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Artificial Liver Assist Devices for the Treatment of Liver Failure

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Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

This medical policy has become inactive as of the end date above. See medical policy ADM1001.028 for dates of service 01/01/2026 and after.

Artificial liver assist devices, including extracorporeal bioartificial liver systems **are considered experimental, investigational and/or unproven** to treat chronic liver failure or to provide a bridge to liver transplantation.

NOTE 1: Use of an artificial liver assist device includes, but is not limited to, oversight care and monitoring of device functioning, and required patient care services.

NOTE 2: This policy does not address treatment of acute drug overdose and poisoning.

Policy Guidelines

None.

Description

Liver failure results from the loss of liver function and is associated with a high-risk of mortality. For those requiring long-term therapeutic options for liver failure, liver transplantation may be the only solution; however, the number of patients who need a liver transplant exceeds the number of donor organs available.

Background

To temporarily support a failing liver or as a bridge to liver transplantation, an artificial liver assist device may be utilized. There are two types of extracorporeal liver support devices: artificial liver support (ALS) and bioartificial liver support (BLS).

Artificial livers are designed to filter toxins caused by illness, alcohol, poisons or drugs, from the blood and function similarly to kidney dialysis. (1, 8) These devices often use the same dialysis platform, sorbent-based, with additional modular components and filters. The most advanced liver systems use albumin-based filtration, which removes both protein-bound and water-soluble toxins from the circulating blood. These systems tend to be inadequate for extended long-term use.

ALS devices are cell-free and improves biochemical parameters of liver failure by the simultaneous removal of protein-bound and water-soluble substances. BLS devices are cell-based, extracorporeal devices that detoxify and synthesize proteins and metabolites in the circulating blood. (2, 8) The BLS device utilizes liver cells or hepatocytes from either hepatoblastoma cell lines or porcine livers, and a combination of physical and chemical procedures. Dependent on the BLS device design, the hepatocytes may or may not have direct contact with the patient's circulating blood. BLS treatment is considered temporary while the patient is awaiting a compatible donor liver or to help the liver regenerate spontaneously. They can be used up to 30 days.

Clinical trials have reported that the most common adverse event associated with extracorporeal liver support system (ELSS) treatment is transient hypotension. (8) Graft rejection, bleeding, renal failure, thrombocytopenia, sepsis, cardiac arrhythmias, and hypoxia were also associated with the clinical trials and utilization of these devices.

Regulatory Status

Currently there are no ELSSs that have received U.S. marketing approval from the Food and Drug Administration (FDA). These systems may be available only in the context of clinical trials or compassionate use.

Extracorporeal Liver Assist Device® (ELAD®) by Vital Therapies, Inc. (San Diego, CA) has been granted orphan drug designation for immortalized human liver cells used in the ELAD® system for treating acute liver failure, by the FDA in 2004. (5) This designation is intended to provide

financial incentives for developing products to treat rare disease, but it is not equivalent to a marketing approval or clearance.

In 2002, the FDA granted Excorp Medical Inc., (Hong Kong, China) orphan drug designation for its xenogeneic (involving cells or tissues from different species, such as animal to human) hepatocytes used for the hollow fiber bioreactor within the Bioartificial Liver Support System® (BLSS®). (4) As with ELAD®, this designation is not equivalent to a marketing approval or clearance.

One potential competing technology for BLS is the artificial liver. Liver dialysis systems still under clinical evaluation include the Molecular Adsorbents Recirculation System® (MARS®) by Gambro (6) and the Prometheus® system by Fresenius Medical Care; Bad Homburg, German. (7, 8) MARS® has been cleared by the FDA to treat drug overdose and poisoning, but it is not cleared as a BLS. (8)

Rationale

This policy was developed in January 2016 based on PubMed literature review. The key literature summarized below covers the search through January 24, 2024.

Available Literature Review
Clinical trials that provide preliminary results of primary endpoints are shown in Table 1.

Table 1: Completed Clinical Trials with Reported Results

Study	Patient Population	Intervention	Primary Outcome
Thompson et al. (2018) (14)	203 patients with severe alcoholic hepatitis (sAH)	ELAD treatment (n=96) compared with standard of care (n=107) at 40 sites worldwide	The primary objective of the study was to evaluate safety and efficacy of ELAD with respect to overall survival (OS) up to at least study day 91. The secondary objectives were to evaluate the proportion of survivors at study days 28 and 91. Adults with sAH, bilirubin ≥8 mg/dL, Maddrey's discriminant function ≥ 32, and Model for End-Stage Liver Disease (MELD) score ≤ 35 were randomized to receive standard of care (SOC) only or 3-5 days of continuous ELAD treatment plus SOC. After a minimum follow-up of 91 days, OS was assessed by using a Kaplan-Meier survival analysis.

			In an analysis of the intent-to-treat population, there was no difference in OS (51.0% versus 49.5%). The study failed its primary and secondary end point in a population with sAH and with a MELD ranging from 18 to 35 and no upper age limit. In the prespecified analysis of subjects with MELD < 28 (n = 120), ELAD was associated with a trend toward higher OS at 91 days (68.6% versus 53.6%; P = .08).
Bañares et al. (2013) (15)	156 patients with ACLF	Randomized either to MARS (n=95) or to standard therapy (SMT) (n=94).	The main endpoint was 28-day intent to treat (ITT) and per-protocol (PP) survival. There were no significant differences at inclusion, although the proportion of patients with MELD score over 20 points and with spontaneous bacterial peritonitis (SBP) as a precipitating event was almost significantly greater in the MARS group. The 28-day survival was similar in the two groups in the ITT and PP populations (60.7% versus 58.9%; 60% versus 59.2% respectively). After adjusting for confounders, a significant beneficial effect of MARS on survival was not observed (odds ratio [OR]: 0.87, 95% confidence interval [CI] 0.44-1.72).
Hillebrand et al. (2010) (16)	18 patients with acute chronic liver failure (acute decompensation of cirrhosis)	Standard medical treatment plus ELAD® treatment (n=14) compared to standard medical treatment alone (n=4)	Transplant free and overall survival was measured at 30 and 90 days. More patients achieved 30-day transplant free survival in the standard medical treatment plus ELAD® group/test group (23%) versus standard medical treatment/control group alone (0%). There was no difference in 30-day overall survival (standard medical treatment + ELAD® 46% versus controls 50%). The 90-day overall survival was improved for the test group (39%) versus the control group (25%) as was the 90-day transplant free survival (test group 15% versus control group 0%). The rate of liver

			transplantation was higher for the control group 75%) versus the test group (23%).

ACLF: Acute-on-chronic liver failure; ELAD: extracorporeal cellular therapy; MARS: molecular adsorbent recirculating system; n: number.

In 2001, Sechser et al. reviewed the current literature at the time on artificial liver support (ALS) devices for fulminant liver failure to bridge patients until a suitable liver allograft was obtained or the patient's own liver regenerated sufficiently to resume normal function. (9) The momentum was to move from plasma exchange treatment and mechanical liver support devices that filtered toxins to more promising hybrid devices incorporating mechanical and biologic support systems, such as liver assist and extracorporeal devices. The authors' conclusion was hybrid systems appear to be the best option to date, but what type of tissue to use (human or porcine), how much of the liver tissue to use, and final, optimal device or system design to be used for patients with fulminant liver failure has yet to be determined.

In 2009, Frühauf et al. investigated the potential of primary porcine liver cells to transmit porcine endogenous retrovirus (PERV) to primary human cells in a bioreactor-based bioartifical liver (BAL). (10) The authors concluded that the risk of PERV infection in human cells is documented in the study, indicating that short-term contact of primary porcine liver cell supernatants with primary human cells could result in PERV transmission. The potential for viruses and other pathogens to pass from freshly harvested porcine cells from live animals to patients who receive the treatment remains a concern with the use of porcine-cell-based bioreactors in BLS systems. (10) Certain human cell lines used in BLS research were derived from hepatoblastoma, a rare liver tumor usually seen in infants and small children. (8) However, no clinical trial results suggested that these cells caused cancer in patients receiving BLS treatment, as the cells were reportedly contained within the bioreactor cartridge and did not enter the patient's bloodstream. (8)

A 2017 publication from the United Kingdom by Jain and Dhawan, appraised current practices using extracorporeal liver support systems (ELSS), which encompass both artificial and BAL devices, to treat pediatric liver failure. (11) According to the review results, these devices/systems are not widely accepted as routine therapy in adult liver failure and have not seen a benefit for utility in pediatric patients. The authors concluded that the results of recent multicenter trials using ALSs have shown some potential.

The following is a German 2017 review by Gerth et al. comparing ALS and BLS methods to treat acute liver failure. (12) Their review revealed there are no prospective randomized studies on the treatment of liver failure by intoxication; however there have been several case series reporting positive treatment effects using the MARS® therapies, particularly in mushroom poisoning or acetaminophen intoxication. The authors stated, "In acute liver failure (ALF) studies, the usage of BLS showed no survival advantage. Using ALS systems, a positive effect on mortality could be demonstrated in patient subgroups after several consecutive MARS® therapies. The first randomized controlled trial demonstrating a survival benefit used large-volume plasmapheresis. Apparently, immunomodulatory and hemodynamic effects of the

treatment play a crucial role in this context. In patients with acute-on-chronic liver failure (ACLF) accompanied by hyperbilirubinemia without any further organ failure (singular hepatic dysfunction), prognostic favorable effects by using a BLS system have been shown. However, once other extrahepatic organ systems are affected, indicating a progressive transition to multi-organ failure, a survival advantage could be achieved with the MARS® and Prometheus system. Decisive for a successful therapy is the exact indication of the respective liver dialysis procedure for this very heterogeneous disease. Future studies are needed to define more accurate patient selection criteria for each liver support."

In a review article from García Martínez and Bendjelid (2018), the reviewers evaluated artificial liver support systems over the past decade. (13) They noted that from the 1990s and onwards, several systems based on the concept of albumin dialysis have been developed, the best-known being the following: the Molecular Adsorbent Recirculating System™ (MARS™), the Single-Pass Albumin Dialysis system (SPAD) and the Fractionated Plasma Separation and Adsorption system–FPSA (Prometheus™). These devices remove the albumin-bound toxins that accumulate in liver failure and can also remove water-soluble substances, such as ammonia, creatinine or urea and smaller proteins such as some cytokines, by standard dialysis. The reviewers acknowledge that the precise roles of different cytokines in the pathophysiology of liver failure have not yet been fully elucidated; most of the published studies were retrospective and of an uncontrolled nature. The few randomized controlled trials (RCT) assessing survival presented conflicting results. The authors noted that trials included few patients suffering from acute on chronic liver failure (AoCLF) which was defined in a variable way according to each study. The reviewers concluded that there is a clear need for a liver support system to provide a "bridge" to a final treatment however, the survival benefit is still uncertain, given the scarcity of available results of RCTs. The reviewers note several factors could account for this uncertainty: liver failure patients constitute a heterogeneous population with severe multimorbidity; and there is no precise recommendation on the effective timing of the initiation of artificial liver support systems. In this regard, the reviewers indicated that future prospects of artificial liver support systems should rely on the completion of adequately powered RCTs addressing these crucial clinical issues and endpoints.

Summary of Evidence

To date, there have been few studies in peer-reviewed journals that support the efficacy of artificial liver assist devices or the effect on health outcomes. The available evidence includes clinical trials, review editorials, and product information. The completed clinical trials are few, with some having been terminated early or withdrawn. Devices and treatment protocols under investigation vary. Orphan drug designation allows for further clinical investigation. Currently there are no extracorporeal liver support systems that have received U.S. marketing approval from the Food and Drug Administration (FDA). MARS® has been cleared by the FDA to treat drug overdose and poisoning, but it is not cleared as a bioartificial liver support. Without concrete published scientific evidence, the use of these devices is considered experimental, investigational and/or unproven.

Practice Guidelines and Position Statements

In 2017 the American Gastroenterological Association (AGA) Institute provided guidelines for the diagnosis and management of acute liver failure. (3) Recommendation 9 is noted below:

Table 3: AGA Institute Guidelines for the Diagnosis and Management of Acute Liver Failure

Statement	Strength of Recommendation	Quality of Evidence
Recommendation 9: In patients presenting with ALF, the AGA recommends that extracorporeal artificial liver support systems only be used within the context of a clinical trial.	No recommendation	No recommendation

The authors further noted in the guidelines "When evaluating all of the data, there may be benefit to liver support systems in ALF, although the data are not robust enough to render a recommendation. Notably, the support systems also have significant potential toxicities, are costly, and demanding of resources." (3)

Ongoing and Completed Clinical Trials

A search of ClinicalTrials.gov in January 2024 yielded the following clinical trials:

Table 2: Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04597164	Combination of double plasma molecular adsorption system (DPMAS) and Low Volume plasma exchange (PE) for Patients With HBV Related Acute-on-Chronic Liver Failure (ACLF)	200	Sep 2023 (recruiting)
NCT05129904	Precise Profiling of Liver Disease Patients With DPMAS Therapy, Treating Optimal Patients and Achieving Hard Endpoint (PADSTONE Study) (PADSTONE)	1300	Dec 2024 (recruiting)
Unpublished			
NCT03882346	Study to Evaluate Safety and Efficacy of LifeLiver in Acute or Acute-on-Chronic Liver Failure Patients	40	Jun 2022 (status unknown)
NCT05035108	The Treatment of Bioartificial Liver With hiHep Cells After Extensive Hepatectomy	10	Dec 2021 (status unknown)

NCT: National Clinical Trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	99499
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/31/2025	Document became inactive.
03/15/2025	Reviewed. No changes.
03/15/2024	Document updated with literature review. Coverage unchanged. No new references were added.
03/15/2023	Reviewed. No changes.
07/01/2022	Document updated with literature review. Coverage unchanged. Reference number 3 was added; one reference removed.
06/15/2021	Reviewed. No changes.
05/15/2020	Document updated with literature review. Coverage unchanged. The following references were added: 4-6, 13-15.
10/15/2018	Reviewed. No changes.
11/15/2017	Document updated with literature review. Coverage unchanged.
11/01/2016	Reviewed. No changes.
01/01/2016	New medical document. Artificial liver assist devices, including extracorporeal bioartificial liver systems are considered experimental, investigational and/or unproven to treat chronic liver failure or to provide a bridge to liver transplantation. NOTE 1: Use of an artificial liver assist device

	includes, but is not limited to, oversight care and monitoring of device functioning, and required patient care services. NOTE 2: This policy does not address treatment of acute drug overdose and poisoning.