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Impact of extracorporeal circuits on systemic drug levels – A scoping review

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Abstract

Background: This scoping review explores the potential effects of various extracorporeal technologies on the clearance of commonly used drugs. Understanding these interactions is essential for ensuring patient safety and treatment effectiveness.

Methods and Results: A comprehensive search was performed including the PubMed, Cochrane and clinicaltrials.gov databases, with additional searches of relevant reference lists. Specific keywords relating to drug removal, therapeutic drug monitoring, and individual extracorporeal circuit platforms were used including drug removal / drug elimination / drug levels AND Continuous Renal Replacement Therapy (CRRT) or Extracorporeal Membrane Oxygenation (ECMO) or Therapeutic Plasma Exchange (TPE) or Molecular Adsorbent Recirculating Systems (MARS) or CytoSorb. CytoSorb was chosen as the representative hemoadsorption platform due to it having by far the most publications on this topic. In total 2231 articles were found with 300 included in the final review. Ten articles clearly reported removal by more than one platform so were included twice. The impact on drug levels was discussed for 157 different drugs with several publications including more than one drug. Most evidence was found for CytoSorb (158 publications / 72 drugs) followed by ECMO (112 publications / 55 drugs). The majority of data came from single case reports (126 articles), and case series (100 articles) with 68% (203) reporting on unwanted removal of therapeutic drugs.

Conclusion: The potential for drug removal by various extracorporeal therapies in critical care is an important topic worthy of serious consideration. Available evidence to support informed decision making is limited and further research to advance the current evidence base is urgently needed. Therapeutic drug monitoring remains recommended to support clinical decision-making to enhance patient safety when using such technologies.

WORD COUNT 272 / 350

Keywords: Extracorporeal therapy; hemoadsorption; blood purification; therapeutic drug monitoring; drug removal; TPE; ECMO

Background

Extracorporeal therapies (ECT) including continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), therapeutic plasma exchange (TPE), albumin dialysis including the molecular adsorbent recirculating system (MARS) and hemoadsorption (HA) devices are widely used in managing critically ill patients (1). The potential interaction between these therapies and concurrently administered medications is of significant clinical importance. While platforms may be used to remove excess levels of a drug, for e.g. in acute poisonings (2, 3), it has been shown that they can also alter therapeutic drug levels (4-6) which might put critically ill patients at risk of under-dosing due to inadvertent, unwanted removal (7).

CRRT, arguably the most frequently used extracorporeal platform in clinical practice, is routinely used to manage volume overload, eliminate metabolic waste, and maintain electrolyte balance in patients with renal failure (8). However, maintaining effective pharmacological regimens for patients undergoing CRRT is challenging due to the many variations in dialysis treatments, lack of dedicated pharmacokinetic (PK) studies defining the impact on systemic drug levels, and the frequent omission of therapeutic drug monitoring (TDM) (9).

ECMO is increasingly utilized as a life-saving intervention for severe acute respiratory distress syndrome (ARDS) and severe circulatory failure (10). Currently, there is limited information on the extent to which ECMO influences systemic drug levels, but initial reports indicate that ECMO may impact antibiotic levels (11, 12). As of now, there is a lack of evidence-based guidance on whether specific dosing adjustments should be considered for critically ill patients on ECMO (13).

TPE is an extracorporeal procedure whereby plasma is separated from the other blood components and discarded, while remaining components are returned to the patient occasionally accompanied by replacement fluids, such as albumin or fresh-frozen plasma. Clinically, TPE is employed to eliminate harmful substances in the plasma, including pathogenic antibodies such as in autoimmune diseases (14). Along with the use of TPE in the fields of sepsis (15) and liver failure (16), its use is becoming increasingly prevalent in neuro-intensive care, given the established role of autoimmunity in various acute neurological conditions (17). However, it is important to recognize that TPE may also remove drugs (18).

Albumin dialysis techniques are intended to treat patients with liver failure, particularly in situations where the liver can no longer perform its essential functions, such as detoxifying the blood and metabolizing drugs (19, 20). MARS is used through a circuit containing a special dialyzer and albumin to clear both water-soluble and protein-bound toxins from the blood through a process of filtration and adsorption.

Regarding HA therapy, the most commonly used device with the most available data is the CytoSorb (CS) cartridge (21). CS is a biocompatible HA cartridge filled with sorbent beads primarily binding hydrophobic substances with a size-selective capacity for molecules up to approximately 60 kDa. The device is approved for use in critically ill patients with high cytokine levels due to conditions such as sepsis, cytokine storm syndrome, and other hyperinflammatory disorders (22). It has also shown potential in treating critical conditions linked to cardiac surgery (23), trauma (24), rhabdomyolysis (25), liver dysfunction (26) and ARDS (27).

A significant gap persists, however, in our understanding of the removal dynamics for a broader spectrum of drugs during ECTs which was the rationale for our review. Therefore, the objective of this scoping review was to present a thorough analysis of the available data on drug removal by extracorporeal therapies, comparing the published knowledge for the different platforms and potential effects on the safety profile of these treatments and thereby raising awareness for a potentially overlooked problem.

Methods

This review was conducted as a comprehensive scoping literature review followed PRISMA-ScR guidance, but without structured risk-of-bias assessment. A search of the National Library of Medicine PubMed database (https://pubmed.ncbi.nlm.nih.gov/) was performed on 2nd Dec 2025 using the key search words listed below. The same search was done in Clinicaltrials.gov (https://clinicaltrials.gov/), Cochrane (https://www.cochranelibrary.com/) with additional searches including reference lists from obtained articles. Key search terms included separate searches for the following: (drug removal or drug elimination or drug levels) AND (Continuous Renal Replacement Therapy or Extracorporeal Membrane Oxygenation or Therapeutic Plasma Exchange or Molecular Adsorbent Recirculating Systems or CytoSorb). Finally, a scan of the CytoSorbents online literature database (www.cytosorbents.com/lit-db) was done. Where identified, referenced congress and supplement abstracts were included if they contained relevant information. All abstracts were reviewed by two researchers, and where there were discrepancies a third opinion was sought.

From the initial findings articles were excluded due to the following reasons: duplicates, off topic (i.e. no information provided regarding drug removal), no original data (including reviews) and non-English language. In the second round of analysis, all articles considered initially that included more than one ECT platform were then excluded if the impact of the differing therapies on the drug levels was not clearly distinguishable between the platforms. Articles were screened for when drug removal was wanted (e.g. in overdose scenarios) as opposed to unwanted (e.g removal of therapeutic drugs as side effect of ECT). In this

review, the term ‘drug removal’ is used as a general umbrella term, while specific mechanisms such as clearance, adsorption, or sequestration are distinguished where appropriate.

Results

In total 300 articles were included after the two review rounds (see Figure 1). Studies ranged from in-vitro to randomized controlled trials (see Table 1). Due to studies including more than one drug, these were counted more than once (total publications 431, see Table 2). Also, 10 articles clearly published data on drug removal in more than one platform so were included twice where relevant. Evidence of removal was found for 157 different drugs in these publications, with most evidence found for antibiotics (175 publications for 40 different antibiotics, see Supplementary Table 1). In total 4146 patients were included in all clinical studies. ECMO studies included the most patients (1776), followed by CRRT (1307), whereas CS had the most publications (158), on the biggest range of drugs (72) – see Tables 1 and 2.

In total, 78% of CRRT, 97% of ECMO, 56% of TPE, 50% of MARS and 40% of CS publications reported on the unwanted removal of a particular drug (see Table 1). Not surprisingly, all evidence for anti-infective removal was unwanted rather than deliberate removal (supplemental Table 2). The most published data was for the unwanted removal of vancomycin and meropenem.

Conversely, 60% of the CS publications and 50% of MARS publications reported on the deliberate removal of a particular drug, either due to iatrogenic intoxication or deliberate overdose situations (see Table 1). In the case of CS, the majority of these publications focused on removal of antiplatelet drugs, particularly intraoperatively in cardiac surgery, to reduce bleeding risks.

Insert Figure 1 here: Overview of results of literature search.

Insert Table 1 here: Details of Quality of Evidence of Included Studies

Insert Table 2 here: Details of all drug types and number of publications per platform (some publications are included more than once as they report on multiple drugs).

Discussion

This scoping review summarizes the number of studies looking at the impact of extracorporeal therapies on concomitant pharmacotherapy in the intensive care setting. Therapeutic interventions such as TPE, CRRT, MARS, and HA with CS play significant roles in drug removal, both as therapeutic approaches and as potential sources of unintended

drug elimination. Understanding how different extracorporeal platforms affect systemic drug levels is essential to ensure that adequate pharmacological coverage is maintained during extracorporeal treatments.

Among the investigated drugs, antibiotics seem to emerge as a major focus within this field. This is also one of the drug classes where unintended subtherapeutic exposure is clinically consequential, reinforcing the need for therapeutic drug monitoring and individualized dosing. Similarly, immunosuppressants represent a critical drug class in which inadequate exposure can lead to graft rejection, while excessive exposure increases the risk of severe toxicity and infections. Their narrow therapeutic windows and high interindividual pharmacokinetic variability further underscore the importance of precise dosing strategies and close concentration monitoring. In both drug classes, therapeutic drug monitoring serves as a key tool to guide dose adjustments, optimize efficacy, and minimize the risk of adverse outcomes.

While all extracorporeal therapies can significantly impact drug removal, their mechanisms and effects differ. ECMO may lead to altered pharmacokinetics primarily through circuit sequestration, TPE actively removes drugs alongside pathogenic substances, CRRT varies in its impact depending on multiple factors, MARS works via albumin binding and HA mainly influences hydrophobic substances. Because extracorporeal techniques act through different mechanisms, the terms sequestration, adsorption, and clearance should not be used interchangeably (28). In general, hydrophilic drugs are primarily affected by filtration or dialysis and lipophilic drugs more likely to be affected by adsorption or sequestration(29). Please refer to Figure 3 for schematic overview of drugs at risk for each platform based on their chemical properties.

For hydrophilic drugs the impact of CRRT is particularly relevant and drug clearance varies based on factors such as the mode of therapy (e.g., hemofiltration vs. hemodialysis), the drug's pharmacokinetic properties, and the rate of concomitant fluid removal (30, 31). Furthermore, augmented renal clearance is frequently observed in critically ill patients and may coexist with extracorporeal therapies, particularly during antibiotic treatment (32). In such patients, residual native renal clearance can add to extracorporeal clearance, increasing the risk of subtherapeutic exposure. This is clinically important because underdosing of anti-infective agents may be more harmful than overdosing in severe infection, and therapeutic drug monitoring should be considered whenever feasible to guide dose optimization (32). Reductions in drug levels by membrane filtration as well as through sticking to surfaces and tubes is a widely underestimated topic (33). It can lead to increased clearance of certain medications. The variability in drug removal clearance necessitates individualized dosing regimens and close therapeutic drug monitoring, as standard dosing may not apply to patients on CRRT.

TPE is known to effectively remove both pathogenic antibodies and certain drugs from the circulation (34, 35). While TPE can be beneficial for clearing harmful substances, it may also lead to subtherapeutic levels of essential medications, necessitating careful monitoring and potential dose adjustments. The extent of drug removal can vary depending on the drug's molecular weight and binding characteristics.

Lipophilic drugs may primarily be affected by sequestration by ECMO or adsorption by MARS or CS. Studies suggest that ECMO can alter the pharmacokinetics of certain drugs, often leading to lower serum concentrations (36, 37). This is particularly true for hydrophilic drugs that may be sequestered in the ECMO circuit, but there is limited consensus on specific dosing adjustments. There is a lack of robust guidelines on adjusting dosages for critically ill patients on ECMO. ECMO seems to play no role in intentional treatment of drug overdose.

Albumin dialysis, and more specifically the MARS system has also been explored for its role in removing drugs and drug metabolites from the blood, particularly in cases of drug overdose or toxicity (38, 39). MARS is particularly effective at adsorbing drugs that are highly protein-bound, such as certain anticonvulsants, antiarrhythmics, and other medications. These drugs can be difficult to clear from the bloodstream using conventional dialysis, as they bind to proteins like albumin.

When compared to other hemoadsorption technologies, CS is the most frequently studied, which likely reflects differences in research activity and availability of experimental models, but also providing a clear understanding of its benefits and risks and (22, 40, 41). However, the marked predominance of CS-related publications raises the possibility of publication imbalance and industry-driven research focus, which should be considered when interpreting the apparent weight of evidence for this platform. CS is an effective tool for reducing cytokines and other mediators in inflammatory conditions, but as with all other HA devices, it may also inadvertently remove therapeutic drugs, which requires appropriate management to avoid adverse effects or treatment failure (40, 42). This is particularly relevant for hydrophobic, non-dialyzable substances (43). Available data suggest that CS can influence pharmacokinetics, particularly early after CS start, when adsorption may be greatest (44). However, measured changes in drug concentrations do not necessarily translate into uniform or persistent clinical impact throughout treatment, as adsorption is time-dependent and may decrease as cartridge saturation occurs (44). Therefore, interpretation of data should consider the temporal course of therapy rather than assuming constant adsorption over the entire treatment period. Also, most evidence is derived from in-vitro studies, case reports, and small observational series, limiting clinical predictability. This is especially relevant for life-saving medications such as antibiotics and immunosuppressants, where maintaining therapeutic levels is crucial (45, 46). CS may also

be advantageous regarding intended drug adsorption in overdose situations, or, for e.g. antithrombotic removal in cases of active bleeding or where an operation is imminent (47, 48).

Furthermore, drug exposure in critically ill patients is determined by the interaction of patient-related, drug-related, and technique-related factors (see Figure 2). Therefore, extracorporeal device effects should not be interpreted in isolation, but rather as one component of a broader, individualized dosing framework (36, 49).

Knowledge gaps

Despite a growing body of literature, significant knowledge gaps remain regarding the impact of extracorporeal therapies on drug exposure in critically ill patients. Most available data are derived from in-vitro experiments, case reports, or small observational studies, limiting their generalizability to clinical practice. In particular, robust evidence linking pharmacokinetic alterations to meaningful clinical outcomes is lacking. Furthermore, heterogeneity in extracorporeal techniques, study designs, and reporting standards complicates comparisons across studies and prevents the development of standardized dosing recommendations.

Implications for practice

Pharmacotherapy is of utmost importance in intensive care medicine and considering unintentional removal of drugs in critically ill patients is vital when employing extracorporeal therapies (50). Correct dosing is especially crucial for potentially life-saving medications like antibiotics or immunosuppressants. A crucial aspect to consider in drug removal by extracorporeal circuits is the differentiation between wanted and unwanted drug removal. While the elimination of certain drugs may be therapeutically desirable, unintended removal of essential medications can lead to adverse clinical outcomes. Depending on the clinical context, these effects may be leveraged, for instance, by using drug removal to mitigate toxicity. On the other hand, necessary dosing adjustments should be considered whenever starting an extracorporeal circuit and TDM should be performed whenever feasible to ensure adequate drug dosing especially for drugs not titrated according to clinical effect such as anti-infectives or immunosuppressants. Importantly, loading doses should generally not be reduced solely on the basis of renal replacement therapy, because the initial dose is primarily driven by volume of distribution rather than clearance (51). For time-dependent antibiotics, achieving PK/PD targets may require higher maintenance dosing, particularly during high-intensity CRRT, and therapeutic drug monitoring should be used whenever available to support individualized dosing. For detailed dosing guidance and clinical decision-making during CS therapy, readers are referred to already published dedicated reviews (40, 41).

Implications for future research

Future research should focus on generating high-quality, prospective clinical data to better characterize the pharmacokinetic and pharmacodynamic effects of extracorporeal therapies. Standardized studies, including detailed reporting of device settings and patient characteristics, are essential to improve comparability across studies. Additionally, investigations should aim to define clear dosing strategies for commonly used drugs, particularly antibiotics and immunosuppressants, and to evaluate the role of therapeutic drug monitoring in optimizing treatment. Greater emphasis on clinical outcomes will be crucial to translate pharmacokinetic findings into evidence-based recommendations for patient care.

Limitations

This is, to the best of our knowledge the first detailed review of published data on the impact of extracorporeal therapies on drug levels in critically ill patients. This scoping review followed PRISMA-ScR guidance but was not registered and did not include formal risk-of-bias assessment. Another limitation is the grouping of targeted unspecific adsorbers (e.g., CytoSorb) with broader extracorporeal therapies (CRRT, ECMO, TPE), despite their differing primary mechanisms and therapeutic goals, potentially oversimplifying heterogeneous adsorption dynamics. Furthermore, our scoping review may not encompass all relevant studies, as it focused on specific search terms, which might have benefited some platforms over others and potentially led to some important literature being overlooked. Also, included studies vary in type and quality. Benchtop experimental or in-vitro results may not necessarily translate to in-vivo situations. Other extracorporeal devices and other hemoadsorption devices were not included in the analysis as this would have gone beyond the scope of this work but have recently been published elsewhere (6). The intent of this review was to raise awareness on the importance and complexity of concomitant drug administration during the use of extracorporeal therapies and stimulate interest in further evidence generation so appropriate dosing guidelines can be created that ensure patient safety in the intensive care setting.

Conclusion

In conclusion, the potential for drug removal by extracorporeal therapies in the critical care setting is an important topic worthy of serious consideration. Most data derive from case reports, case series, and other low-level evidence, so further research to advance the current evidence base is urgently needed. Until then, therapeutic drug monitoring remains an important strategy to support clinical decision-making to enhance patient safety when using such technologies.

List of Abbreviations

ARDS Acute respiratory distress syndrome

CRRT Continuous renal replacement therapy

CS CytoSorb

ECMO Extracorporeal membrane oxygenation

ECT Extracorporeal therapies

HA hemoadsorption

kDa Kilo Dalton

MARS Molecular adsorbent recirculating systems

PK Pharmacokinetic

TDM Therapeutic Drug Monitoring

TPE Therapeutic plasma exchange

Declarations

Ethics Approval: Due to the nature of the study (review of already published data), ethics approval was deemed unnecessary.

Consent for publication: Not applicable

Availability of Data and Materials: Data are available from the corresponding author upon reasonable request.

Competing Interests: PMH has received grants for CytoSorbents. HA and TK are full-time employees of CytoSorbents Europe GmbH. All other authors declare no conflict of interest.

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Figure 1. Overview of results of literature search.

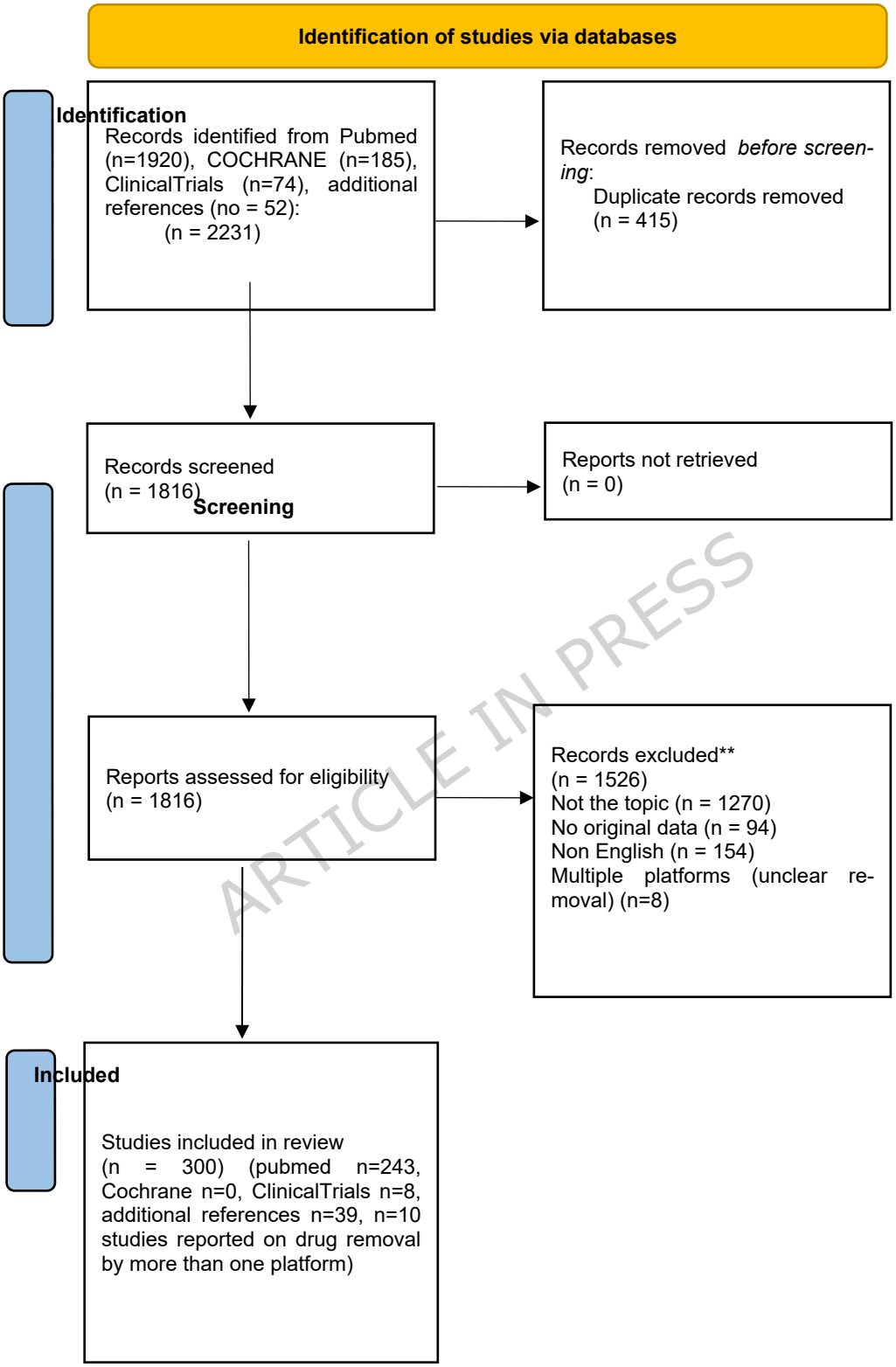

Figure 2. Framework of influential factors of drug exposure in extracorporeal therapy

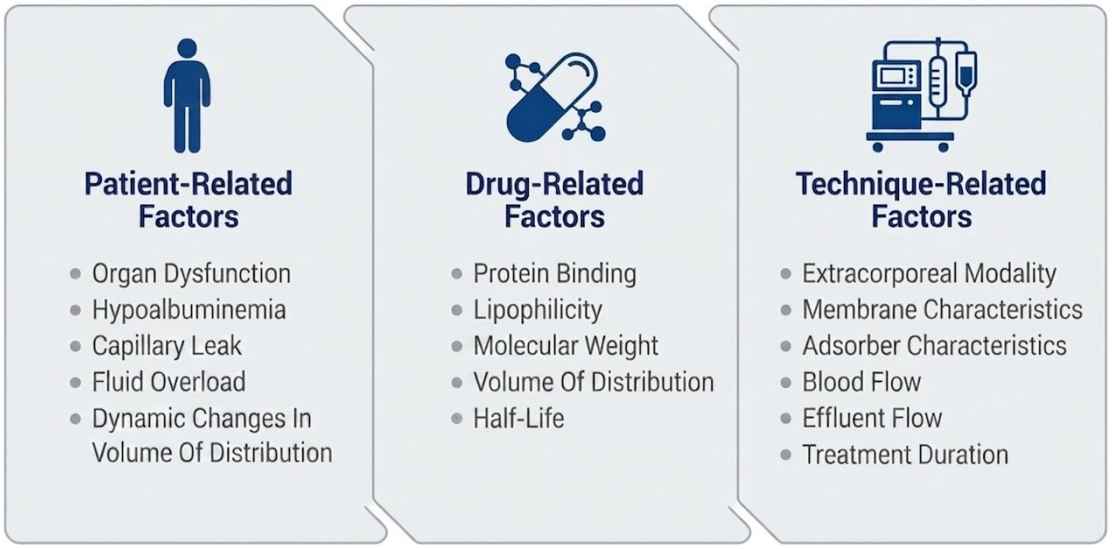

Figure 3. Susceptibility for removal by extracorporeal therapies according to key physiochemical properties

Please note: this figure provides a general overview of drugs at high susceptibility for respective extracorporeal removal and does not exclude the possibility of removal of other drugs.

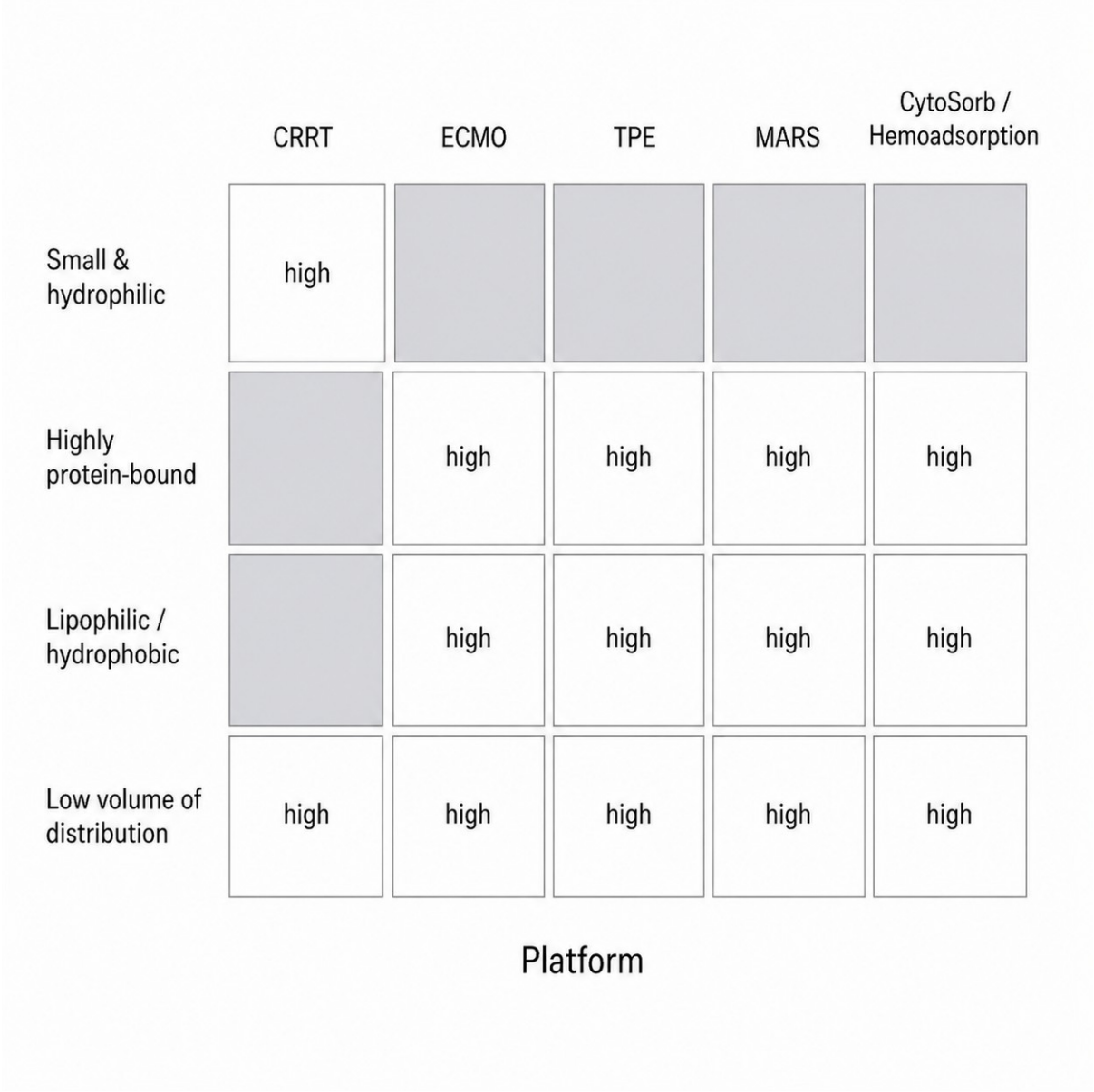

Table 1. Details of Quality of Evidence of Included Studies

	Total	RCT	Prospect-ive Co-hort	Retrospect-ive Cohort	Case Series	Case Study	An-imal	In-vitro	Wanted Re-moval	Un-wanted Re-moval	No of Pts
CRRT	68	0	6	2	29	19	2	10	11	53	1307
ECMO	78	2	4	8	37	13	2	12	0	76	1776
TPE	68	0	1	0	11	54	1	1	30	38	199
CytoSorb	74	1	0	4	18	34	3	14	44	30	843
MARS	12	0	0	0	5	6	1	0	5	6	21
Total	300	3	11	14	100	126	9	37	90	203	4146

Legend CRRT: Continuous Renal Replacement Therapy; ECMO: Extracorporeal Membrane Oxygenation; TPE: Therapeutic Plasma Exchange; RCT: Randomized Control Trial

Table 2. Details of all drug types and number of publications per platform (some publications are included more than once as they report on multiple drugs and also for multiple platforms).

Drug Type	Total No of Drugs/ Publications	CRRT	ECMO	TPE	MARS	CytoSorb
Antibiotics	40/175	21/56	22/47	8/10	1/2	19/48
Anticoagulation/Antithrombotic	12/53	2/2	0	5/6	0	7/53
Antiepileptic	7/27	4/7	2/3	6/11	1/1	4/5
Antifungal	9/37	6/7	7/20	2/2	1/1	6/7
Antituberculosis	4/4	0	4/4	0	0	0
Antiviral	10/15	4/5	5/6	1 / 2	0	2/2
Cardiovascular	20/38	3/4	2/2	6/10	6/8	11/14
Immunosuppressants	12/27	1/1	1/1	5/7	1/1	9/17
Psychiatric	9/23	2/4	1/1	3/5	0	7/13
Sedatives and Analgesics	13/31	2/2	9/16	5/7	3/3	3/3
Other	21/19	3/3	1/1	8/10	1/1	4/4
TOTAL	**157/449**	**48/112**	**55/71**	**49/71**	**14/17**	**72/158**

Legend CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; TPE: therapeutic plasma exchange; MARS: molecular adsorption recirculating system