂片、EDTA 抗凝管、含其他添加剂的采血管和血清采血管[282]。以上修正的规定防止了小凝血块的形成和血小板的凝聚，它们对检测结果有明显的影响[282,283,284]。采血管制造商运用不同的颜色使区分采血管添加剂变得容易。

蛋白酶抑制剂

血液包含多种多样的蛋白酶抑制剂[285]，抑制剂的数目超过活化的蛋白酶的数目。螯合剂（比如 EDTA 和枸橼酸盐）并不能抑制丝氨酸蛋白酶，但是可以通过阻止钙离子介导的结合而减慢凝血蛋白酶的激活，凝血酶和因子 Xa 抑制剂都是抗凝剂，它们可以维持蛋白质的稳定性，使单个样本的化学和血液学检查顺利进行，然而由于费用高昂不能够广泛使用[286,287]。小肽类在血浆中常常有更好的稳定性，但是注意到比起 EDTA 抗凝的血浆，血清中的甲状旁腺激素有更高的回收率[288,289]。EDTA 可能会干扰一些免疫学的检测系统。部分肽类，像脑型利钠肽，它们的稳定性会因为添加胰蛋白酶抑制剂而增强[290]。因此，一些参考实验室建议在生物活性肽测试的采血管中使用抑肽酶或其他蛋白酶抑制剂。肽的稳定性在血浆中高度可变。胰高血糖素样肽 1 会被二肽基肽酶 IV 迅速裂解[291]；采血管应包括肽酶抑制剂，以确保完整肽的高回收率。通常建议使用 EDTA 管进行蛋白质组学分析[292]。小肽在血清标本中迅速降解，蛋白酶抑制剂增加了血浆中的肽稳定性[293]。小肽可能更易于降解，因为小肽：（1）通过与α2-巨球蛋白复合的位阻蛋白酶进行肽水解[296]；（2）缺乏球状结构；（3）具有更强的外肽酶作用可及性，一些抑制剂如磺酰卤可能会化学修饰蛋白质[294]。另一种蛋白质稳定策略是通过降低标本 pH 值来抑制蛋白酶[295]。高分子量内源性蛋白酶抑制剂在血浆中含量丰富，并且主要针对丝氨酸蛋白酶，与外肽酶相比活性很小。添加低分子量外源性抑制剂或小的合成化合物可定量增加抑制剂的平衡，并提供位阻蛋白酶的途径以扩展抗蛋白水解活性。

蛋白酶的活性可能会因为白细胞分泌蛋白酶或者红细胞溶解过程中释放蛋白酶而增强。例如，在发生溶血的样本中胰岛素的稳定性大大地降低，这是由红细胞释放一种硫基蛋白酶引起的[297]。添加蛋白酶抑制因子限制了对血浆中化学增活素和细胞因子得率的影响。样本处理时间是最重要的因素[298]。

由于蛋白质和肽类的稳定性会发生很大程度的改变，所以外源性蛋白酶抑制因子的添加取决于预期的样本的价值。因此，应该分析感兴趣的样本成分的稳定性，以此来决定蛋白酶抑制因子的使用。

微量采血装置

分析仪器的发展允许使用微量的血样本进行诊断性的实验（例如，通过穿刺手指、脚后跟或者耳垂采集的血样）。用毛细管和微量导管进行微量采血典型的用于婴幼儿、老年病人或者那些不适于做静脉穿刺的患者[299,300]。可从制造商购得各种尺寸、体积和形状的有/无肝素、EDTA 和柠檬酸盐微量管[300]。为了最大程度地减少破损、破碎和暴露于血源性病原体，并提供灵活性，尽管建议使用塑料毛细管，但应在玻璃管或塑料管中添加 Mylar™膜[45]。微量采血管实际上已经替代了不能单独标记的 Caraway/Natelson 管[301]。琥珀色微量采血管有利于保护新生儿的样本，使胆红素免受可见光的分解，并且可能会包含一支毛细管，改善毛细血管血的采集[302]。与较大的真空采血管相比，微量管采集标本的处理更加耗时[304,305]。塑料微量采血装置因为可以降低损伤和血液暴露的风险而被推荐使用[306]。管壁通常由透明的热塑性塑料制成，例如聚丙烯（首选）、聚乙烯和聚氯乙烯，这样，医护人员就可以轻松看到血液[129]。对比微量采血管和真空采血管的分析物水平，在统计学意义上有显著差异，而在临床意义上并无差异可能得归因于管壁材料[304]。微量采血管的缺点包括毛细管采样时加速溶血，收集组织液过程中激活血液凝固，和血清血浆的低得率[307]。

与静脉血标本一样，毛细血管血中的血小板、纤维蛋白和血凝块可能会附着在塑料管壁上[129,308]。在微量采血管中，因为更小的管径使这种现象更为严重[129,308]。因此微量采血管可能会被涂上一层表面活性剂来增强血液的流动性，减少蛋白质和细胞粘附在管壁上[129,308]。用上述采血管采集静脉血液标本进行免疫学的检测，该管中的表面活性剂对检测结果有干扰，同样地，用微量采血管采集毛细管血样检测免疫学相关指标，表面活性剂也会干扰检测结果[150]。微量采血管中的分离胶和

用于静脉采血管的分离胶是一样的。有研究表明，有或者没有分离胶的微量采血管都适用于做临床检测的标本，包括治疗性药物水平的检测[301,304,305,309]。尽管微量采血管常常用塑料螺旋帽来运输、离心和保存，但是没有证据显示这些材料会对临床化学检测产生干扰。

抗凝剂对微量采血装置的影响还没有被很好的说明[253]。两个最近的新生儿的案例表明，含有锂肝素钠的血液采集管导致了血清锂离子浓度的提高[310,311]。充盈不足的微量采血装置可以导致锂离子水平错误地增高到毒性的范围[311]。

因此，医护人员应该知道微量采血装置正确的采血、混合和添加剂使用的重要性。制造商和检验师都必须知道微量采血管的所有组成部分，并且了解它们对临床分析潜在的影响。

POCT 检测

需要检测的样本有：常规样本，如手术室或重症监护病房；但更常见的是在如办公室、床边、或住宅内等地点，皮肤穿刺毛细管取血得到的样本。皮肤穿刺，要求首先清洁取血部位，然后刺血针（lancet）穿刺。擦去第一滴血，然后利用微细取血装置收集后续血滴。

微量采血管通过轻轻接触取血，而毛细管则通过毛细效应取血。快速充盈可防止凝血和气泡生成。微量采血管材质有塑料和玻璃两种，均有含抗凝剂（如肝素）或不含抗凝剂的类型。褐色玻璃微量采血管用于检测光敏感性的待测物，如胆红素。

它利用改进的 i-STAT 卡夹（i-STAT cartridge），可让血液从采血部位直接流入卡夹[312]。目前证明可应用于 12 项检测，包括：血气分析、电解质、血细胞比容、血糖。常规检测常需要血量较检测实际需要血量高 10 倍，而 i-STAT 只需要检测所需样本量（95 μL 全血）[312]。

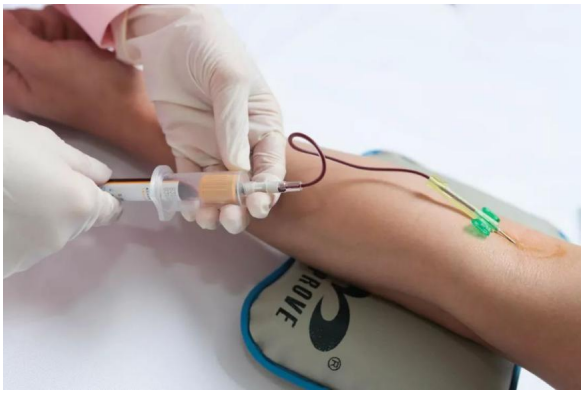
冷沉淀蛋白

冷沉淀蛋白（cryoprotein）是一类在 37℃以下会发生可逆性沉淀的血浆蛋白，包括免疫球蛋白、纤维蛋白/纤维蛋白原、纤连蛋白。

冷沉淀球蛋白包括免疫球蛋白和免疫球蛋白-纤连蛋白复合物，常规从血清中检测。冷沉淀纤维蛋白原由纤维蛋白原-纤维蛋白复合物组成，仅从血浆中沉淀。但冷沉球蛋白也会从血浆中沉淀，因此需要并行测定血清和血浆，以测定冷沉纤维蛋白原血症。

对于冷沉纤维蛋白原检测，需将血液收集在 EDTA 管中，其他步骤同上[261]。由于前面提到的原因，肝素抗凝管不能用于冷沉蛋白、冷沉纤维蛋白原检测[260,261]。但是，最近 UK National Quality Assessment Service 质控项目对 137 个实验室冷沉球蛋白检测评估显示，其中有一家实验室使用的是肝素抗凝管用于冷沉球蛋白检测[313]。

适当的收集和处理样本对于冷沉蛋白检测至关重要[261,313]。推荐做法是将血抽入预温的普通红头管或注射器中，转入装满预温沙子的开水瓶中转运至实验室，在 37℃水浴中让其凝固，并在可维持 37℃的离心机中分离血清[260]。



（静脉采血操作）

减少临床检测影响的建议

制造商在将一款新的采血设备推向市场前，需通过分析研究和临床研究证明该设备的安全性和有效性。虽然在所有检测平台上测试产品不太现实，但制造商需保证采血管成分和添加剂的数量和质量的一致性。对于新产品和大幅度改动的采血管，制造商还必须在最大干扰的情况下（如，样本量少、样本与试管成分长时间接触），评估产品。还必须分析采血管稳定性，以确定采血设备的恰当储存方法和使用期限。理想情况下，制造商需执行 Design for Six Sigma、Six Sigma 和类似方法，以减少采血管成分的差异[314,315]。此外，分析采血管成分对临床测试的影响，需考虑测试总体允许误差；因此，采血管成分不应增加临床测试的总体误差，而使测试无效[314,315]。对制造商而言，更恰当的做法是，利用质控血清按采血管批次测试采血管的影响。

临床实验室改用其他采血管时，需执行合理计划的采血管验证方案。该方案需描述清验证步骤，验收标准和统计方法，并遵循实验室所在机构审查委员会或伦理委员会关于测试人类样本的政策和步骤。且需对整个血液采集系统（采血针、夹具、试管等）用健康人和病人的血液样本进行评估，而不是某一个装置。

欲确定新采血管产品或大幅改动的产品用于检测时结果的准确性，需按 CLSI EP 9-A 指南要求进行试管比较研究。临床实验室需获取含各待测物所有可能范围的样本，样本数量需保证数据统计分析的统计效能。比较结果需用线性回归或类似的回归方法及 Bland–Altman 型图表进行分析。

评估测试结果不精确性，实验人员须比较现有设备和新设备所得结果的差异。这可按 CLSI EP5-A 指南所述对质控材料或病人样本做重复检测或按前述试管比较研究方法进行重复检测。

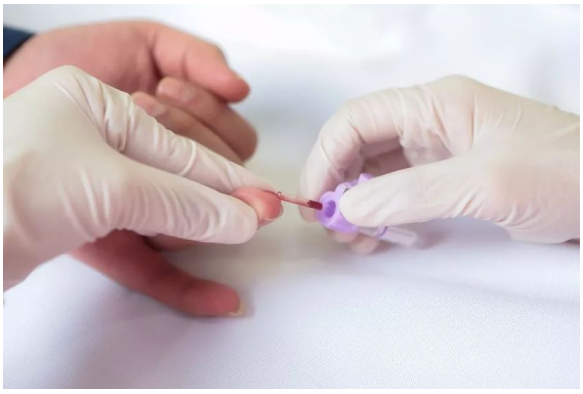
某些待测物在健康人群中检测不到或其浓度较低时，需往样本中加入要检测的待测物。验证研究所需进行的测试次数，取决于采血装置的用途。

比较研究的目的是验证现有设备和新设备用于诊断测试时，误差和不精确性水平是否相当。当结果不符时，实验人员须联系制造商以便进一步分析。临床实验室需监测参考区间和群体趋势，并向设备制造商报告偏差或不一致情况。这些问题还需立即通过 MedWatch 向 USFDA 等管理机构报告。

采血管是整体测试系统的一部分，因此技术水平测试组织者需要求临床实验室在技术水平测试报告中包括所用采血管类型。

对于临床试验或实验研究，如何选择采血管也十分重要，因为采血管材料和其中的添加剂可能和样本发生反应。在多中心临床试验或多中心实验研究整个过程中，需使用同一制造商的同种采血管，以减少采血管相关的影响因素导致的差异。这对于基因组学和蛋白质组学领域的新技术尤其重要，因为这类技术多用于分析低浓度待测物，或有更高灵敏度；因此即使采血管中微量的干扰物也可能影响结果。

CLSI 即将制定的新的指导方针，也将有助于制造商，体外诊断产品制造商，和临床实验室验证静脉和毛细管采血管的可用性，保证化学、免疫化学、血液学和血凝测试结果的可靠性。



（末梢采血操作）

总结

现代采血管技术的发展，极大方便了血液样本采集，但许多试验人员对于采血管成分的复杂性及其对于测试结果可能产生的负面影响，不甚了解。作为医疗器械，采血管需在指定的使用情况下，能取得预期的性能水平[318]。已知和可预见的危险因素及不佳效果，应尽可能消除或减少。

在本文中，我们讨论了采血设备以及采血管成分对实验室测试结果可能产生的影响。此外，我们建议：当怀疑存在干扰因素时，实验人员须：（1）利用替代方法测试相同待测物；（2）联系采血设备和试剂制造商；（3）将样本与所用的各个采血设备，分别温育，确定干扰的来源；（4）如果必要，向 US FDA 等相关管理机构提交医疗设备警示报告；（5）如果可能，选择其他采血设备制造商。

由于测试结果的质量取决于所获取样本的完整性，因此实验人员须警惕采血装置可能产生的干扰，并与制造商和诊断设备厂商密切合作，以减少采血管的相关问题，或更理想情况是防止此类问题的发生。

致谢

作者感谢 Kathryn Hargis 女士设计了图 1。

Impact of blood collection devices on clinical chemistry assays

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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

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 tion 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].

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]
Stopper	Interaction with specimen Drug assays	Bowen et al. [157] 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

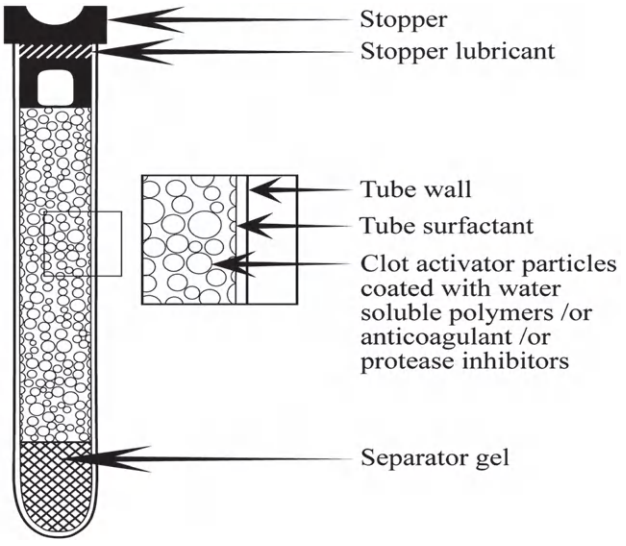

Fig. 1. Components of an evacuated blood collection tube.

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 triiodothyronine [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.

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促凝管分离胶内气泡对临床生化检验结果的影响

陈学东，许铭飞，覃思华，张宇彬

关键词：分离胶；气泡；真空采血管；生化检验；溶血

随着临床实验室室间质评的开展以及检验新技术的发展，分析前变异对检验结果的影响已成为所有检测变异中非常重要的一环[1-2]。在临床生化检测的分析前阶段，许多因素都能导致错误的结果，包括被采血者采血时的体位、压脉带捆扎时间的长短、采血量及是否使用合适的添加剂和附加物的采血管等[3]。

在临床实际应用中，真空采血管内附加物的异常可能会导致采血管不合格，其中促凝管分离胶内气泡是一个外观异常现象。促凝管分离胶一般无气泡，但偶尔也会出现胶内有气泡的现象。我国行业标准 YY 0314-2007《一次性使用人体静脉血样采集容器》未对真空采血管分离胶内气泡进行规定，WS/T 224-2018《真空采血管的性能验证》中仅提及真空采血管分离胶胶体应呈凝胶状，也未对胶内无气泡提出要求。在实际工作中，真空采血管分离胶内偶尔会出现气泡，当使用这些有气泡的促凝管采血并进行常规生化项目检测时，其检测结果是否受影响尚未见有报道。为此，本研究拟探讨促凝管分离胶气泡对 9 项生化常规指标检测结果的影响，为临床使用和相关标准的修订提供参考。

1 材料和方法

1.1 仪器和试剂

将含 T 分离胶的促凝管简称为 T 管（5 mL，13 mm/100 mm，批号 180606；其中有气泡的促凝管简称为 $T_{有}$，气泡直径为 2 ~ 3 mm，数量为 4 ~ 5 个；无气泡的简称为 $T_{无}$；分离胶含量均为 8.49 g），含 G 分离胶的促凝管简称 G 管（5 mL，13 mm/100 mm，批号 180606；其中有气泡的促凝管简称为 $G_{有}$，气泡直径为 4 ~ 5 mm，数量为 3 ~ 4 个；无气泡的促凝管简称为 $G_{无}$；分离胶含量均为 8.48 g）。所有促凝管均购自广州阳普医疗科技股份有限公司，在有效期内使用。

1.2 方法

选取 22 名健康志愿者，其中男 16 名、女 6 名，年龄 18 ~ 44 岁，分成 6 批，每批 3 ~ 4 名，完成采血。采血时，受检者取坐位，使用 20 G 蝶翼针采集所有对象肘前静脉血，以随机顺序置于 4 支采血管（$T_{有}$、$T_{无}$、$G_{有}$、$G_{无}$）中。所有采血步骤都严格按标准[4]执行；使用同批次采血管和采血针，所有对象均无采血不畅的情况。标本在室温下放置 30 min 促进凝固，室温下 1710 × g 离心 10 min，分离血清，4 h 内直接上机检测。每批标本同时采用 BS 2000M 全自动生化分析仪（深圳迈瑞公司）及配套试剂检测以下项目：丙氨酸氨基转移酶（alanine aminotransferase，ALT）、天门冬氨酸氨基转移酶（aspartateaminotransferase，AST）、钾离子（potassiumion，K^+）、肌酸激酶（creatine kinase，CK）、乳酸脱氢酶（lactate dehydrogenase，LDH）、α- 羟丁酸脱氢酶（hydroxybutyrate dehydrogenase，HBDH）、同型半胱氨酸（homocysteine，Hcy）、乳酸、CO_2。

1.3 统计学方法

采用 SPSS 21.0 软件进行统计分析。组间比较采用配对 t 检验。以 $p < 0.05$ 为差异有统计学意义。偏移以不高于 WS/T 403-2012《临床生物化学检验常规项目分析质量指标》规定的允许总误差（allowable total error，TEa）的 1/2 为可接受。

2 结果

$T_{有}$与 $T_{无}$之间 CO_2 和乳酸差异有统计学意义（$p < 0.05$），偏移分别为 0.92%和 2.31%；$G_{有}$与 $G_{无}$之间 K^+和乳酸差异有统计学意义（$p < 0.05$），偏移分别为 1.37%和 1.53%；以上项目的偏移均在临床可接受范围内。其他项目各管之间差异均无统计学意义（$p > 0.05$）。见表 1。

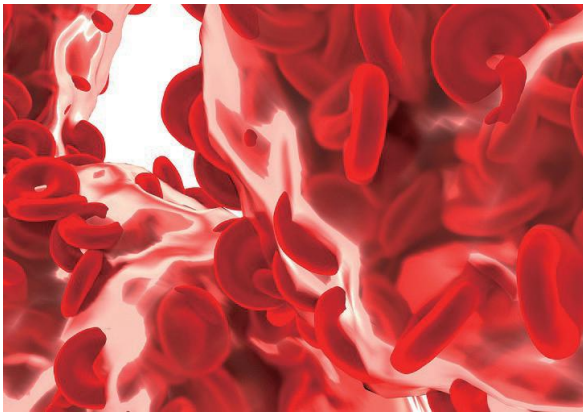

表 1. 有或无气泡的分促管 9 项生化指标检测结果比较（x ± s）

促凝管	例数	K^+（mmol/L）	CO_2（mmol/L）	CK（IU/L）	LDH（IU/L）
$T_{有}$	22	3.93 ± 0.04	26.33 ± 0.47	125.74 ± 6.06	157.75 ± 25.61
$T_{无}$	22	3.93 ± 0.04	26.08 ± 0.43	125.44 ± 6.01	158.22 ± 26.06
$G_{有}$	22	4.00 ± 0.05	26.61 ± 0.46	126.25 ± 6.09	159.54 ± 25.84
$G_{无}$	22	3.94 ± 0.04	26.44 ± 0.48	126.02 ± 6.03	157.60 ± 25.07

促凝管	HBDH（IU/L）	ALT（IU/L）	AST（IU/L）	Hcy（μmol/L）	乳酸（mmol/L）
$T_{有}$	127.71 ± 4.62	27.79 ± 4.99	19.42 ± 0.99	10.53 ± 0.41	2.20 ± 0.10
$T_{无}$	127.29 ± 4.81	27.92 ± 4.93	19.46 ± 1.02	10.54 ± 0.42	2.15 ± 0.10
$G_{有}$	132.04 ± 5.62	27.92 ± 4.97	19.17 ± 1.11	10.44 ± 0.41	2.24 ± 0.12
$G_{无}$	129.33 ± 5.00	27.96 ± 4.95	19.21 ± 1.04	10.49 ± 0.41	2.21 ± 0.11

注：与 $T_{有}$比较，*$p < 0.05$；与 $G_{有}$比较，#$p < 0.05$

3 讨论

在血液标本离心的过程中，在离心力作用下，促凝管中的分离胶与纤维蛋白网包裹的血块做相对运动，胶内气泡会接触到血块中的血细胞，若气泡突然破裂，血细胞会受不同程度的冲击，有些红细胞可能会破裂，从而出现溶血现象。有研究结果显示，分离胶促凝管的溶血率 < 1%[5]，但一旦发生溶血，其对临床生化检测的影响很大[6]。为此，本研究探讨了促凝管分离胶中有无气泡对临床生化检测的影响。

本研究结果显示，ALT、AST、CK、LDH、HBDH、Hcy 不管 T 胶还是 G 胶均无明显影响，而对于 K^+、CO_2 和乳酸，使用的分离胶不同，受影响的程度也不同。这可能是因为不同分离胶的主要基材及相关物理特性参数不同。T 胶是全烯烃类聚合物，具有较好的疏水性，其黏度较大，这可能会导致气泡在胶中存在的时间较长且数量较多。在标本离心过程中，分离胶与血块发生相对运动，会导致气泡内的气体释放，从而引起 CO_2 含量增加，本研究结果显示，CO_2 的检测结果产生了正偏移（0.92%），但偏移在临床可接受范围（ < ±10%）内，因此可以忽略 T 胶内气泡对 CO_2 检测的影响。G 胶是丙烯酸酯类聚合物，其黏度较 T 胶低，气泡易消除。该种分离胶内的 CO_2 气体易释放，因此 G 胶内残留的 CO_2 含量少于 T 胶，这与本研究的结果一致。因此，可以忽略分离胶内的气泡对 CO_2 检测的影响。

本研究结果显示，有气泡的 G 胶对 K^+的检测产生了明显影响，而 T 胶对 K^+的检测无明显影响，原因可能是有气泡的 G 胶与血块做相对运动时的速度相对 T 胶快，G 胶内气泡快速破裂导致红细胞破裂释放 K^+所致，因红细胞内的 K^+浓度是血清中的 20 多倍，导致 K^+显著升高。本研究结果显示，K^+检测产生的正偏移（1.37%）在临床可接受（ < ±3%）的范围内。因此，可以忽略分离胶内的气泡对 K^+检测的影响。

本研究结果显示，不管是有气泡的 T 胶还是 G 胶均会对乳酸的检测结果产生影响（$p < 0.05$），其结果产生了正偏移（2.31%、1.53%），但均在临床可接受范围（ < ±5%）内。这可能与本研究从血液离体到分离血清有 40 min，在无氧状态下糖酵解[7]发生相关。有气泡的分离胶促凝管血清 CO_2 含量略高于无气泡分离胶促凝管，表明有气泡的分离胶促凝管中血液的无氧代谢状态相对活跃，导致乳酸轻度增高[8]。

综上所述，促凝管中分离胶内的气泡对临床生化检测项目无明显影响，检测结果的偏移均在临床可接受范围内。由于实验条件所限，本研究的对象皆为健康者，在病理状态下血清 K^+、CO_2、乳酸的变化可能会放大至临床不可接受，尤其对于红细胞脆性大、易破裂者的血液样本的情况仍需进一步研究。这些研究可以帮助实验室建立分离胶促凝管的产品标准和拒收标准，保证分离胶促凝管的产品质量，进而保证临床检验分析结果的准确性和稳定性。

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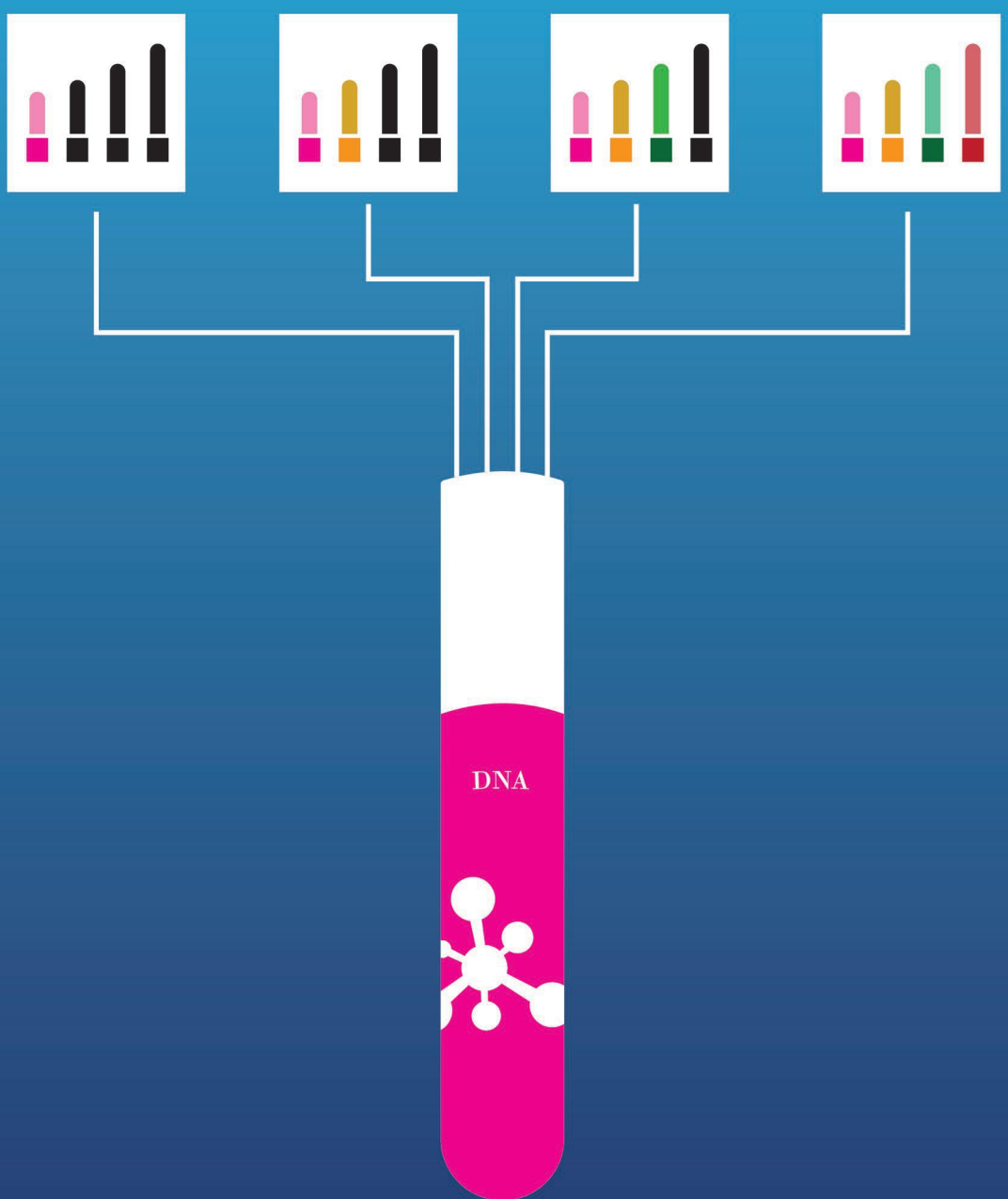

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