Review

Bench-to-bedside review: Antidotal treatment of sulfonylurea-induced hypoglycaemia with octreotide
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Abstract
The major potential adverse effect of use of sulfonylurea agents (SUAs) is a hyperinsulinaemic state that causes hypoglycaemia. It may be observed during chronic therapeutic dosing, even with very low doses of a SUA, and especially in older patients. It may also result from accidental or intentional poisoning in both diabetic and nondiabetic patients. The traditional approach to SUA-induced hypoglycaemia includes administration of glucose, and glucagon or diazoxide in those who remain hypoglycaemic despite repeated or continuous glucose supplementation. However, these antidotal approaches are associated with several shortcomings, including further exacerbation of insulin release by glucose and glucagon, leading only to a temporary beneficial effect and later relapse into hypoglycaemia, as well as the adverse effects of both glucagon and diazoxide. Octreotide inhibits the secretion of several neuropeptides, including insulin, and has successfully been used to control life-threatening hypoglycaemia caused by insulinoma or persistent hyperinsulinaemic hypoglycaemia of infancy. Therefore, this agent should in theory also be useful to decrease glucose requirements and the number of hypoglycaemic episodes in patients with SUA-induced hypoglycaemia. This has apparently been confirmed by experimental data, one retrospective study based on chart review, and several anecdotal case reports. There is thus a need for further prospective studies, which should be adequately powered, randomized and controlled, to confirm the probable beneficial effect of octreotide in this setting.

Introduction
Although the number of oral medications available to treat diabetes mellitus has increased, sulfonylurea agents (SUAs) remain a mainstay of therapy for hyperglycaemia in type 2 diabetes. The major potential adverse effect of use of SUA is a hyperinsulinaemic state that causes hypoglycaemia. It may be observed during chronic therapeutic dosing, even with very low doses of a SUA, and especially in older patients. It may also result from accidental or intentional poisoning in both diabetic and nondiabetic patients [1].

The traditional approach to SUA-induced hypoglycaemia includes the administration of glucose, and glucagon or diazoxide in those who remain hypoglycaemic despite repeated or continuous glucose supplementation [2,3]. However, these antidotal approaches are associated with several shortcomings, including further exacerbation of insulin release by glucose and glucagon, leading only to a temporary beneficial effect and later relapse into hypoglycaemia [3], as well as the adverse effects of both glucagon and diazoxide [2,4]. Other measures that have been proposed include corticosteroids and urinary alkalinization to enhance urinary elimination of the SUA (e.g. chlorpropamide) [5], but their usefulness has not clearly been established.

Octreotide inhibits the secretion of several neuropeptides, including insulin, and has been successfully used to control life-threatening hypoglycaemia caused by insulinoma [6,7] or persistent hyperinsulinaemic hypoglycaemia of infancy [7,8]. Therefore, this agent should in theory also be useful to decrease glucose requirements and the number of hypoglycaemic episodes in patients with SUA-induced hypoglycaemia – effects that are related to the hyperstimulation of endogenous insulin production. This hypothesis has been evaluated in a few studies and clinical case reports, and these are reviewed here.

Pharmacology of octreotide
Octreotide acetate (Sandostatine®; Novartis Pharma, Basel, Switzerland) is a synthetic analogue of the natural hormone somatostatin that is able to bind to the same receptors. The molecular weight of this cyclic octapeptide is 1019.3, and binding of octreotide to plasma protein is about 65%.

Octreotide has effects similar to those of somatostatin but with greater potency and longer duration of action; these effects include inhibition of pituitary release of growth hormone and thyrotropin, inhibition of glucagon or insulin release, and inhibition of the secretion of various gastrointestinal tract hormones (e.g. serotonin, pepsin, gastrin,
For these indications the initial dose is usually 50 µg [15,16].

Octreotide is clinically used to suppress excessive growth hormone secretion in acromegaly, to inhibit thyrotropin-secreting pituitary adenomas (thyrotophinomas), and to treat flushing and diarrhea associated with certain gastroenterological or pancreatic neuroendocrine tumours, especially carcinoid tumors and pancreatic islet cell tumors (insulinomas), which produce a variety of peptide hormones and biogenic amines [10-12]. Trials in patients with tumors producing vasoactive intestinal peptide demonstrated that octreotide may be an effective first-line treatment for this condition. Octreotide has also been used to control bleeding oesophageal varices; to treat chronic secretory diarrhea associated with cryptosporidiosis, microsporidiosis and intestinal amoebiasis; to reduce the output of small bowel fistulas [13] and pancreatic pseudocyst drainage [14]; and to obtain relief from dumping syndrome after gastric surgery [15,16].

For these indications the initial dose is usually 50 µg, which is injected subcutaneously once or twice daily. The number of injections and dosage may then be increased gradually (from 300 to 600 µg, divided into two or three daily doses) based on tolerance and response.

Octreotide appears to be well tolerated. The most frequently reported adverse effects are moderate pain at the injection site and gastrointestinal symptoms (abdominal cramps, nausea, bloating, flatulence, diarrhoea). Like somatostatin, long-term administration of octreotide appears to promote the formation of cholelithiasis [10,12,17].

Other analogues of somatostatin are currently under development [10] and indium-111 or yttrium-90 radiolabelled somatostatin analogues have been use as diagnostic and/or therapeutic agents in patients with extensive liver metastases from neuroendocrine tumours [18-20].

**Pharmacology and toxicology of sulfonylurea agents**

SUAs act by reducing potassium conductance of an ATP-dependent potassium channel, thereby decreasing potassium ion efflux, stimulating the depolarization of pancreatic β cells and leading to calcium influx through voltage-sensitive calcium channels. The elevated intracellular concentration of calcium ions increases the sensitivity of β cells to glucose. The resultant effect of SUAs is thus to promote glucose-stimulated endogenous insulin secretion (exocytosis) from the pancreas [21-23]. In addition, there is evidence that SUA can inhibit hepatic clearance of insulin – an effect that also contributes to hyperinsulinaemia. On the other hand, hyperinsulinaemia suppresses endogenous (predominantly hepatic) glucose production. Therefore, the main toxic effect of SUA is hypoglycaemia [24]. Differences in pharmacokinetic characteristics (duration of action, hepatic metabolism and/or renal excretion, enterohepatic circulation, active metabolites) may have important implications for the severity and duration of SUA-induced hypoglycaemia [24].

Serious hypoglycaemia is usually defined as hypoglycaemia that causes death or that requires prehospital team intervention, hospitalization, or emergency department admission. The annual incidence of SUA-induced hypoglycaemia is probably about 1–2% of SUA-treated patients [25]. Case fatality rates of up to 10% have been reported [26], and 5% of survivors may have permanent neurological impairment [27]. Unfortunately, the prognostic factors of death or brain sequelae are not known. Predisposing factors for severe SUA-induced hypoglycaemia include advanced age [28,29] and use of potent or long-acting agents such as chlorpropamide, glimepiride and (mostly) glibenclamide [29,30].

Severe hypoglycaemia leading to hospital admission and sometimes fatal outcome has mainly been reported in the settings of overdose and type 2 diabetes managed with long-acting rather than short-acting SUAs [30-33]. Poor nutritional status or calorie restriction, sustained physical exercise, acute systemic illnesses, alcohol consumption, and renal, hepatic and cardiovascular disease [24,34,35] are other risk factors for development of severe hypoglycaemia. In the elderly the clinical presentation of SUA-induced hypo-
glycaemia may be atypical, and so a high index of suspicion is required; moreover, even shorter acting SUAs can cause hypoglycaemia, especially if renal or hepatic dysfunction is present. Polypharmacy also increases the risk for hypoglycaemia in the elderly, either by direct pharmacokinetic interaction (binding sites on plasma proteins, or impairment in hepatic metabolism or renal excretion) or by effects on appetite, food intake, or carbohydrate absorption [24,36]. Other relevant metabolic problems that may be observed in long-acting SUA intoxication include hypokalaemia and hypophosphataemia. Chlorpropamide has been associated with specific toxic effects including hyponatraemia due to inappropriate secretion of antidiuretic hormone, cholestatic jaundice and bone marrow depression.

**Traditional treatment of sulfonylurea agent-induced hypoglycaemia**

The traditional approach to SUA overdose includes repeated measurement of blood glucose levels, every 20–60 min, and infusion of hypertonic glucose as needed. Indeed, hypoglycaemia can be prolonged and may recur during a period of more than 24–48 hours despite glucose supplementation. Hypertonic glucose infusion rapidly corrects hypoglycaemia, but it then acts as a potent secretagogue for SUA-sensitized β cells; insulin secretion is stimulated, and so the hypoglycaemia recurs [37-40]. This effect is particularly important in nondiabetic persons, non-insulin-dependent diabetic patients and those not previously treated with SUAs [23]. Therefore, central venous access is often required for continuous and prolonged infusion of hypertonic glucose, and frequently repeated measurement of blood glucose level is mandatory; strict euglycaemia should be the goal and hyperglycaemia, as well as hypoglycaemia, should be avoided [3].

Apart from glucose administration, two antidotal approaches to SUA overdose have been employed, one using glucagon and the other diazoxide. Glucagon has been shown to produce only transient beneficial effects on glycaemia. Indeed, it also dramatically stimulates the release of endogenous insulin and thereby contributes to subsequent hypoglycaemia [3,41]. Diazoxide, an antihypertensive agent, acts as a potassium channel opener and has been used to reduce insulin release and limit rebound hypoglycaemia [2,3], but its efficacy appears limited [39]. It must be administered by intravenous infusion and its use could be associated with hypotension, reflex tachycardia, nausea and vomiting [2,4,42]. Such adverse effects may be especially problematic in elderly patients.

**Octreotide in sulfonylurea agent-induced hypoglycaemia: experimental and clinical data**

**Animal and volunteer studies**

Few animal and volunteer human studies have examined the effects of somatostatin or octreotide on SUA-induced hypoglycaemia. These have demonstrated the short-term inhibitory effect of somatostatin on insulin release during glucose infusion or tolbutamide administration [43,44].

Compared with somatostatin, octreotide is expected to confer at least an equal inhibitory effect on insulin release but with a longer duration of action. This was confirmed in a controlled randomized crossover study [39]. Eight healthy volunteers were given glipizide orally (1.45 mg/kg) on 3 separate days. All volunteers developed hypoglycaemia (glucose concentration <50 mg/dl) within 3 hours. They were initially treated with 25 g of 50% glucose. Then, the treatment consisted of the following: glucose infusion alone to maintain euglycaemia (glucose concentration 85 mg/dl; treatment limb 1); same as treatment limb 1 plus continuous intravenous octreotide (30 ng/kg per min; treatment limb 2); or same as treatment limb 1 plus intravenous diazoxide every 4 hours (300 mg; treatment limb 3). Octreotide infusion significantly lowered insulin levels as compared with treatment limbs 1 and 3 ($P<0.01$). Glucose requirements to reach euglycaemia in treatment limbs 1 and 3 were similar but greater than those with octreotide treatment ($P<0.001$). When therapy was stopped 13 hours after glipizide ingestion, only two out of eight volunteers developed hypoglycaemia within 4 hours after therapy with octreotide, whereas all individuals in treatment limbs 1 and 3 had rebound hypoglycaemia within 90 min. Overall, octreotide reduced the need for exogenous glucose (in four out of eight it was entirely eliminated) in this clinical model of glipizide overdose, demonstrating the prolonged suppressive action of octreotide on glucose-stimulated insulin secretion by SUA-sensitized β cells.

**Clinical data**

Although SUA-induced hypoglycaemia remains an unlicensed indication, several authors have reported successful use of octreotide in patients with SUA overdose, and this clinical experience seems to confirm the clinical antidotal value of this agent [3,38,45-55].

In 1993 Krentz and coworkers [38] reported on a nondiabetic patient with SUA-induced hypoglycaemic coma, who relapsed despite resuscitation with intravenous boluses of 50% glucose and continuous 10% glucose infusion. Subcutaneous injection of octreotide (50 μg every 12 hours; three doses over 24 hours) prevented further recurrence of hypoglycaemia such that no further bolus of 50% glucose was needed. No adverse effects were observed.

Boyle and colleagues [39] reported the case of a 36-year-old male who attempted suicide with a large overdose of tolbutamide. Initial therapy with dextrose resulted in repeated hypoglycaemia. A regimen of octreotide administration similar to that reported by Krentz and coworkers allowed euglycaemia to be maintained, without need for additional dextrose support, by decreasing plasma insulin and C-peptide levels. Several other isolated reports have also
confirmed the clinical value of octreotide in patients with severe refractory SUA-induced hypoglycaemia [45,48,56].

Graudins and coworkers [3] reported an interesting case of a 42-year-old nondiabetic man who attempted suicide on two separated occasions by ingesting 150 mg glipizide. On the first occasion he was treated only with glucose and required 1511 g glucose over a 72-hour period to treat recurrent hypoglycaemia. On the second occasion, 50 µg octreotide was administered subcutaneously at 2 hours after ingestion of glipizide, followed by 100 µg at 8, 20 and 32 hours after ingestion. Only 826 g glucose had to be administered on the second occasion. Octreotide administration was associated with a marked reduction in serum insulin levels.

The largest (although relatively small) retrospective observational series was that reported by McLaughlin and colleagues [49]. They reviewed the charts of nine adult patients treated with octreotide for SUA-induced hypoglycaemia (six had ingested gliburide and three had ingested glipizide) from 1995 to 1998. Octreotide (ranging from a single subcutaneous dose of 40 µg to an intravenous infusion of 125 µg/hour) significantly reduced the number of hypoglycaemic events recorded per patient from a mean of 3.2 before administration to a mean of 0.2 after (P = 0.008). The amount of 50% glucose ampoules used per patient was also markedly reduced (from a mean of 2.9 before to 0.2 after; P = 0.004), although the maintenance glucose infusion rate was similar. This stabilization of blood glucose concentration occurred immediately after octreotide administration in all nine patients. Two treatment failures were observed, defined as occurrence of hypoglycaemia 14 hours after octreotide administration (and 30 hours after the ingestion of gliburide) and 36 hours after octreotide (40 hours after ingestion of extended release glipizide), respectively. It is likely that more prolonged administration of octreotide would have prevented relapsing hypoglycaemia.

Carr and Zed [51] reported on the use of octreotide in the management of two cases of SUA-induced hypoglycaemia following overdose in two young women (500 mg and 1 g gliburide, respectively). Despite administration of bolus doses of glucose 50% and infusions of glucose 10%, both patients exhibited refractory hypoglycaemia. Three doses of octreotide 50 µg were administered subcutaneously, 8 hours apart, to both patients, resulting in a reduction in hypoglycaemic episodes and reduced need for dextrose administration.

Nzerue and coworkers [52] reported the case of a patient with chronic renal failure who developed recurrent and prolonged episodes of hypoglycaemia associated with the use of SUA. He was hospitalized with neuroglycopenic symptoms that persisted in spite of large doses of parenteral glucose. On administration of octreotide, the hypoglycaemia resolved and blood glucose levels were maintained even after cessation of parenteral glucose. Only two subcutaneous doses of octreotide 12 hours apart were needed, and the patient fully recovered.

Green and Palatnik [53] reported the case of a 20-year-old woman who ingested 900 mg gliburide, causing hypoglycaemia that was refractory to treatment with intravenous glucose, glucagon, and diazoxide. Octreotide administration (100 µg intravenously) rapidly reversed the hypoglycaemia, stabilizing the patient and permitting eventual discharge without significant adverse events.

More recently, successful management of SUA-induced refractory hypoglycaemia with octreotide was reported by Crawford and Perera [55] in two elderly patients. A 76-year-old man with type 2 diabetes controlled with gliclazide 80 mg twice daily was admitted after an acute myocardial infarction and cardiac arrest. He was successfully resuscitated and underwent emergency bypass surgery, but developed cardiac and renal failures. Frequent and refractory hypoglycaemic episodes were observed, associated with seizures and coma, in spite of gliclazide discontinuation and intravenous infusion of glucose 10%. An intravenous infusion of octreotide (30 ng/kg per min) was associated with rapid control of blood glucose level, but the infusion had to be maintained for 13 hours. The patient was discharged home 2 days later. A 75-year-old man with type 2 diabetes taking glibenclamide 2.5 mg/day developed recurrent hypoglycaemia associated with impaired renal function. Hypoglycaemic coma occurred despite glibenclamide discontinuation and repeated supplementation with intravenous boluses of glucose 50% and continuous infusion of glucose 10%. The high volume of intravenous fluid precipitated cardiac failure and pulmonary oedema, requiring inotropic support. A single subcutaneous injection of 50 µg octreotide was administered. One hour later the blood glucose level was normalized and no further episodes of hypoglycaemia occurred. In this case, marked reductions in insulin and C-peptide levels were documented (before octreotide treatment: insulin 1250 pmol/l and C-peptide 20,949 pmol/l; 8 hours after octreotide treatment: insulin 153 pmol/l and C-peptide 5654 pmol/l). The patient fully recovered.

Only two cases of antidotal use of octreotide have been reported in children [47,54]. A 5-year-old child was erroneously given glipizide in repeated doses over 3 days [47]. He was admitted in status epilepticus and his blood glucose was 12 mg/dl. The seizures stopped after lorazepam was given, but recurrent hypoglycaemia developed despite glucose supplementation (up to 18 g/hour). A 25 µg (1.25 µg/kg in this 20 kg child) dose of octreotide was administered intravenously and resulted in a rapid increase in glycaemia to 150–200 mg/dl, thereby allowing the amount of glucose administered to be reduced and completely stopped 4 hours later. A marked decrease in insulin concentration was also documented after octreotide administration in this case.
(before octreotide treatment: insulin 53 µIU/ml and blood glucose 45 mg/dl; after octreotide treatment: insulin 16 µIU/ml and blood glucose 183 mg/dl). A 16-month-old child (weight not reported) was admitted 1 hour after ingesting glyburide accidentally [54]. Despite continuous infusion of 10% dextrose and repeated boluses of 50% glucose, recurrent hypoglycaemia developed. Approximately 5 hours after ingestion, he received 10 µg octreotide intravenously over 15 min. Euglycaemia was then maintained with 10% glucose infusion, without any additional bolus. A second dose of octreotide had to be given 8 hours later. Glucose 10% infusion was completely stopped 5 hours after the second octreotide injection.

This clinical experience suggests that octreotide is effective in treating prolonged or refractory hypoglycaemia induced by SUA, as well as in preventing rebound hypoglycaemia by breaking the vicious circle that can result from glucose supplements and consequent insulin release. It should be used in adults [57] as well as in children [58-60], despite the limited clinical experience.

**Route and dosage**

There is clinical experience with both subcutaneous and intravenous administration. Octreotide has most frequently been administered subcutaneously in doses ranging from 40 to 100 µg in adults. The most commonly used regimen consists of an initial 50 µg dose, which is repeated two to three times a day. Doses ranging from 1 to 10 µg/kg have been well tolerated by children in other conditions [58]. Intravenous administration usually consists of a continuous infusion (30 ng/kg per min). In a paediatric case, a 25 µg intravenous dose was used in a 20 kg child [47]. Bioavailability of both routes appears to be similar, but subcutaneous injection seems to increase markedly the duration of action [61].

Octreotide administration may be required for several days, especially for long-acting or sustained release SUAs. However, in the majority of reported cases, a treatment course limited to 12–72 hours was needed to resolve the hypoglycaemia. Because some patients experience delayed hypoglycaemia after cessation of octreotide therapy, they should be observed for rebound hypoglycaemia for at least 12–24 hours after the last dose [39].

**Adverse effects**

Treatment with octreotide appears to be safe and is usually well tolerated. In nontoxicological indications such as acromegaly or insulinoma, octreotide has been associated with various adverse effects, including nausea, diarrhoea, abdominal cramps and flatulence, especially at the beginning of the treatment [10]. These symptoms result from the physiological actions of somatostatin on the gastrointestinal tract and exocrine pancreas, and begin within hours after the first injection. Their severity is dose dependent [10]. Reduced glucose tolerance and hyperglycaemia that might be expected is limited with long-term therapy by the ability of octreotide to delay absorption of carbohydrate and to inhibit the secretion of growth hormone and glucagons. Long-term treatment with octreotide (>1 month) has been associated with an increased incidence of cholesterol gallstones (occurring in approximately 20–30% of patients).

When it is used to counteract SUA-induced hypoglycaemia, both in chronic and acute overdose, complications appear very few and mortality is nil. Rare reported adverse effects include injection site pain, nausea, vomiting, dose-related transient abdominal pain and diarrhoea [39].

**Economical considerations**

Octreotide is not currently licenced for the indication of SUA-induced hypoglycaemia. Depending on local regulations, this may prevent reimbursement of its cost by social insurance agencies.

Although it would not be expected to reduce mortality and long-term morbidity rates markedly compared with a carefully monitored glucose infusion, octreotide does have some advantages. For example, it renders the management of SUA-poisoned patients easier. The treatment is also economical because octreotide is inexpensive (costing less than €10 for a 100 µg vial) and it potentially reduces the need for frequent glucose measurements, insertion of central line access or intensive care unit admission.

These advantages may be particular prominent in elderly people. Indeed, the classical autonomic adrenergic symptoms and signs of hypoglycaemia may not be present, and neuroglycopenic features, such as drowsiness and confusion, may dominate the clinical picture. The diagnosis can be easily missed if the blood glucose level is not frequently monitored. In addition, intravenous glucose replacement may carry a risk for fluid overload in those patients who often suffer impairment in cardiac or renal function, and so close observation of haemodynamic parameters in the intensive care unit setting is mandatory.

It is unwise to discharge patients with SUA-induced hypoglycaemia after a satisfactory initial response. Indeed, both intravenous glucose supplements and subcutaneous octreotide administration may be required for several days. Therefore, the hospital stay is not likely to be shortened, whatever the treatment option.

**Conclusion**

Few experimental data are currently available on the use of octreotide in SUA-induced hypoglycaemia. The reported clinical experience, which is limited to one retrospective study based on chart review, and several anecdotal case reports may clearly be biased. There is thus a need for further prospective studies, which should be adequately powered,
randomized and controlled, to confirm the beneficial effect of octreotide in this setting.

From available data, however, octreotide appears to be highly efficacious and safe in the management of SUA-induced hypoglycaemia. It should be considered, along with glucose supplementation and gastrointestinal decontamination, for first-line therapy in any patient with SUA-induced hypoglycaemia, either symptomatic or with a serum glucose concentration less than 60 mg/dl, especially if hypoglycaemia is refractory to glucose supplementation or relapses.

The following scheme is recommended:

- Glucose 15–25 g must be delivered immediately as intravenous 50% glucose to restore the patient to euglycaemia in the short term (0.5 g/kg as intravenous 25% glucose in children); oral glucose may be an alternative in fully conscious and cooperative patients.
- The glucose bolus must be followed immediately by an infusion of 5% or 10% glucose, usually at a rate of 100–200 g/day glucose.
- Blood glucose should be regularly monitored for at least 24 hours; the blood glucose concentration should be maintained at around 90–120 mg/dl because this is sufficient to prevent neuroglycopenia while avoiding maximal insulin secretion.
- Potassium concentration should be also be monitored (there is a risk for hypokalaemia with insulin and glucose).
- Gastrointestinal tract decontamination, especially administration of activated charcoal, may be considered if drugs have recently been ingested, in accordance with usual recommendations.
- Methods to enhance elimination are usually not applicable. However, multiple dose activated charcoal may be considered for certain SAUs (e.g. glipizide) because of the enterohepatic recirculation, although clinical benefit has not been demonstrated. It has also been suggested that urine alkalinization reduces the half-life of chlorpropamide.
- Octreotide (adults: 50 µg subcutaneously every 8–12 hours; children: 1–1.25 µg/kg) is recommended if hypoglycaemia relapses in spite of continuous glucose infusion. Alternatively, octreotide could be used to prevent relapse of hypoglycaemia; to reduce glucose requirements and fluid administration, especially in elderly patients with cardiac dysfunction or impaired renal function; or to obviate the need to insert a central venous line access for prolonged infusion of more concentrated hypertonic glucose solutions, especially in children.
- If octreotide is not available, then diazoxide (adults: 300 mg intravenously over 30 min every 4 hours; children [recommended but not supported by clinical experience]: 3–8 mg/kg per day orally divided into two to three doses [i.e. every 8–12 hours]) remains a viable alternative to reduce insulin secretion. However, it should be used cautiously in elderly patients or those with coronary heart disease because of its cardiovascular adverse effects.

- Glucagon should not be used in the management of SUA-induced hypoglycaemia because it further stimulates insulin secretion dramatically.

As mentioned above, continuing research is required to confirm the clinical findings that support these provisional recommendations, and to establish the optimal route and dosing guidelines, dosing interval, duration of treatment and inpatient monitoring requirements. Because recruitment of large series of patients with SUA-induced hypoglycaemia in a single centre is almost impossible, only a multicentre approach will be able to answer these questions.

Competing interests
The author(s) declare that they have no competing interests.

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