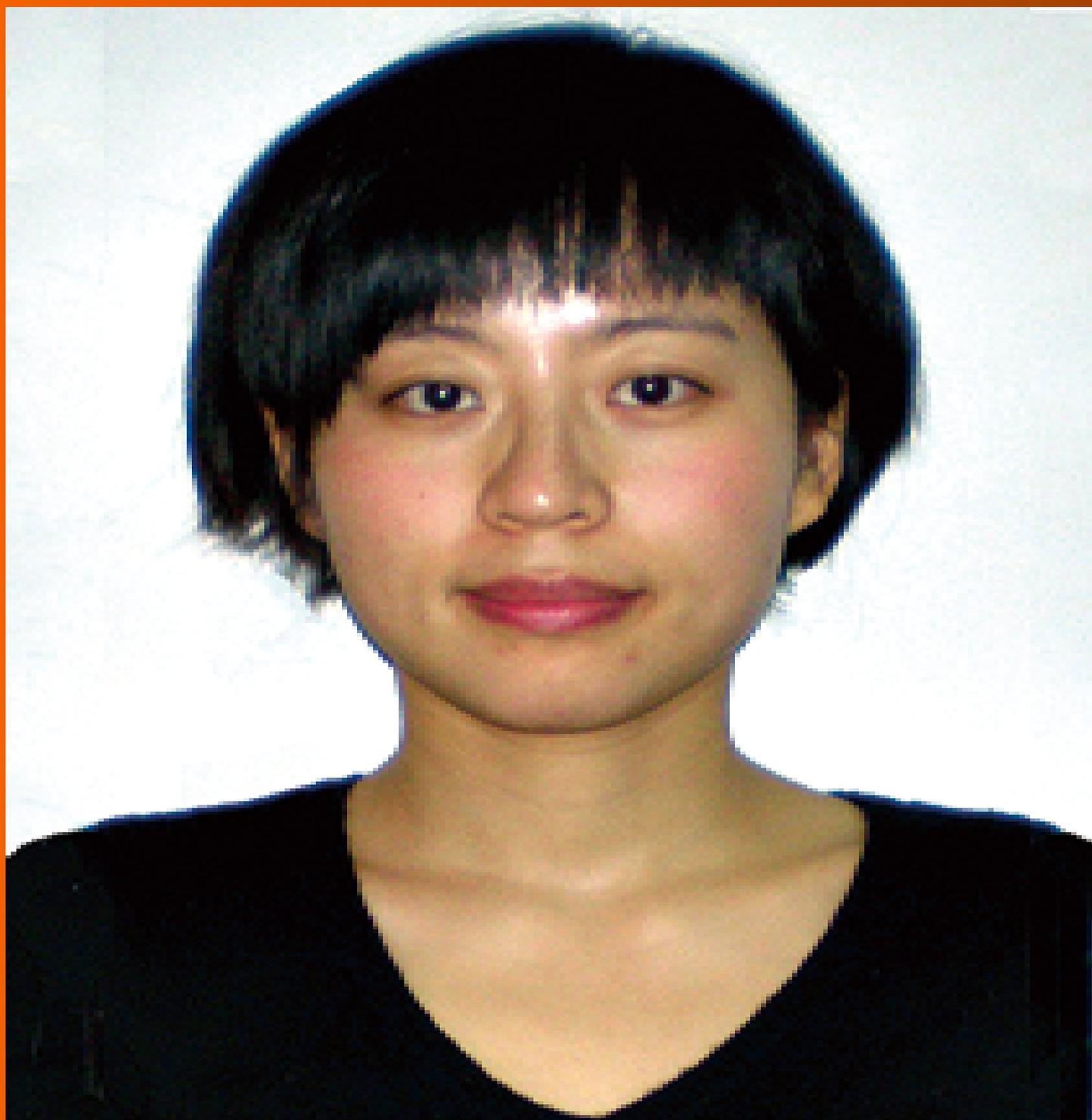


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Anticoagulation with direct thrombin inhibitors during extracorporeal membrane oxygenation

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Abstract

Use of extracorporeal membrane oxygenation to support patients with critical cardiorespiratory illness is increasing. Systemic anticoagulation is an essential element in the care of extracorporeal membrane oxygenation patients. While unfractionated heparin is the most commonly used agent, unfractionated heparin is associated with several unique complications that can be catastrophic in critically ill patients, including heparin-induced thrombocytopenia and acquired antithrombin deficiency. These complications can result in thrombotic events and subtherapeutic anticoagulation. Direct thrombin inhibitors (DTIs) are emerging as alternative anticoagulants in patients supported by extracorporeal membrane oxygenation. Increasing evidence supports DTIs use as safe and effective in extracorporeal membrane oxygenation patients with and without heparin-induced thrombocytopenia. This review outlines the pharmacology, dosing strategies and available protocols, monitoring parameters, and special use considerations for all available DTIs in extracorporeal membrane oxygenation patients. The advantages and disadvantages of DTIs in extracorporeal membrane oxygenation relative to unfractionated heparin will be described.

Key words: Extracorporeal membrane oxygenation; Anticoagulants; Antithrombins; Bivalirudin; Argatroban; Heparin

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Core tip: In contrast to unfractionated heparin, direct thrombin inhibitors are not

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associated with heparin-induced thrombocytopenia or acquired antithrombin deficiency. Direct thrombin inhibitors, specifically bivalirudin and argatroban, are equally safe and possibly more efficacious than unfractionated heparin. Dosage and monitoring parameters are easily manageable and more predictable than unfractionated heparin. As extracorporeal membrane oxygenation increases in use, direct thrombin inhibitors may potentially be considered as a primary anticoagulant in patients with or without complications of unfractionated heparin.

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is increasingly used in patients with refractory respiratory or cardiogenic shock^[1]. Patients can be supported in either a veno-venous (VV) or veno-arterial (VA) configuration. Systemic anticoagulation is necessary and crucial due to continuous contact between the patient's blood and the foreign surfaces of all components of the ECMO circuit. This interaction triggers the coagulation cascade and can lead to pump or oxygenator thrombi, or fibrin stranding within the inflow cannula resulting in potentially devastating thromboembolic events^[2]. The ideal anticoagulant has rapid onset and offset, is easily titratable based on available monitoring parameters, is reversible, and is not affected by organ dysfunction commonly seen in ECMO patients^[3]. Intravenous unfractionated heparin (UFH) is the standard anticoagulant in most centers due to its availability, rapid onset of action, reversibility, cost profile, and familiarity among practitioners^[4].

Complications related to UFH are common: bleeding, non-immune and immune heparin-induced thrombocytopenia (HIT), and heparin-resistance have all been described^[5,6]. HIT is of particular concern, with mortality as high as 20%-30%^[7]. The incidence of HIT in patients treated with UFH is approximately 2.6%, although this does not reflect the incidence in ECMO patients^[8]. HIT is often suspected in ECMO patients; however available data are inconsistent, suggesting that the incidence ranges from less than 0.36% to 17%^[9-12]. HIT reverses the anticoagulant effect of heparin and leads to massive platelet activation and thrombosis, which can be catastrophic^[13]. All forms of heparin must be immediately discontinued once the diagnosis of HIT is suspected. In ECMO patients, the heparin-coated elements of the circuit must also be exchanged. UFH can also lead to acquired antithrombin deficiency which may result in heparin resistance and suboptimal anticoagulation^[2]. This is of particular concern in patients receiving ECMO secondary to the inability to liberate from cardiopulmonary bypass due to high intraoperative heparin loads. Alternative anticoagulation strategies have been proposed. In non-ECMO patients with suspected or confirmed HIT, direct thrombin inhibitors (DTIs) are the primary alternative^[13]. This article will review DTI anticoagulation strategies in adult ECMO patients, as well as available safety and outcome data. Heparin alternatives in pediatric ECMO patients have previously been reviewed^[14].

PHARMACOLOGY OF DIRECT THROMBIN INHIBITORS

Thrombin is a serine protease that plays a crucial role in the coagulation cascade and the generation and stabilization of clot. Upon activation, thrombin facilitates the formation of insoluble fibrin from soluble fibrinogen^[15,16]. Thrombin contains three binding sites that are essential to its coagulant-and thereby anticoagulant-effects, including the catalytic site, exosite-1, and exosite-2.

The DTIs obtain their name from their direct binding to thrombin to exert anticoagulant effects. This is in contrast to UFH and low molecular weight heparins, which are indirect thrombin inhibitors. These indirect inhibitors bind to antithrombin, a hepatically-synthesized glycoprotein, forming a heparin-antithrombin complex which subsequently binds to exosite-2 on thrombin and blocks the catalytic site^[16,17]. Because of this binding, indirect thrombin inhibitors only exert effects on circulating

thrombin, as the catalytic site of fibrin-bound thrombin is occupied in preformed clot^[17]. DTIs, on the other hand, bind directly to either the catalytic site or both the catalytic site and exosite-1 on thrombin, depending on the valency of the agent, in the absence of antithrombin^[15,17]. Because of this, a major pharmacologic advantage over indirect thrombin inhibitors is the ability of DTIs to bind both circulating and fibrin-bound thrombin. DTIs for clinical use vary based on their valency, modality of binding (reversible *vs.* irreversible), and pharmacokinetic profile (Table 1).

ADVANTAGES OF DIRECT THROMBIN INHIBITORS

Anticoagulation is an essential element of ECMO support. While UFH remains the standard at most ECMO centers, DTIs are emerging as a reasonable and safe alternative due to several advantages when compared to UFH. The advantages of DTIs over UFH are: (1) Direct binding of both circulating and clot-bound thrombin, which results in increased efficacy relative to UFH^[17]; (2) Anticoagulant effect that is independent of antithrombin, allowing for more consistent and predictable effect without concern for antithrombin depletion^[15,17]; (3) Avoidance of HIT, as thrombocytopenia is common among ECMO patients and the diagnosis of HIT in this setting is challenged by the multitude of factors that can precipitate a drop in platelet count. Healthcare teams must maintain a low threshold of concern when HIT is suspected. DTIs appear to be at least as safe as UFH with no evidence of increased bleeding or thrombosis, and evidence suggests that patients who receive DTIs are more often in therapeutic targeted range of anticoagulation. While DTIs are an appropriate choice in the setting of suspected or confirmed HIT, they may be a reasonable option as first-line anticoagulation for better efficacy in maintaining ECMO circuit patency and to avoid concerns for HIT altogether. Although DTIs do not have target-specific antidote, their half-life is very short and the anticoagulant effect tapers off rapidly despite the widely prevalent end organ dysfunction in ECMO patients. ECMO patients rarely require complete reversal of anticoagulation given the high risk of thrombosis.

AVAILABLE AGENTS

Bivalirudin

Bivalirudin is a synthetic, bivalent DTI, which binds directly to both the catalytic site and exosite-1 on thrombin in a reversible fashion^[6] (Table 1). Bivalirudin dissociates from the catalytic site following proteolytic cleavage, reconstituting thrombin's ability to facilitate fibrin formation^[18]. This may be problematic during states of blood stasis as will be discussed. It is administered by intravenous infusion, has an onset of action within minutes, and has a half-life of 25 min in patients with normal renal function^[18]. Bivalirudin has a low volume of distribution and is therefore widely distributed in plasma and has negligible protein binding.

Bivalirudin is available as an adjunct to anticoagulation therapy during percutaneous coronary interventions, as well as the primary anticoagulant during coronary artery bypass grafting in patients with HIT^[19]. Use in ECMO, with or without HIT, is off-label. The available literature for use in adults supported by ECMO is derived from retrospective studies, a single case control trial, and multiple case reports^[20-26] (Table 2). Two studies compared bivalirudin to a matched control group who received UFH^[20,25]. Four studies described patients with suspected or confirmed HIT due to previous UFH use^[21,23,24,26]; the remaining studies used bivalirudin as the initial anticoagulation strategy^[20,22,24,25]. Both VV and VA configurations are described. There is one published protocol describing initial bivalirudin dosing and subsequent dose adjustments^[22].

In most reported studies of bivalirudin, initial bolus doses were administered followed by a weight-based infusion. The described dosing is heterogeneous; bolus dosing ranges from 0.04 mg/kg to 2.5 mg/kg. In reports without bolus dosing there was no sign of increased thromboembolic risk during the time until therapeutic anticoagulation was achieved^[21,24-26]. The maintenance infusion was adjusted based on monitoring parameters, and doses ranged from 0.025 mg/kg/h to 2.5 mg/kg/h. In studies where average infusion rate is described, the dose ranges from 0.05 mg/kg/h to 0.26 mg/kg/h to maintain therapeutic targets^[21,23,26]. When compared to patients receiving UFH infusions, patients treated with bivalirudin are more often in therapeutic range^[20,24].

Renal dysfunction: Bivalirudin is metabolized in the plasma by proteolytic cleavage

Table 1 Pharmacology of direct thrombin inhibitors

	Valence	Thrombin binding	Onset of action	Half-life	Protein binding	Metabolism	Special considerations
Bivalirudin	Bivalent	Reversible	2-4 min	25 min	None	Serum proteases	Avoid during low-flow states Removed by non-diffusive dialysis modalities Dose reductions necessary in renal dysfunction
Argatroban	Univalent	Reversible	30 min	45 min	20% albumin 34% alpha-acid glycoprotein	Hepatic (hydroxylation, aromatization)	Dose reductions necessary in hepatic dysfunction

and has a prolonged half-life in the setting of renal dysfunction^[27]. Renal dysfunction is therefore an important consideration when initiating and adjusting bivalirudin infusions. Initial dosing, as well as adjustments in the maintenance infusion rate, may vary, and over-anticoagulation is an important concern in these patients. Limited studies with established protocols describe lower initial bolus doses in patients with renal dysfunction^[25], while others use the same bolus dose as patients without renal dysfunction while adjusting subsequent maintenance infusion rates^[22]. Ranucci *et al*^[25] administered half-dose initially in patients with renal dysfunction, followed by the regular dose adjustment protocol. The protocol by Netley *et al*^[22] stratified patients based on creatinine clearance above 30 mL/min, between 10-29 mL/min, and less than 10 mL/min or requiring intermittent hemodialysis. The initial bolus dose was standardized for all patients regardless of creatinine clearance, and subsequent dose adjustments were limited as the severity of renal dysfunction progressed.

Continuous renal replacement therapy (CRRT) utilizing convective (hemofiltration) or combination convective/diffusive (hemodiafiltration) modes has been found to modestly remove bivalirudin, but purely diffusive modalities are not expected to be major determinants of clearance due to bivalirudin's larger molecular size (1980 Da)^[28]. There are multiple reports of successful anticoagulation with bivalirudin while supporting patients with CRRT^[20,22,24]. Walker *et al*^[26] described moderately reduced dose requirements in patients on CRRT, although the doses were higher than those with renal dysfunction who were not receiving CRRT. While it would be expected that patients with renal dysfunction require less bivalirudin to maintain a similar anticoagulation profile, retrospective data suggest that these patients may require higher doses^[24]. The reasons for this finding are unclear. Given the tendency to reduce initial and/or maintenance bivalirudin doses in patients with renal dysfunction, careful attention should be paid to avoid under-anticoagulation which may result in thrombotic events. The currently available reports do not signal an increased risk of thrombosis in patients with renal dysfunction, although the number of studied patients is limited.

Hepatic dysfunction: There is no bivalirudin dose adjustment necessary in patients with hepatic dysfunction, although there are no specific reports of outcomes in patients with hepatic disease.

Monitoring: Bivalirudin prolongs the activated clotting time (ACT), activated partial thromboplastin time (aPTT), thrombin time, prothrombin time, and international normalized ratio^[19]. Ecarin clotting time and chromogenic anti-factor IIa assay are the most reliable methods for DTI monitoring; however, they are not readily available in clinical laboratories. The aPTT testing is the most commonly used and well validated assay to monitor DTIs. The manufacturer recommends monitoring with ACT in certain conditions, namely HIT, with an ACT target greater than 225 s. No specific recommendation from the manufacturer is available in ECMO patients as this is an off-label indication. Most reviewed studies, including available protocols, used aPTT as a monitoring parameter. Netley *et al*^[22] used aPTT alone with adjustable target based on physician preference; 40-60 s, 50-70 s, or 60-80 s were all described, with adjustments in bivalirudin doses based on the difference between the measured aPTT and the target aPTT. The aPTT was measured 2 h after the initial dose and then every 4 h afterwards. Ranucci *et al*^[25] adjusted bivalirudin dosing based on ACT primarily (target 160-180 s), followed by aPTT (target 50-80 s) and then kaolin-activated thromboelastography (TEG, TEG 5000; Haemonetics Corp, Braintree, MA, United

Table 2 Summary of studies reporting on argatroban in adult patients supported with extracorporeal membrane oxygenation

First author, Year	Study type	Population	Circuit (VA/VV)	CRRT	Bolus dose (mg/kg)	Initial infusion (mg/kg/min)	Monitoring	Duration	Major bleeding	Thrombosis	Other adverse events	Outcome
Jyoti <i>et al</i> ^[21] , 2013	Case report	54M ARDS, HIT	VV	No	NA	0.6	ACT 200-220 s aPTT 60-80 s	552 h (23 d)	NA	NA	NA	
Pappalardo <i>et al</i> ^[23] , 2009	Case report	71F post-cardiotomy, HIT	VA	No	0.5	0.5	ACT 180-220 s	6 d	NA	Ventricular fibrillation due to LA thrombus, suspected to be due to heparin in tubing with residual HIT. BIV dosing increased	NA	Decannulated and discharged in stable condition
Pieri <i>et al</i> ^[24] , 2013	Case control	n = 10 (4 HIT)	VV (n = 5) VA (n = 5)	n = 7 (70%)	N/A	0.025	aPTT 45-60 s	8 d (range 6-23)	n = 3 (30%)	n = 1 (10%)	No difference in bleeding or thrombosis compared to UFH patients. Less dose corrections than UFH. Less supratherapeutic aPTTs than UFH.	n = 4 (40%) died
Berei <i>et al</i> ^[20] , 2018	Retrospective	n = 44 CS (n = 37) Sepsis (n = 11) Respiratory (n = 3) Mixed (n = 4)	VA (n = 26) VV (n = 2)	n = 17 (39%)	UFH 80 units/kg at cannulation No BIV bolus	0.04	aPTT 45-65 s (low intensity) or 60-80 s (high intensity)	156.9 h (mean)	n = 20 (45.5%)	n = 10 (22.7%)	Increased flow rates during first 96 h. High intensity BIV had more TTR with no difference in outcomes	No difference in death at 30 d between BIV and UFH (36% vs 32%)
Netley <i>et al</i> ^[22] , 2017	Retrospective	n = 11 ARDS (n = 8) ECLS (n = 3)	VA (n = 4) VV (n = 7)	n = 4 (36%)	NA	2.5	aPTT 40-60 s, 50-70 s, or 60-80 s	Mean 9.9 d (range 4-22)	n = 8 (72.7%)	n = 2 (18.2%), both after hospital discharge	NA	n = 5 (45%) died after withdrawal of care n = 6 (55%) discharged from hospital
Ranucci <i>et al</i> ^[25] , 2011	Retrospective	n = 8, post-cardiotomy	VA	NA	NA	0.03-0.05 ½ dose if reduced CrCl	ACT 160-180 s or aPTT 50-80 s or TEG r 12-30 min	39-262 h	NA	None	Bleeding not reported, but less average blood loss (mL/kg/d) in BIV patients	n = 2 (25%) survived n = 2 (25%) dead on ECMO n = 4 (50%) weaned but died

Walker <i>et al</i> ^[26] , 2019	Retrospective	n = 14	VV (n = 11)	VA (n = 3) (43%)	0.2 (n = 1, others NA)	0.04-0.26	aPTT 1.5-2.5 × baseline	Median 5.2 d (range 0.9-28.4 d)	n = 4 (29%)	Circuit clotting (n = 5, 36%)	Infusion held during major bleeding episodes with no need for correction	n = 9 (64%)
			ARDS (n = 12)	Post-cardiotomy (n = 2)							Higher infusion rates noted with CRRT	decanulated n = 7 (50%) survived to discharge

ACT: Activated clotting time; aPTT: Activated partial thromboplastin time; ARDS: Acute respiratory distress syndrome; BIV: Bivalirudin; CRRT: Continuous renal replacement therapy; CS: Cardiogenic shock; ECLS: Extra-corporeal life support; HIT: Heparin-induced thrombocytopenia; NA: Not available; TEG: Thromboelastography; UFH: Unfractionated heparin; VA: Veno-arterial; VV: Veno-venous.

States) *r* time (target 12-30 min). Parameters were checked every 4, 12, and 8 h, respectively. In the retrospective study by Berei *et al*^[20], aPTT targets between 45-65 s (low intensity) and 60-80 s (high intensity) were chosen based on physician preference. Given the wide variability of monitoring modalities used and goal ranges reported in the literature, and the possibility of DTI resistance and unreliable aPTT monitoring at very high DTI doses, it is of utmost importance to use clinical indicators including ECMO circuit patency and potential thrombotic and bleeding complications as ultimate guidance for anticoagulation titration rather than solely relying on numbers of certain lab values.

Safety and outcomes: Bivalirudin appears to be a safe anticoagulation strategy for patients supported by ECMO, with no overall evidence of increased bleeding or thrombotic complications relative to UFH^[20,24,25]. One study demonstrated an increased incidence of bleeding events in patients treated with bivalirudin compared to those receiving UFH, without meeting statistical significance^[20]. Walker *et al*^[26] described 4 of 14 patients who required reduction in aPTT targets or complete suspension of bivalirudin due to bleeding, although this rate is similar to reported bleeding rates in UFH patients. Some reports suggest a lower risk of thrombosis and vascular complications, as well as decreased transfusion requirements relative to UFH^[20,25], although cases requiring circuit exchange due to thrombosis have been reported^[26]. Reports of patients who required ECMO support up to 23 d suggest that outcomes with prolonged bivalirudin use are similar to UFH^[21,24].

Argatroban

Argatroban is a synthetic, univalent DTI, and thereby binds directly to the catalytic site on thrombin in a reversible fashion^[16]. Compared to the other DTIs, it has a relatively small molecular size (527 Da). It is administered by intravenous infusion, has an onset of action within 30 minutes, and has a half-life of 45 min in patients with normal hepatic function (Table 1). Of the DTIs, argatroban has the greatest serum protein binding, with 20% to albumin and 34% to alpha₁-acid glycoprotein. Lidocaine-an antiarrhythmic used on occasion in cardiothoracic surgical patients-may decrease argatroban concentrations up to 20% due to its high affinity for alpha₁-acid glycoprotein^[29].

Argatroban is available as therapeutic anticoagulation for confirmed or suspected HIT in patients who develop thrombocytopenia while on ECMO support. There are limited data available regarding argatroban use in ECMO; most are case reports and case series (Table 3)^[30-37]. There is one retrospective study of 39 adult patients treated with argatroban, which also included a small proportion of patients supported with pumpless extracorporeal lung assist^[38]. Patients supported with both VV and VA systems are described, and all are limited to patient population with suspected or confirmed HIT. There are no reported cases with argatroban as a first-line anticoagulant in ECMO patients.

Dosing: Only one patient in the reviewed literature received the manufacturer-recommended initial dose of 2 µg/kg/min. The patient subsequently suffered major bleeding complications and required a rapid dose reduction^[30]. In all other reported cases, patients subsequently received doses at a rate approximately 10% the manufacturer recommended dose, with most initial doses ranging from 0.1-0.3 µg/kg/min. This is consistent with literature from other critically ill populations

Table 3 Summary of studies reporting on argatroban in adult patients supported with extracorporeal membrane oxygenation

First author, Year	Study type	Population	Circuit (VA/VV)	CRRT	Bolus dose	Initial infusion	Monitoring	Duration	Major bleeding	Thrombosis	Other adverse events	Outcome
Sin <i>et al</i> ^[37] , 2017	Case report	27M ARDS, HIT	VV	Yes	NA	0.2 µg/kg/min	aPTT 50-60 s	60 d	Hemothorax developed while on heparin, resolved on ARGA day 27	None	Transient elevations in liver enzymes, no clinical consequence	Patient transferred for lung transplantation
Ratzlaff <i>et al</i> ^[35] , 2016	Case report	58M ARDS, HIT	VV	No	NA	0.1-0.3 µg/kg/min	aPTT 60-90 s	11 d	None	None	NA	Withdrawal of care after 28 d of ECMO support
Johnston <i>et al</i> ^[34] , 2002	Case report	32M CS, HIT	VA	No	10 mg	2 µg/kg/h	ACT 200-400 s aPTT 80-90 s	7 d	None	NA	NA	Decannulated on ECMO day 10
Dolch <i>et al</i> ^[32] , 2010	Case report	40M ARDS, HIT	VV	No	NA	0.35 µg/kg/min	aPTT 45-60 s	108 d	Major bleeding after lung transplant (ECMO day 114) – ARGA held	NA	Hepatic failure post-transplant infusion reduced to 0.02 µg/kg/min	Patient underwent lung transplant on ECMO day 114, complicated by graft failure. Died on post-operative day 17 (multi-organ failure)
Fernandes <i>et al</i> ^[33] , 2019	Case report	44M CS, HIT	VA	Yes	NA	1.5 mg/h	aPTT 60-70 s	20 d	Mediastinal bleeding due to pulmonary edema. Massive intraoperative hemorrhage during LVAD insertion, DIC	LV and RV thrombus during intraoperative DIC	NA	Survived to discharge
Cornell <i>et al</i> ^[31] , 2007	Case series	n = 4 with HIT ARDS (n = 3) CS (n = 1)	VA (n = 2) VV (n = 2)	No	NA	0.2-2.0 µg/kg/min	ACT 210-230 s	88-184 h	Major bleeding (n = 2)	NA	NA	Survival to discharge (n = 2, 50%) Death (n = 2, 50%)
Beiderlin <i>et al</i> ^[30] , 2007	Case series	n = 9 with ARDS, HIT	VV	n = 8	NA	2.0 µg/kg/min (n = 1) 0.2 µg/kg/min (n = 8)	aPTT 50-60 s	4 ± 1 d (mean)	Major bleeding (n = 1) in patient who received higher initial infusion dose	None	NA	Survived (n = 6) Died (n = 3)

Rougé <i>et al</i> ^[36] , 2017	Case series	49M CS, HIT 69M ARDS, HIT	VA	n = 1	NA	0.2 µg/kg/min	aPTT 1.5-3.0 × baseline	10 d 8 d	NA	Circuit clotting (n = 1)	ALF requiring dose reduction	Survived (n = 1) Decannulated, but died prior to discharge (n = 1)
Menk <i>et al</i> ^[38] , 2017	Retrospective	n = 34 ARDS, HIT or heparin resistance	VV (n = 24) pECLA (n = 9)	NA	NA	0.3 µg/kg/min	aPTT 50-75 s	265 h (131-460)	n = 11—no differences compared to matched UFH cohort	n = 6—no differences compared to matched UFH cohort	NA	n = 21 (54%) died

ACT: Activated clotting time; aPTT: Activated partial thromboplastin time; ARDS: Acute respiratory distress syndrome; ARGA: Argatroban; CRRT: Continuous renal replacement therapy; CS: Cardiogenic shock; DIC: Disseminated intravascular coagulation; ECLS: Extra-corporeal life support; HIT: Heparin-induced thrombocytopenia; LVAD: Left ventricular assist device; NA: Not available; TEG: Thromboelastography; UFH: Unfractionated heparin; VA: Veno-arterial; VV: Veno-venous.

which suggests that an initial dose of 0.2 µg/kg/min results in adequate dosing based on aPTT measurement, without excessive bleeding or thrombosis^[39].

Renal dysfunction: No dose adjustment is required for patients with renal dysfunction, with or without renal replacement therapy, which is a major advantage relative to other agents. There are several reports of successful clinical outcomes with argatroban in patients who require CRRT while supported by ECMO^[30,33,37].

Hepatic dysfunction: Argatroban is metabolized hepatically by hydroxylation and aromatization, and therefore has a prolonged half-life of up to four times normal in the setting of liver dysfunction^[40]. While CYP3A4 and CYP3A5 provide a minor metabolic pathway, co-administration of inhibitors or inducers of these enzymes do not result in significant changes in argatroban concentrations^[41].

Argatroban is not contraindicated in patients with hepatic dysfunction; however significant dose reductions may be required. There are few described cases of argatroban use in patients with liver dysfunction. One reported case of a patient with acute respiratory distress syndrome who underwent lung transplantation complicated by postoperative hepatic dysfunction describes a maintenance dose of 0.02 µg/kg/min in order to achieve the target aPTT^[32]. The patient did not suffer from any adverse bleeding or thrombotic events related to the relatively low dose requirement.

Monitoring: The majority of reported cases and the single retrospective study used aPTT as the target for dose adjustment^[30,32,33,35,37,38]. Some cases reported use of ACT, either alone or in conjunction with aPTT, as the therapeutic monitoring parameter^[31,34]. In cases where aPTT was used, there was no standardized target; most reported a goal of 50-70 s. Of note, Menk *et al*^[38] found that bleeding events occurred when the maximum aPTT was above 50-60 s, and two thirds of bleeding events occurred when the maximum aPTT was above 75 s. Conversely, transient aPTT values below 50 s did not signal an increase in thromboembolic events. The authors of that study therefore recommended strict aPTT monitoring with a target of approximately 50 s. This is consistent with published guidelines which suggest an aPTT goal range of 1.5-2.5 times baseline^[38]. ACT monitoring, although less frequently used, varies substantially with reported targets between 200 and 400 s. As discussed previously, clinical end points remain the ultimate guidance for adequacy of anticoagulation in these critically ill and complex ECMO patient populations.

Safety and outcomes: There are many reported cases of successful clinical outcomes using argatroban in ECMO patients with suspected or confirmed HIT. In cases in which patients did not survive, none were reported to be directly associated with argatroban use. The reported duration of support is as long as 95 d. The rate of bleeding or thrombosis is low. In the retrospective study of 39 ECMO patients treated with argatroban, the rate of major bleeding or thrombosis was comparable to patients who received heparin^[2,38]. There are few reported major bleeding events with argatroban, many of which were related to surgical interventions. Bleeding at cannulation sites is reported, and blood transfusions were frequent, however the reported rate is similar to that seen with heparin^[38].

Other agents

Desirudin and lepirudin are recombinant-DNA forms of the naturally occurring peptide, hirudin, present in the salivary glands of leeches. These recombinant hirudins are bivalent DTIs and thereby bind directly to both the catalytic and exosite-1 of thrombin in an irreversible fashion^[42]. Because they are composed of non-human proteins, anti-hirudin antibodies may be formed leading to potential immunologic reactions including anaphylaxis^[42]. The clinical use of recombinant hirudins during ECMO is limited by these factors and the more favorable pharmacokinetic profiles of the newer synthetic DTIs. Only lepirudin has been reported in adult patients requiring ECMO support. The single case report noted a successful outcome^[43]. Lepirudin was withdrawn from market in 2012 and is no longer in production.

Dabigatran etexilate is an oral, synthetic, peptide-like DTI^[44]. The onset of action is approximately 1 h and the half-life is 12 to 17 h. Renal excretion is the primary determinant of dabigatran removal, with up to 80% in the urine, and therefore the half-life is prolonged in the setting of renal dysfunction. Dabigatran is a substrate of p-glycoprotein and is therefore prone to a large number of clinically relevant drug interactions with p-glycoprotein inhibitors or inducers. Because of all of these reasons, there is no role for dabigatran in anticoagulation during ECMO.

LIMITATIONS AND SPECIAL USE CONSIDERATIONS

Bleeding

Bleeding is a common cause of morbidity and mortality among ECMO patients, regardless of anticoagulation strategy^[2]. There are no formal recommendations for anticoagulation management when bleeding is encountered while on ECMO. For patients receiving DTI therapy, holding DTIs temporarily or short term can be considered. As previously mentioned, there is no specific antidote for DTIs; however, the short half-life of available agents results in rapid offset of anticoagulant effect when the infusion is held or decreased. Once surgical bleeding has been excluded, treating teams can consider performing TEG to further assess the cause of bleeding and transfuse blood products as needed. In patients with hyperfibrinolysis, successful TEG-guided use of tranexamic acid has been described in patients on ECMO and DTIs^[45]. Once hemostasis has been achieved, DTI infusions can be restarted at a lower infusion rate, targeting a lower anticoagulation goal based on aPTT or ACT. In the protocol published by Netley *et al*^[22], significant bleeding triggered the reduction of the bivalirudin infusion rate, targeting the lower limit of the therapeutic range (*i.e.*, aPTT 40 s). Prothrombin complex concentrates may be used in life-threatening situations^[2]. As a general rule, ECMO flow should be increased whenever anticoagulation is reduced or suspended in order to minimize the risk of thrombus formation.

Prothrombin time interference

DTIs commonly prolong the prothrombin time and international normalized ratio in a dose-dependent manner, which may confound monitoring of warfarin in clinical practice. The derangement in these values may depend on the specific assay used^[46]. However, it typically does not interfere with ECMO anticoagulation as we primarily use aPTT/ACT. Factor Xa testing may be considered during DTI transitions to warfarin.

Low circuit flow states

While argatroban undergoes mostly hepatic metabolism, bivalirudin is primarily metabolized by proteolytic enzymes which rapidly cleave the molecule. This results in the short half-life that has been described. However, instances where blood is stagnant may induce thrombosis due to rapid local cleavage of bivalirudin^[47]. Although ECMO is a continuous circuit without any “low-flow” chambers, in cases of cardiac dysfunction the cardiac chambers may act as a source of stagnation. This may particularly be realized in patients who are undergoing active ECMO “wean” trials where circuit flows are down-titrated to assess ability to decannulate. In addition, any setting wherein the native myocardium experiences low pulsatility and allows blood to pool in the ventricles is of very high concern. This may result in localized thrombosis despite adequate bivalirudin dosing. This can be particularly problematic in post-cardiotomy ECMO patients with prosthetic heart valves as valve thrombosis may lead to significant morbidity and mortality. It has been suggested that these circumstances may be avoided by minimizing intracardiac blood flow in cases of cardiogenic shock or avoid low-pulsatility states, and by using UFH as alternative anticoagulation in cases where intracardiac spontaneous echo contrast, or “smoke

effect," is noted, or low-flow states are suspected^[47]. During EMCO weaning and trial-off period, especially in setting of VA ECMO wean and if the duration of the trial-off is prolonged, preemptive heparin administration is essential to minimize thrombus formation.

Direct thrombin inhibitor resistance and high-dose response

Resistance to UFH has been reported both in ECMO and non-ECMO cases, with multiple potential explanations^[48,49]. Less is known regarding DTI resistance, although cases have been reported using both bivalirudin and argatroban^[50-53]. Very few described cases included patients requiring extracorporeal support. In cases of DTI resistance, increasing doses are required to achieve the target aPTT. This has been reported with initial dosing of DTI, although there are also delayed presentations with therapeutic levels initially followed by progressive unexplained dose increases to maintain therapeutic aPTT levels^[26,50,53]. The mechanism of DTI resistance is unclear but may be associated with elevated factor VIII and fibrinogen, which has been reported in some cases^[52,53]. Notably, these patients ultimately require very high doses of DTI to achieve aPTT targets, often well above the maximum recommended dose. It has been suggested that increases in DTI dosage may result in less aPTT prolongation at high doses than at low doses, which may explain why patients on high doses of DTI require greater than expected dose increases^[51]. Conversely, the increase in the international normalized ratio may be more pronounced at high DTI doses^[51,53]. Early recognition and rapid titration are essential, as there are multiple reports of clinical thrombosis due to subtherapeutic anticoagulation during delayed titration to target aPTT levels^[53]. This point highlights the importance of applying clinical end points (circuit patency, bleeding vs. thrombosis) as ultimate guidance for ECMO anticoagulation management. In cases of DTI resistance, alternative monitoring parameters have been proposed as aPTT may be unreliable. These include ACT, thrombin time, or direct drug level measurement^[53,54]. The therapeutic targets for these parameters, however, are variably defined.

CONCLUSION

Systemic anticoagulation with DTIs in ECMO patients is a feasible and safe alternative, with several advantages over UFH. The primary indication for DTIs is in cases of suspected or confirmed HIT, however reports suggest that DTIs may be effective as an initial anticoagulation strategy for all ECMO patients. Multiple dosing and monitoring protocols have been proposed for both bivalirudin and argatroban, and further prospective trials should determine the optimal pathway to safe, effective anticoagulation in this critically ill population.

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Fatal *Legionella pneumophila* serogroup 1 pleural empyema: A case report

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Abstract

BACKGROUND

Legionella pneumophila (*L. pneumophila*) is a gram-negative intracellular bacillus composed of sixteen different serogroups. It is mostly known to cause pneumonia in individuals with known risk factors as immunocompromised status, tobacco use, chronic organ failure or age older than 50 years. Although parapneumonic pleural effusion is frequent in legionellosis, pleural empyema is very uncommon. In this study, we report a case of fatal pleural empyema caused by *L. pneumophila* serogroup 1 in an 81-year-old man with multiple risk factors.

CASE SUMMARY

An 81-year-old man presented to the emergency with a 3 wk dyspnea, fever and left chest pain. His previous medical conditions were chronic lymphocytic leukemia, diabetes mellitus, chronic kidney failure, hypertension and hyperlipidemia, without tobacco use. Chest X-ray and computed tomography-scan confirmed a large left pleural effusion, which puncture showed a citrine exudate with negative standard bacterial cultures. Despite intravenous cefotaxime antibiotherapy, patient's worsening condition after 10 d led to thoracentesis and evacuation of 2 liters of pus. The patient progressively developed severe hypoxemia and multiorgan failure occurred. The patient was treated by antibiotherapy with cefepime and amikacin and with adequate symptomatic shock treatment, but died of uncontrolled sepsis. The next day,

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cultures of the surgical pleural liquid samples yielded *L. pneumophila* serogroup 1, consistent with the diagnosis of pleural legionellosis.

CONCLUSION

L. pneumophila should be considered in patients with multiple risk factors and undiagnosed pleural empyema unresponsive to conventional antibiotherapy.

Key words: Legionella pneumophila serogroup 1; Legionellosis; Legionnaire's disease; Pleural empyema; Case report

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Core tip: *Legionella pneumophila* (*L. pneumophila*) is a gram-negative bacillus known as a common cause of pneumonia, with frequent parapneumonic pleural effusion. In contrast, pleural empyema seems very uncommon. We report here the case of an 81-year-old man with multiple comorbidities who presented with a large left pleural effusion. Despite wide antibiotic courses against extracellular bacteria associated to surgical thoracentesis, patient died of uncontrolled septic shock. *L. pneumophila* serogroup 1 was isolated from the surgical pleural liquid sample, consistent with a pleural localization of Legionnaire's disease. We therefore would emphasize that *L. pneumophila* is an exceptional cause of pleural empyema in patients with multiple risk factors.

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INTRODUCTION

Legionella pneumophila (*L. pneumophila*) is a Gram-negative, slow-growing intracellular bacillus, originally discovered in 1976 in Philadelphia among the delegates of the American Legion conference^[1]. Since then, sixteen different serogroups have been described, with a large predominance of serogroup 1, responsible for approximately 85% of the cases^[2]. Risk factors for infection include male sex, aged more than 50 years, current or historical smoking, alcohol abuse, diabetes, cancer, chronic kidney failure, iron overload and immunocompromising diseases or treatments^[3]. Although it is mostly known to cause acute severe pneumonia, with frequent parapneumonic pleural effusion, *L. pneumophila* infection may rarely cause pleural empyema.

We report here a case of pleural empyema caused by *L. pneumophila* serogroup 1 in an immunocompromised patient, followed by a review of the literature.

CASE PRESENTATION

Chief complaints

In August 2018, an 81-year-old caucasian man presented to the emergency department with fever, progressive dyspnea, dry cough and left pleuritic chest pain.

History of present illness

Patients symptoms started 3 wk ago and worsened progressively.

History of past illness

His medical history was consistent with chronic lymphocytic leukemia, initially treated in 2007 with Fludarabine, Cyclophosphamide and Rituximab therapy with chronic lymphocytosis, type 2 diabetes mellitus, hypertension, hyperlipidemia and chronic kidney failure with an eGFR of 28 mL/min/1.73 m². He reported no smoking or alcohol abuse and used to work as an upholsterer.

Personal and family history

None.

Physical examination upon admission

Physical examination revealed fever (38.1°C), tachycardia (105 bpm), peripheral percutaneous oxygen saturation was 100% with 2 liters of oxygen with tachypnea, normal blood pressure and almost abolished left vesicular murmur. Adenopathy, hepatomegaly or splenomegaly were not observed. Cardiovascular and neurologic examination were normal.

Laboratory examination

Biology tests revealed neutrophilia (18.7 g/L) and elevated CRP (297 mg/L) consistent with inflammatory response, along with stable lymphocytosis (242 g/L) and anemia (7.8 g/L).

Imaging examination

Chest X-ray at admission (Figure 1) showed a large left pleural effusion with contralateral tracheal deviation. Complementary computed tomography (Figure 2) confirmed a walled-off, loculated left pleural effusion, with right lung parenchyma considered normal.

Further diagnostic work-up

First bedside pleural puncture showed a citrine exudate (pleural protein 37 g/L, pleural fluid protein to serum ratio 0.61), unfortunately cytological examination was not performed.

Despite intravenous treatment with cefotaxime, the patient condition worsened with persistence of fever, neutrophilia, and severe hypoxemia appeared. Bacteriological standard culture of the pleural liquid sample was negative, as well as repeated blood cultures. In order to look for a tuberculosis etiology, auramine stained sputum smears and cultures were performed but remained negative. Spot-test for tuberculosis was not performed. Ten days after his admission, because of the uncontrolled large pleural effusion with acute hypoxemic respiratory failure, the patient underwent surgical thoracentesis with evacuation of 2 liters of purulent liquid. We chose surgery instead of repeated pleural drawings, because local sepsis was not controlled nor bacteriologically documented. Pleura was thick and nodular, with white pseudo-membranes. Treatment with metronidazole was added to cefotaxime after the surgery in order to cover anaerobic bacteria. Cytobacteriological examination and cultures of the liquid were negative. Lymphocyte phenotyping ruled out B-cell lymphoma as a complication of his chronic lymphocytic leukemia. Three days after, the patient progressively developed multiple organ failure requiring intensive care unit admission. As no massive transfusion was initiated during surgery and shock was the main matter, fluid overload could not explain the evolution in multiple organ failure. After a slow unfavorable evolution during the ten first days of hospitalization, the patient's condition worsened brutally three days after surgical thoracentesis leading to septic shock complicated of multiple organ failure. Despite antibiotherapy with cefepime and amikacin, invasive mechanical ventilation, vasopressor infusion and renal replacement therapy, the patient died of uncontrolled septic shock few hours after ICU admission.

The day after, mycobacterial culture of surgical pleural samples yielded Gram-negative bacilli (Figure 3). Rapid identification using matrix-assisted desorption ionization–time of flight mass spectrometry (MALDI-TOF MS; Microflex LT; Bruker Daltonics, Leipzig, Germany) was performed and *L. pneumophila* was identified. The bacteria were addressed to the National Reference Center of Legionella and molecular typing analysis by sequence-based typing was performed and showed that the strain of *L. pneumophila* serogroup 1 belonged to Sequence Type 1. Urinary antigen research retrospectively performed on a urine sample of the patient confirmed the presence of *L. pneumophila* serogroup 1.

We believe that chances of super infection or co-infection with another bacterium are scarce. Patient indeed received broad spectrum antibiotics directed against common bacteria causing pleural empyema (including anaerobic bacteria, gram-negative bacillus, streptococci and staphylococci), and repeated standard bacteriological cultures remained negative.

Retrospectively, our patient presented the following risk factors: Male sex, aged more than 50 years, chronic lymphocytic leukemia with history of immunocompromising treatments, chronic kidney failure, diabetes mellitus and weaned smoking.



Figure 1 Chest X-ray at admission: Large left pleural effusion with contralateral deviation of the mediastinum.

FINAL DIAGNOSIS

Fatal pleural empyema caused by *L.pneumophila* serogroup 1.

TREATMENT

No specific treatment could have been introduced because of post-mortem diagnosis. Unfortunately, the *L. pneumophila* strain identified in our patient was naturally resistant to all the antibiotics received.

OUTCOME AND FOLLOW-UP

Patient died of uncontrolled sepsis caused by *L. pneumophila* serogroup 1 pleural empyema.

DISCUSSION

Pleural effusion is a common manifestation of Legionnaire's disease. In a case series of 36 microbiologically proven legionellosis, Sakai *et al*^[4] reported in 2007 unilateral or bilateral scannographic pleural effusion in 60% of pneumonia caused by *L. pneumophila*, considered as a parapneumonic aseptic transudate. Similarly, Poirier *et al*^[5] reported in 2017, in a 33 individuals canadian cohort, a scannographic frequency of 66% (22/33). In contrast, pleural empyema, defined as a septic exudate with presence of *L. pneumophila*, seems exceptional.

Prevalence of pleural empyema in legionellosis is largely unknown. Since 1979, only 11 cases have been reported. These cases involved mostly men with an age ranging between 36 and 83^[6-12]. *L. pneumophila* serogroup 1 seems to be involved in most cases, but one serogroup 5 nosocomial *L. pneumophila* has been described in a patient following esophageal perforation after esophageal dilatation for carcinoma^[6-8]. All infected patients with detailed history presented classic risk factors: Tobacco use, relative immunosuppression caused by advanced age, high-dose steroids as a treatment for systemic lupus erythematosus^[9], immunosuppressive drugs in a kidney transplant recipient^[10]. In 1981, Winn and Myerowitz reported two necropsias of fatal legionellosis with unilateral empyema with presence of *L. pneumophila* in pleural fluid^[11]. Characteristics of pleural liquid, available for six cases, seem to be those of a classic empyema : Macroscopically purulent or serofibrinous, elevated LDH (5 out of 5, 1 non tested, range 342-2371 UI/L) and proteins (6 out of 6, range 31-57 g/L), with a predominance of neutrophils (6 out of 6) , with hypoglycopleuria and acid pH.

L. pneumophila infection is associated with a poor outcome: In a retrospective study of 136 consecutive cases of communitary *L. pneumophila* infection in Spain between 2001 and 2015, 85% of patients were hospitalized, including 11.7% in intensive care unit, and the mortality rate was 4.4%^[13]. Of the 11 patients described, 2 died with unrecorded treatment, 7 patients survived with adequate antibiotic course, and the

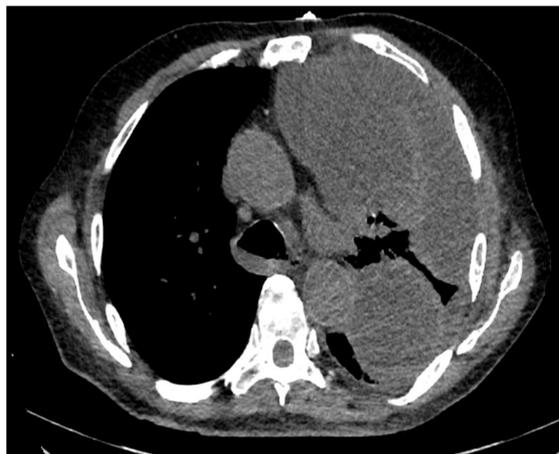


Figure 2 Computed tomography of the chest at admission: Multiloculated left pleural effusion

outcome of the 2 last was unknown. Choice of antibiotic stewardship and duration of antibiotic course for pleural legionellosis is widely empirical: 4 patients received a 4 wk course of IV erythromycin, 2 received a combination of erythromycin and rifampicin during 8 wk, and the last one was treated with levofloxacin for an undetermined duration of time.

Early identification of sepsis and early administration of adapted antibiotherapy is now recommended by international clinical practice guidelines^[14]. In our case report, identification of sepsis and its pleural origin was easy. Unfortunately, empirical antibiotherapy did not cover *Legionellosis*, and probably led to the patient's death.

Extrapulmonary legionellosis is a very challenging diagnosis and might involve many different organs^[15-18]. In patients with immunocompromising conditions, *L. pneumophila* can cause septic arthritis, endocarditis, myocarditis, myositis or cutaneous involvement, including panniculitis, exanthema, subcutaneous nodules, pustules or even abscesses. Other *Legionella* species include, among others, *L. bozemanii*, and *L. micdadei*^[2]. These other species, much rarer than *L. pneumophila*, can also exceptionally cause pneumonia with pleural empyema, which seems to be overrepresented compared to *L. pneumophila*^[19,20]. *Mycoplasma pneumoniae*, another intracellular bacteria known to cause pneumonia, has also been reported a few times as the causative agent of pleural empyema^[21].

CONCLUSION

Although uncommon, pleural empyema caused by *L. pneumophila* is associated with a poor outcome, and is therefore a very challenging diagnosis. We suggest that Legionnaire's disease should be considered in patients with multiple risk factors and pleural empyema with negative bacteriological standard culture and unresponsive to conventional antibiotherapy.

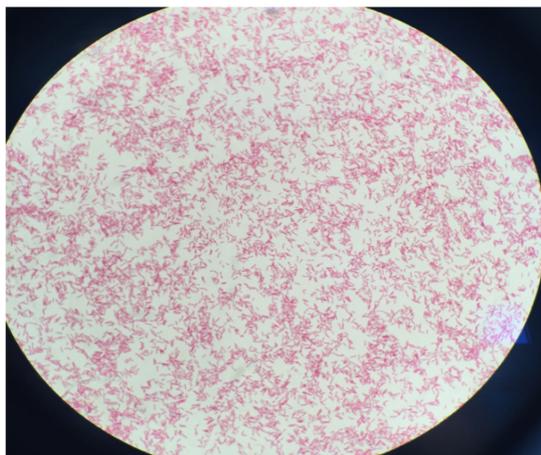


Figure 3 Gram staining of pleural culture confirmed gram-negative bacillus, consistent with *Legionella pneumophila*.

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