

Desmopressin (DDAVP): indications and practicalities

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Published
30 September 2026

doi
<https://doi.org/10.57187/5030>

Cite this as
Swiss Med Wkly. 2026;156:5030

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Summary

BACKGROUND: Desmopressin (1-deamino-8-D-arginine vasopressin, or DDAVP) is available in Switzerland for the treatment of non-severe haemophilia A and von Willebrand disease.

OBJECTIVE: To provide practical guidance for the use of desmopressin in patients with non-severe haemophilia A, von Willebrand disease, bleeding disorders of unknown cause and mild platelet function disorders.

METHODS: Based on the available literature and clinical experience in Switzerland, the Swiss Society of Haematology's Haemostasis Working Group and the Swiss Haemophilia Network worked together to reach a consensus on the use of desmopressin.

RESULTS AND CONCLUSIONS: Desmopressin may increase and normalise factor VIII and von Willebrand factor levels in patients with non-severe haemophilia A and von Willebrand disease and can prevent or treat bleeding in patients with bleeding disorders of unknown cause and mild platelet function disorders. A desmopressin trial is recommended to verify tolerability and identify responders, as the response to the drug is not predictable based on baseline levels of factor VIII and von Willebrand factor. Previously observed side effects and current contraindications must be carefully evaluated prior to every administration.

What is desmopressin (DDAVP) and how does it work? Physiology and history

Desmopressin (1-deamino-8-D-arginine vasopressin, or DDAVP) is a synthetic analogue of vasopressin, the antidiuretic hormone produced by the pituitary gland. Among other functions, vasopressin has a vasoconstrictive effect and influences haemostasis by releasing von Willebrand factor, factor VIII (FVIII) and tissue plasminogen activator, while also enhancing platelet function [1].

Desmopressin was synthesised in the 1960s to treat diabetes insipidus. Compared to vasopressin, desmopressin has a longer half-life, virtually no binding to V1 receptors and an increased affinity for the V2 receptors, thereby retaining the haemostatic properties of vasopressin but lacking its effect on blood pressure. From the very beginning, it was clear that desmopressin could possibly be used to treat haemophilia A [1-3]. Moreover, desmopressin appears to directly enhance platelet function as well [4-6].

In the 1970s, desmopressin was tested in healthy individuals [7] and in mild/moderate haemophilia A patients, and shown to increase FVIII [8]. A major motivation for testing desmopressin in clinical practice stemmed from the limited availability of cryoprecipitate, FVIII and FVIII/von Willebrand factor concentrates, and from the viral infection risks associated with blood-derived products [9].

Desmopressin was shown to increase FVIII levels in patients with mild and moderate haemophilia A and to increase FVIII/von Willebrand factor levels in patients with mild and moderate type 1 and type 2 von Willebrand disease [8]. This release of autologous FVIII and von Willebrand factor is a favourable effect that decreases the requirement for exogenous factor use/consumption. However, the response to the drug is not predictable based on baseline levels but remains consistent throughout adult life [9, 10]. Therefore, a trial is needed to identify non-responding patients and prevent the use of desmopressin in them.

The use of desmopressin is recommended by the World Federation of Hemophilia and by the ASH-ISTH-NHF guidelines for patients affected by mild/moderate haemophilia A and von Willebrand disease [11, 12].

Methods

This practical guidance is based on the available literature and clinical experience with patients treated in Switzerland. A literature review was conducted using PubMed with the search terms "desmopressin" and "bleeding disorders". The first consensus was reached by the authors after informal discussions and the final consensus required approval of at least 95% of the authors. The authors participated in the writing of the first draft and subsequent revisions. The final draft was circulated among all members of the Swiss Society of Haematology's Haemostasis Working Group and the Swiss Haemophilia Network for the final endorsement.

Indications, dose and route of administration

Desmopressin is licensed in Switzerland to treat patients with mild/moderate haemophilia A, von Willebrand disease, as well as in case of uraemic platelet dysfunction.

The use of desmopressin in patients with moderate haemophilia A must be carefully considered, since the clinical phenotype of these patients is highly heterogeneous. Patients with a clinically relevant bleeding phenotype will rather require prophylaxis [13]. In addition, only a minority of patients affected by moderate haemophilia A respond to desmopressin: a complete response, defined as FVIII:C ≥ 50 IU/dl, was observed in 15% of the RISE study population [14], while an adequate response (FVIII:C ≥ 30 IU/dl) was achieved in 40% and 25% of the populations in the RISE [14] and DYNAMO [15] studies, respectively. In patients with moderate haemophilia A and an adequate (but not complete) response to desmopressin, this treatment may be useful for treating minor bleeding events or for preventing bleeding during low-risk interventions. This may be particularly relevant in patients with genetic mutations associated with inhibitor development, in order to avoid unnecessary exposure to FVIII concentrate.

In von Willebrand disease, desmopressin is the treatment of choice in most patients with low levels of von Willebrand factor, type 1 and some patients with type 2 von Willebrand disease [4, 8, 9].

Desmopressin can be administered at a dose of 0.3 mcg/kg, either intravenously or subcutaneously, every 12–24 hours.

A capped dose of 20 mcg has been proposed [16]; however, we suggest reducing the dose only in obese patients, by calculating the dose on the ideal body weight. Reducing the dose to 20 mcg in patients with normal body mass index (e.g. 80 kg and 180 cm) is not recommended, as it may lead to an insufficient FVIII and von Willebrand factor response.

For intravenous administration, desmopressin should be diluted in 50–100 ml of physiological saline and infused over 20–30 minutes. Rapid intravenous infusion of desmopressin may result in tachycardia, flushing, tremor and abdominal pain. These side effects are milder with subcutaneous injection, for which dilution is not required.

A comparison between intravenous and subcutaneous administration of desmopressin demonstrated comparable FVIII levels post-administration. Peak levels are similar one hour after administration [17, 18].

Octostim® and Minirin® are the commercial preparations available for i.v. and s.c. application in Switzerland, with vials containing, respectively, 15 and 4 mcg of desmopressin in 1 ml. Unfortunately, intranasal self-administration of desmopressin is no longer available, as the production of nasal sprays delivering 150 mcg desmopressin acetate per puff (e.g. Octostim Spray® or Stimat®) has been suspended and currently available sprays lack sufficient concentration [19, 20].

The repeated administration of desmopressin may be associated with a diminished FVIII and von Willebrand factor response due to endogenous storage depletion (tachyphylaxis); therefore, in cases of prolonged use of desmopressin (>2 consecutive days), monitoring the response of FVIII and von Willebrand factor levels as well as sodium (Na) levels is necessary.

Desmopressin is stored at 2–8 °C and protected from light.

Special considerations in children

In children, there is only limited evidence regarding the subcutaneous administration of desmopressin, so intravenous administration is preferred.

For intravenous administration, desmopressin should be diluted in physiological saline at a concentration of 0.4 mcg of desmopressin per ml NaCl and infused over 30 minutes. (e.g. 12 mcg desmopressin: 0.4 = 30ml NaCl).

Due to the risk of water retention, hyponatraemia and seizures in young children, we suggest to perform the desmopressin trial only in children aged 4 years and older. During the trial, children and their parents/guardians should be instructed that they/their child refrain from drinking any fluids until they are able to spontaneously void urine afterwards.

The response to desmopressin has been reported to be age-dependent [21]. If a desmopressin trial was performed in childhood, and showed a poor or non-response, a desmopressin trial can be repeated to assess for response in late adolescence/early adulthood.

Off-label use of desmopressin

Desmopressin has been used in clinical practice for mild platelet function disorders since 1984 [22]. Although the data collected on patients with this indication are limited [22–25], desmopressin is recommended by national guidelines in this setting [26]. Its use is also supported by the increase in procoagulant platelets after the administration of desmopressin [6], which can confer additional support for coagulation, along with increases of FVIII and von Willebrand factor.

More recently, the use of desmopressin has been proposed as second-line treatment in clinical practice for patients with bleeding disorders of unknown cause [27].

Rarely desmopressin is used to treat acquired bleeding disorders (acquired haemophilia A or acquired von Willebrand syndrome) as the inherent increased clearance of FVIII or von Willebrand factor often renders this treatment ineffective. Desmopressin may be considered in cases of mild bleeding symptoms or during low-risk invasive procedures [28]. In particular, in acquired haemophilia A, desmopressin has been used in patients with a low inhibitor titre (<5 Bethesda Units) or circulating FVIII:C levels >5 IU/dl [29]. Regarding the use of desmopressin in patients with acquired von Willebrand syndrome, it may be beneficial in cases with a low or mildly elevated von Willebrand factor propeptide/antigen ratio [30].

Bleeding symptoms associated with Ehlers-Danlos syndrome have been treated with desmopressin in case reports and case series, with shortening of bleeding time [31, 32]. The use of desmopressin is suggested by Orphananesthesia guidelines [33].

Side effects and contraindications

The most common side effects of desmopressin include vasoactive reactions (which are milder following subcutaneous administration) and the antidiuretic effect, which can lead to hyponatraemia (preventable through fluid restriction, table 1).

Table 1: Desmopressin's side effects.

Mechanism	Symptoms	Contraindications or special warnings	Possible management / prevention	Frequency
Hypersensitivity	Anaphylactic reaction	Known hypersensitivity	N/A	Rare
Vasoactive reaction	Facial flushing, headache, hypotension and tachycardia		Subcutaneous administration	Common
Antidiuretic	Mild hyponatraemia: nausea, headache, low energy, muscle weakness, dizziness. Severe hyponatraemia: seizures, respiratory depression, death. Risk factors: female sex, older age, repeated desmopressin doses	Relative contraindications: children under 4 years of age; elderly patients (>60 years); loop diuretics; chronic hyponatraemia; history of seizures; kidney failure with creatinine clearance <50ml/min	Fluid restriction during the first 12 hours (≈ 750–1000ml according to body weight) and subsequent 12 hours (≈ 1000–1500ml); in children: no fluids until they void urine spontaneously. Na+ evaluation before and after desmopressin administration in case of repeated doses	Common with repeated administration (mild hyponatraemia); severe hyponatraemia is rare
Release of HMWM?	Arterial thromboembolic events (MI, stroke); venous thromboembolism	Patients with active cardiovascular disease (e.g. coronary heart disease, cerebrovascular disease and peripheral vascular disease) or increased risk of thrombosis; patients with preeclampsia; patients with previous venous thromboembolism	N/A	Rare
Release of pathological von Willebrand factor	Thrombocytopenia	Type 2B von Willebrand disease	N/A	Rare
von Willebrand factor clearance	Increased clearance of von Willebrand factor after release	Type 1C von Willebrand disease	N/A	Rare

N/A: not applicable.

Several risk factors associated with the development of hyponatraemia have been identified, including age below 4 years or above 65 years, treatment with loop diuretic therapy, a history of chronic hyponatraemia and female sex. These represent relative contraindications to desmopressin use; while they do not preclude its administration, they necessitate careful monitoring in the patients concerned. Desmopressin should be used with caution in patients with a history of seizures, as hyponatraemia may act as a trigger [12].

Arterial thromboembolic events (such as myocardial infarction and stroke) have been reported following desmopressin administration. Although this adverse effect is very rare, its potential severity means that a thorough evaluation of arterial thrombotic risk factors is recommended in older patients prior to desmopressin administration. While no specific age cut-off is defined for desmopressin use, in cases of clinically relevant cardiovascular risk, its use is contraindicated [12]. We suggest special caution when using DDAVP in patients aged between 60 and 70 years, and to avoid its use in patients over 70 years of age.

The clearance of desmopressin is decreased in patients with advanced chronic kidney failure [34], and the use of desmopressin is contraindicated in patients with creatinine clearance <50 ml/min. This does not contradict the potential use of desmopressin in uraemic patients, since, in this setting, a single dose is typically administered to cover invasive procedures and prevent bleeding.

Desmopressin is contraindicated in patients with type 2B von Willebrand disease accompanied by thrombocytopenia, due to the risk of exacerbating thrombocytopenia [12]. A subtype of type 2B von Willebrand disease – the New York/Malmö variant, characterised by the mutations p.P1266Q, p.P1266R or p.R1308L – is not considered a contraindication for desmopressin use, as it is not associated with thrombocytopenia [35]. These patients generally have a mild deficiency of von Willebrand factor and respond to desmopressin.

Desmopressin trial

A desmopressin trial is recommended by the World Federation of Haemophilia guidelines for patients with mild and moderate haemophilia A and by the ASH-ISTH guidelines for those with von Willebrand disease [11, 12].

The desmopressin trial is useful because the response to desmopressin cannot be predicted based on baseline factor levels in haemophilia A or von Willebrand disease, although a recent meta-analysis demonstrated that baseline levels of FVIII and von Willebrand factor antigen are

the primary determinants of the response [18]. Once a response is recorded, desmopressin is suggested as the preferred treatment because individual patient responses tend to remain consistent over time in adulthood [9, 10].

The duration of response is also assessed during the desmopressin trial, as a transient response may occur following desmopressin administration. The recommended time points are baseline, 1 hour and 4 hours post-administration; a time point at 2 hours post-administration may also be useful to more accurately evaluate the response, though it is not mandatory.

The evaluation of sodium at baseline is likewise not mandatory, but it may be useful for excluding chronic hyponatraemia or borderline values, and determining the need for additional monitoring.

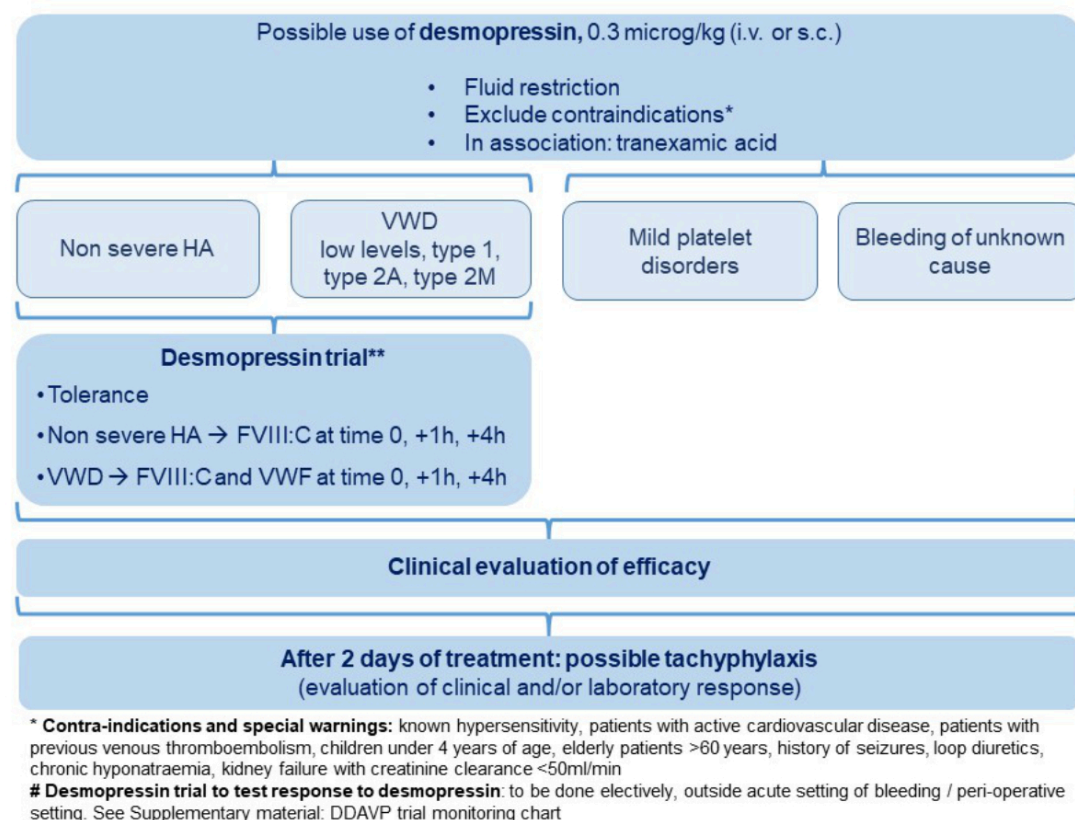


Figure 1: Treatment algorithm.

Haemophilia A

Recently, a large genetic study in mild/moderate haemophilia A patients showed a transient response to desmopressin in individuals with specific mutations, some of which involve the von Willebrand factor-binding site [36]. As genetic characterisation may not be available in all patients with mild/moderate haemophilia A, we suggest measuring FVIII levels four hours after desmopressin administration to assess sustained response.

The decision to use desmopressin for treating bleeding events is based on the FVIII increment observed during the desmopressin test, as well as the anticipated duration of treatment [11].

von Willebrand disease

The desmopressin trial can reveal a transient response to the drug, which may limit its effectiveness in clinical practice. This is seen in type 1 von Willebrand disease, characterised by very low FVIII and von Willebrand factor levels, an elevated von Willebrand

factor:propeptide/antigen ratio and mutation p.R1205H. Similar transient responses have also been observed in other von Willebrand disease patients, now classified as von Willebrand disease type 1C as well as in von Willebrand disease type 2AII [37].

The desmopressin trial is useful in type 2N von Willebrand disease, to evaluate the duration of FVIII response, since its clearance can be increased in this von Willebrand disease subtype [38].

In cases of mild deficiency of von Willebrand factor, it is preferable to confirm desmopressin responsiveness prior to its use. Since this may not always be feasible, adult patients with baseline von Willebrand factor levels ≥ 30 IU/dl may be presumed to be desmopressin responsive and the desmopressin trial may be omitted; however, it is still advisable to confirm the response by measuring von Willebrand factor levels after administration [12].

Platelet count at baseline and 1-hour post-administration can be useful for excluding type 2B von Willebrand disease with thrombocytopenia, as platelet count may decrease following the release of pathological von Willebrand factor.

Mild platelet function defects and bleeding disorders of unknown cause

There is no specific indication for monitoring the response to desmopressin in cases of mild platelet defects and bleeding disorders of unknown cause. The efficacy of desmopressin is clinically evaluated.

A chart for recording the response to desmopressin is available as supplementary file for download at <https://doi.org/10.57187/5030>.

Table 2: Desmopressin trial.

Desmopressin trial	Mild/moderate haemophilia A	von Willebrand disease (type 3, type 2B excluded)	Mild platelet function disorders
Administration	Intravenous or subcutaneous	Intravenous or subcutaneous	Intravenous or subcutaneous
Laboratory tests	FVIII:C one-stage; FVIII:C chromogenic (in case of discrepancy at baseline)	Full blood count at baseline and post-1 hour; FVIII:C, VWF:Ag, VWF:activity* (all time points)	–
Time points for blood draws	Baseline, post-1-hour, post-4-hours	Baseline, post-1-hour, post-4-hours	–
Vital parameters during test	Blood pressure, heart rate	Blood pressure, heart rate	Blood pressure, heart rate
Subjective symptoms (facial flushing, headache...)	Register any symptoms at all time points	Register any symptoms at all time points	Register any symptoms at all time points

Only one test is recommended to evaluate VWF:response (VWF:RCo or VWF:GPIbR or VWF:GPIbM VWF:Ab or VWF:CB) at all time points [45].

Response to desmopressin and possible combination treatment

There is no specific definition of desmopressin response in haemophilia A. Most experts define a complete response as the normalisation of FVIII:C levels (≥ 50 IU/dl) and an adequate response as an increase of FVIII:C levels to ≥ 30 IU/dl [39].

The proposed definition of desmopressin response in von Willebrand disease is an increase of at least 2-fold in baseline von Willebrand factor activity and a sustained elevation of both von Willebrand factor and FVIII:C levels above 50 IU/dl for a minimum of four hours [40].

These definitions are valuable for standardising response criteria across studies. Nevertheless, in clinical practice the primary consideration is whether the increase in FVIII/von Willebrand factor following desmopressin administration is sufficient to manage a specific bleeding episode or to prevent bleeding during specific invasive procedures.

Desmopressin administration is often combined with tranexamic acid. This combination may be particularly effective due to the increased release of tissue plasminogen activator following desmopressin administration.

A recent study evaluated the combined use of desmopressin and FVIII concentrate in non-severe haemophilia A prior to minor medical procedures. Although the study included only 32 patients, it showed how the combination treatment is feasible and may reduce FVIII concentrate consumption, thereby lowering overall treatment costs [41].

Desmopressin during pregnancy and delivery

Desmopressin is not currently licensed for use during pregnancy.

Limited data are available regarding the use of desmopressin during pregnancy. Mannucci described its use during the first trimester to support chorionic villus sampling or amniocentesis in 27 carriers of haemophilia A and five patients with von Willebrand disease type 1 [42]. In this case series, desmopressin use (dose 0.3 mcg/kg) appeared to be feasible, effective and safe, without an increase in bleeding or miscarriage. Measurement of FVIII and von Willebrand factor levels following desmopressin administration in these cases is advisable.

More data are available regarding the use of desmopressin for peripartum bleeding prophylaxis, as reported in a systematic review of 172 pregnancies [43]. At the time of delivery, desmopressin administration is recommended after umbilical cord clamping (0.3 mcg/kg intravenously to achieve a shorter time to peak). Repeated doses may be given for 3–4 days postpartum, particularly when a midline episiotomy is performed [44]. Monitoring FVIII, von Willebrand factor and sodium levels is advisable, especially when repeated doses are administered [44].

Desmopressin is contraindicated during pregnancy in case of preeclampsia, due to the risk of exacerbation of arterial hypertension [43].

Gaps in knowledge and limitations of this guidance

Although the use of desmopressin in patients was first introduced more than 50 years ago, several aspects still require further investigation. In particular, current gaps in knowledge include:

- Determining the optimal desmopressin dose in obese patients.
- Identifying which patients may safely not need a desmopressin test.
- Assessing whether desmopressin can be used in patients with other bleeding disorders (with a non-specific mechanism, increasing FVIII/von Willebrand factor levels).

The limitations of this guidance are as follows: consensus was not reached via a Delphi process and patient organisations were not involved.

Conclusions

More than 50 years after its first use, desmopressin remains a valuable therapeutic option and continues to serve as a cornerstone in the management of bleeding disorders, particularly in non-severe haemophilia A and von Willebrand disease.

This guidance provides practical recommendations for its use in clinical settings.

Table 3: Practical recommendations for desmopressin.

Desmopressin s.c. or i.v. 0.3 mcg/kg is indicated for prevention or treatment of bleeding in patients with non-severe haemophilia A and von Willebrand disease (depending on the DDAVP trial result)
Desmopressin use may also be considered to prevent and treat bleeding events in mild platelet function disorders and bleeding disorders of unknown cause
Administration of desmopressin >2 days requires evaluation of response, due to the possible development of tachyphylaxis
Fluid restriction is recommended the day of desmopressin administration to avoid hyponatraemia; in case of repeated administration, sodium levels should be evaluated
Desmopressin is contraindicated in cases of hyponatraemia, history of seizures, arterial and venous thrombotic events, preeclampsia, type 2B von Willebrand disease with thrombocytopenia, children <2–4 years
A DDAVP trial is recommended in all patients with non-severe haemophilia A and von Willebrand disease, with assessment of FVIII, von Willebrand factor at baseline and after administration (1 hour and 4 hours)
This trial may be omitted in patients with baseline von Willebrand factor levels between 30 and 50 IU/dl
Administration of tranexamic acid in association with desmopressin is recommended (due to the increased release of tissue plasminogen activator following desmopressin administration)
Specifics in children:
– Desmopressin 0.3 mcg/kg i.v. (not s.c.)
– Fluid restriction during trial until spontaneous urinary voiding occurs

Desmopressin is an effective treatment for mild bleeding disorders, including non-severe haemophilia A (including carriers) and von Willebrand disease. Patients with bleeding disorders of unknown cause and certain mild platelet function disorders may also benefit from desmopressin administration, although the available evidence supporting this indication remains limited.

Due to its subcutaneous formulation, desmopressin is particularly well-suited for home treatment and for managing low-risk procedures such as dental hygiene and dental extractions in adults.

A desmopressin trial is recommended to identify non-responders and to guide clinical decision-making. However, this trial may be omitted in patients with baseline von Willebrand factor levels between 30 and 50 IU/dl, where desmopressin responsiveness can reasonably be assumed.

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Financial disclosure

The authors did not receive any financial support for the preparation of this manuscript.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix A

The supplementary file (DDAVP trial monitoring chart) is available for download as a separate file at <https://doi.org/10.57187/5030>.