orphanaesthesia

Anaesthesia recommendations for

Alport syndrome

Disease name: Alport syndrome

ICD 10: Q87.81

Synonyms: Hereditary nephritis

Disease summary:

The Alport syndrome is a rare inherited form of progressive renal failure with an incidence of one in 10,000 newborns. It is due to genetic mutations of the collagen IV α3-4-5 network that is the major collagenous constituent of basement membranes in glomerulus, cochlea, lens and retina. Inheritance is X-linked in 80% of affected patients, with a more severe clinical course in males. It can lead to end-stage renal disease requiring dialysis and transplantation. The prevalence of autosomal recessive and dominant variants is 15% and 5%, respectively. This low prevalence of dominant cases can be due to their highly variable manifestation in the phenotype, ranging from mild symptoms to clinical patterns comparable to the X-linked disease, although deterioration of renal function occurs more slowly, resulting in several unrecognised dominant cases. Loss of renal function – due to the progressive glomerulosclerosis and tubulointerstitial fibrosis – is the most important clinical manifestation of the syndrome with haematuria, proteinuria and hypertension. Sensorineural hearing loss and ocular abnormalities are common especially in X-linked and autosomal recessive forms of Alport syndrome. Leiomyomatosis in respiratory, gastrointestinal and female reproductive tracts is found in 2-5% of patients with an X-linked genotype. The main anaesthetic problems in the treatment of patients with Alport syndrome are related to chronic renal failure with haemorrhagic diathesis and abnormalities in heart conduction due to hyperkalaemia and altered calcium metabolism. Circulatory collapse or difficulties in ventilation due to the presence of mediastinal leiomyomas compressing heart, large vessels and airways is a possible risk as well as the presence of concomitant comorbidities.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Typical surgeries

Renal biopsy; renal transplantation; eye surgery; hearing aids implantation; removal of leiomyomas.

Type of anaesthesia

Both general and regional anaesthesia can be performed in cases of Alport syndrome.

Doses of sedatives (i.e. midazolam) and opioids should be reduced and titrated to effect in patients with renal failure, since these agents may have delayed metabolism and excretion. Moreover, distribution volume and plasma protein binding of anaesthetic drugs may be altered, resulting in plasma concentrations higher than expected.

Hypnotic agents (i.e. propofol) should be carefully administered as a bolus to avoid haemodynamic and myocardial impairment in these patients who are often hypovolaemic and with coexisting heart failure.

Succinylcholine can be safely used as a neuromuscular blocking agent only in the absence of electrocardiographic changes and if the serum potassium concentration is <5.5 mEq/L.

Regional anaesthesia may limit the risks of deep narcosis and the use of intravenous drugs in patients with multiple comorbidities. It can be performed taking into account: 1) the altered platelet function induced by renal failure; 2) the residual effects of heparin administered during dialysis.

If possible, monitored anaesthesia care (MAC) – in which patient undergoes a procedure in local anaesthesia plus sedation and analgesia – is preferred in patients with end-stage renal disease related to Alport syndrome.

Specific pain management methods do not exist. However, some adjustments are required in patients who develop renal impairment: 1) non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated; 2) opioids (i.e. tramadol) must be administered in lower doses to avoid plasmatic accumulation and subsequent respiratory depression.

Necessary additional pre-operative testing (beside standard care)

Alport syndrome is often associated with cardiovascular diseases (hypertension, arrhythmias, heart failure) and progressive renal failure; these possible pathologies must be specifically investigated:

1. Cardiac function test, such as electrocardiography and echocardiography, should be performed to exclude cardiomyopathy;
2. The pulmonary picture should be evaluated, at least with chest radiography, to exclude oedema or pleural effusion;
3. Renal function, serum electrolytes and acid–base balance should be always evaluated to assess the degree of renal failure, the need of perioperative dialysis and to early adjust electrolytic and acid-base disorders;
4. Standard coagulation tests should always be performed, since haemorrhagic diathesis is a known risk. In end-stage renal disease patients, the use of thromboelastography (TEG) or rotational thromboelastometry (ROTEM) could be particularly indicated.

Particular preparation for airway management

No defined guidelines referring to the patient's airway management and position exist.

Major attention should always be given to airway management in patients with X-linked Alport syndrome due to the high incidence of upper airway lesions that characterise these patients. A preoperative careful airway assessment, possibly benefiting from a more specific examination by otorhinolaryngologist, is hence crucial in planning the best approach for anaesthesia induction.

In patients undergoing oesophageal leiomyoma removal surgery – a frequent complication of Alport syndrome – the lateral position could be particularly indicated to avoid the compression of tracheal and major vessels during the induction of anaesthesia. Fibrobronchoscopy could help in performing oro-tracheal intubation.

Since a case report describing a bilateral vocal cord paralysis following coronary artery aneurysmectomy in Alport syndrome has been published, pointing out the neural vulnerability in all renal failure patients, but especially in those with Alport syndrome, it is advisable for the surgeons to pay close attention to the risk of vocal cord damage.

Particular preparation for transfusion or administration of blood products

Alport syndrome patients developing renal failure may have an elevated risk of intraoperative bleeding due to the altered coagulation process and inhibited platelet function induced by uraemia, impaired vessel reactivity and anaemia. Consequently, a higher need of blood products could be observed during surgery.

Preoperative dialysis has been reported to improve platelet function in patients with end-stage renal disease, reducing the bleeding risk during surgery. In case that there is no time for dialysis, desmopressin could be useful to facilitate platelet aggregation.

Major attention should always be paid to residual heparin in the four hours following dialysis. Protamine could help to reverse heparin in case of emergency surgery.

Even in absence of definite recommendations for an administration of blood products in patients with Alport syndrome, all uraemic and actively bleeding patients should be treated with platelet concentrates immediately before or during surgery, regardless of the platelet counts.

Particular preparation for anticoagulation

If heparin has been used in patients with Alport syndrome on dialysis, normalisation of the coagulation parameters, usually lasting four hours, should be awaited before surgery. Protamine can anyhow reverse the heparin effect.

Particular precautions for positioning, transport or mobilisation

Patients with important oesophageal leiomyomas associated to Alport syndrome should be subject to cautious postural changes and remain in the lateral position to avoid airway, heart and major vessels compression by the mediastinal masses.

Other suggestions for positioning, transport or mobilisation have not been reported.

Interaction of chronic disease and anaesthesia medications

In dialysis-dependent patients with Alport syndrome, the recommendations concerning the use of anaesthetic agents are comparable to those of patients with end-stage renal disease.

Anaesthetic procedure

In patients with renal failure due to the Alport syndrome:

1. Midazolam and opioids (especially morphine) should be avoided or titrated to effect due to their delay in metabolism and excretion possibly resulting in prolonged respiratory depression;
2. Hypnotic agents (i.e. propofol) and volatile agents must be carefully administered in patients with myocardial impairment and/or at risk of hypovolaemia due to dialysis;
3. Non-depolarising neuromuscular blocking agents (NMBA) – such as atracurium and cisatracurium – should be preferred to succinylcholine, whose metabolism by cholinesterase is reduced in end-stage renal disease. Rocuronium may be used in longer surgery or if sugammadex is available, since it is eliminated partially by the kidney and its clearance could be reduced because of renal failure.

In patients requiring rapid sequence of induction and intubation, succinylcholine could be used if serum potassium concentration is <5.5 mEq/L and electrocardiographic alterations are not evident.

In patients requiring total intravenous anaesthesia (TIVA), such as in neurosurgery, continuous infusion of propofol and short-acting opioids (i.e. remifentanil) is not contraindicated.

Regional anaesthesia is safe and feasible, when appropriate, in patients with Alport's syndrome considering that the onset of action of local anaesthetics is slower in end-stage renal disease due to low serum bicarbonate levels and reduced protein binding.

Particularly suggested is the use of combined spinal-epidural anaesthesia to perform renal transplantation in Alport syndrome patients. In fact, a low dose of intrathecal heavy bupivacaine in addition to an epidural volume extension of analgesia during and after the procedure has been reported to provide the necessary motor block and the best pain management, with a low risk of adverse events and no impact on haemodynamic and respiratory muscle activity.

Particular or additional monitoring

Due to the high risk of arrhythmias possibly induced by elevated serum potassium, at least 5-lead, better 12-lead, electrocardiogram (ECG) should be used during surgery in patients with Alport syndrome.

Non-depolarising muscular blockage should be always monitored due to the variability in the pharmacokinetics of NMBAs in end-stage renal disease patients.

In case of high-risk surgery, invasive tools and monitoring, such as arterial cannulation for invasive blood pressure measurement and central venous line placement, are recommended.

Possible complications

Severe cases of Alport syndrome are characterised by a high risk of fatal arrhythmias, hyperkalaemic cardiac arrest, heart failure and intraoperative bleeding. Over-administration of intravenous fluids during surgery may lead to pulmonary oedema, whereas under-administration may cause haemodynamic instability. Sedative drugs (i.e. midazolam) and NMBAs may induce severe and prolonged respiratory depression.

Post-operative care

Post-operative care and monitoring depends on patient and surgical characteristics.

The great majority of Alport syndrome patients could return home after outpatient procedures or be discharged to a regular surgical ward after inpatient surgery.

Admission to the intermediate or intensive care unit could be indicated in dialysis-dependent patients who are haemodynamically instable after major surgical intervention, or if severe peri-operative comorbidities exist. All severe cases of Alport syndrome and all end-stage renal disease patients should be adequately monitored in the post-operative period due to the high risk of electrolytic disorders, pulmonary oedema and bleeding.

Major attention should be given to these patients when undergoing narcosis due to their slower drug metabolism and excretion, monitoring the breathing capacity.

Patients requiring dialysis should receive renal replacement therapy as soon as the risk of surgery-induced fluid shifts and bleeding has been reduced.

Post-operative analgesia should be guaranteed with a multimodal approach, such as regional anaesthetic techniques and wound infiltration with local anaesthetics in order to reduce the need of intravenous analgesics and to avoid NSAIDs.

Disease-related acute problems and effect on anaesthesia and recovery

The emergency-like situations in patients with Alport syndrome are fatal arrhythmias mainly related to end-stage renal disease.

There are evidences supporting the need of standby extracorporeal life support (ECLS) during surgery to remove oesophageal leiomyomas due to the risks of critical haemodynamic and/or breathing problems possibly induced by mediastinal mass compression on heart, major vessels and airway.

Ambulatory anaesthesia

Ambulatory anaesthesia is indicated during the early phases of Alport syndrome, taking into account renal function, electrolytic and acid-base balance and coagulation profile.

If outpatient procedures are necessary for patients with end-stage renal disease, anaesthesiologists should be aware of the recommendations on narcosis drugs and the potential complications detailed above.

Obstetrical anaesthesia

Not specific recommendations are reported.

Since X-linked inheritance is the most frequent form, females with Alport syndrome have often a disease phenotype less severe than males. It is uncommon for end-stage renal disease due to X-linked Alport syndrome to characterise pregnant women, since the risk of severe renal failure increases with increasing age, achieving a 30% probability at the age of 60. On the contrary, the chronic kidney disease and consequent myocardial impairment may occur in women with autosomal dominant forms during childbearing age.

However, central neuraxial block (spinal or epidural) may be safely used for labour analgesia and caesarean surgery in patients on dialysis.

References

1. Savige J. Alport syndrome: its effects on the glomerular filtration barrier and implications for future treatment. J Physiol 2014; 592:4013-4023
2. Kashtan C. Alport syndrome: facts and opinions. F1000Res 2017;6:50
3. Mehta L, Jim B. Hereditary Renal Diseases. Semin Nephrol 2017;37:354-361
4. Bekheirnia MR, Reed B, Gregory MC, McFann K, Shamshirsaz AA, Masoumi A, et al. Genotype-phenotype correlation in X-linked Alport syndrome. J Am Soc Nephrol 2010;21:876-883
5. Rosado C, Bueno E, Felipe C, Valverde S, González-Sarmiento R. Study of the True Clinical Progression of Autosomal Dominant Alport Syndrome in a European Population. Kidney Blood Press Res 2015;40:435-442
6. Savige J, Colville D, Rheault M, Gear S, Lennon R, Lagas S, et al. Alport Syndrome in Women and Girls. Clin J Am Soc Nephrol 2016;11:1713-1720
7. Kashtan CE. Alport syndrome and the X chromosome: implications of a diagnosis of Alport syndrome in females. Nephrol Dial Transplant. 2007;22:1499-1505
8. Heidet L, Gubler MC. The renal lesions of Alport syndrome. J Am Soc Nephrol 2009;20:1210-1215
9. Savige J, Gregory M, Gross O, Kashtan C, Ding J, Flinter F. Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy. J Am Soc Nephrol 2013;24:364-375
10. Kashtan CE, Ding J, Gregory M, Gross O, Heidet L, Knebelmann B, et al. Clinical practice recommendations for the treatment of Alport syndrome: a statement of the Alport Syndrome Research Collaborative. Pediatr Nephrol 2013;28:5-11
11. Izzedine H, Tankere F, Launay-Vacher V, Deray G. Ear and kidney syndromes: molecular versus clinical approach. Kidney Int 2004;65:369-385
12. Shaw EA, Colville D, Wang YY, Zhang KW, Dagher H, Fassett R, et al. Characterization of the peripheral retinopathy in X-linked and autosomal recessive Alport syndrome. Nephrol Dial Transplant 2007;22:104-108
13. Byrne MC, Budisavljevic MN, Fan Z, Self SE, Ploth DW. Renal transplant in patients with Alport syndrome. Am J Kidney Dis 2002;39:769-775
14. Uliana V, Marcocci E, Mucciolo M, Meloni I, Izzi C, Manno C, et al. Alport syndrome and leiomyomatosis: the first deletion extending beyond COL4A6 intron 2. Pediatr Nephrol 2011;26:717-724
15. Anker MC, Arnemann J, Neumann K, Ahrens P, Schmidt H, König R. Alport syndrome with diffuse leiomyomatosis. Am J Med Genet A 2003;119A:381-385
16. Spina SP, Ensom MH. Clinical pharmacokinetic monitoring of midazolam in critically ill patients. Pharmacotherapy 2007;27:389-398
17. Leite TT, Macedo E, Martins Ida S, Neves FM, Libório AB. Renal Outcomes in Critically Ill Patients Receiving Propofol or Midazolam. Clin J Am Soc Nephrol 2015;10:1937-1945
18. Kirvelä M, Olkkola KT, Rosenberg PH, Yli-Hankala A, Salmela K, Lindgren L. Pharmacokinetics of propofol and haemodynamic changes during induction of anaesthesia in uraemic patients. Br J Anaesth 1992;68:178-182
19. Motayagheni N, Phan S, Eshraghi C, Nozari A, Atala A. A Review of Anesthetic Effects on Renal Function: Potential Organ Protection. Am J Nephrol 2017;46:380-389
20. Ebert TJ, Arain SR. Renal responses to low-flow desflurane, sevoflurane, and propofol in patients. Anesthesiology 2000;93:1401-1406
21. Thapa S, Brull SJ. Succinylcholine-induced hyperkalemia in patients with renal failure: an old question revisited. Anesth Analg 2000;91:237-241

22. Staals LM, Snoeck MM, Driessen JJ, van Hamersvelt HW, Flockton EA, van den Heuvel MW, et al. Reduced clearance of rocuronium and sugammadex in patients with severe to end-stage renal failure: a pharmacokinetic study. Br J Anaesth. 2010;104:31-39

23. Min KC, Lasseter KC, Marbury TC, Wrishko RE, Hanley WD, Wolford DG, et al. Pharmacokinetics of sugammadex in subjects with moderate and severe renal impairment. Int J Clin Pharmacol Ther 2017;55:746-752

24. Dahaba AA, von Klobucar F, Rehak PH, List WF. Total intravenous anesthesia with remifentanil, propofol and cisatracurium in end-stage renal failure. Can J Anaesth. 1999;46:696-700

25. Dean M. Opioids in renal failure and dialysis patients. J Pain Symptom Manage 2004;28:497-504

26. Nagar VR, Birthi P. Chronic opioid pain management for chronic kidney disease. J Pain Palliat Care Pharmacother 2015;29:48-50

27. Niscola P, Scaramucci L, Vischini G, Giovannini M, Ferrannini M, Massa P, et al. The use of major analgesics in patients with renal dysfunction. Curr Drug Targets 2010;11:752-758

28. Mazoit JX, Butscher K, Samii K. Morphine in postoperative patients: pharmacokinetics and pharmacodynamics of metabolites. Anesth Analg 2007;105:70-78

29. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. Semin Thromb Hemost 2010;36:34-40

30. Gobbi F, Sales G, Bretto P, Donadio PP, Brazzi L. Low-dose Spinal Block With Continuous Epidural Infusion for Renal Transplantation in a Patient With Alport Syndrome: A Case Report. Transplant Proc 2016;48:3067-3069

31. Srivastava VK, Agrawal S, Das PK, Ahmed M. Low dose spinal with epidural volume extension for renal transplantation in a patient with uremic cardiomyopathy. Indian J Anaesth 2014;58:93-94

32. Srivastava D, Tiwari T, Sahu S, Chandra A, Dhiraaj S. Anaesthetic management of renal transplant surgery in patients of dilated cardiomyopathy with ejection fraction less than 40%. Anesthesiol Res Pract 2014;2014:5259-5269

33. Arulkumaran N, Montero RM, Singer M. Management of the dialysis patient in general intensive care. Br J Anaesth 2012;108:183-192

34. Esposito C, Bellotti N, Fasoli G, Foschi A, Plati AR, Dal Canton A. Hyperkalemia-induced ECG abnormalities in patients with reduced renal function. Clin Nephrol 2004; 62:465-468

35. Ferrari F, Nascimeno P Jr, Vianna PT. Complete atrioventricular block during renal transplantation in a patient with Alport syndrome: case report. Rev Paul Med 2001; 119:184-186

36. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:2215-2245

37. Kanda H, Hirasaki Y, Iida T, Kanao-Kanda M, Toyama Y, Chiba T, et al. Perioperative Management of Patients With End-Stage Renal Disease. J Cardiothorac Vasc Anesth 2017;31;6:2251-2267. https://www.jcvaonline.com/article/S1053-0770(17)30408-1/pdf

38. Watanabe K, Hagiya K, Inomata S, Miyabe M, Tanaka M, Mizutani T. Bilateral vocal cord paralysis in a patient with chronic renal failure associated with Alport syndrome. J Anesth. 2010;24:472-475

39. Dimarakis I, Protopapas AD. Vocal cord palsy as a complication of adult cardiac surgery: surgical correlations and analysis. Eur J Cardiothorac Surg. 2004;26:773-775

40. Hanazaki M, Takata K, Goto K, Katayama H, Yokoyama M, Morita K, et al. Anesthetic management of a patient with Alport-leiomyomatosis syndrome. J Anesth 2009;23: 453-555

41. KDOQI. KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. Am J Kidney Dis 2007;50:471-530

42. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. Semin Thromb Hemost 2010;36:34-40

43. Lee HK, Kim YJ, Jeong JU, Park JS, Chi HS, Kim SB. Desmopressin improves platelet dysfunction measured by in vitro closure time in uremic patients. Nephron Clin Pract 2010;114:248-252

44. American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management*. Anesthesiology 2015;122:241-275

45. Lindsay RM, Friesen M, Aronstam A, Andrus F, Clark WF, Linton AL. Improvement of platelet function by increased frequency of hemodialysis. Clin Nephrol 1978;10:67-70

46. Dhir S, Fuller J. Case report: pregnancy in hemodialysis-dependent end-stage renal disease: anesthetic considerations. Can J Anaesth 2007;54:556-560

47. Chinnappa V, Ankichetty S, Angle P, Halpern SH. Chronic kidney disease in pregnancy. Int J Obstet Anesth 2013;22:223-230.

Last date of modification: July 2018

These guideline has been prepared by:

Authors

Luca Brazzi, Dept. of Surgical Sciences - University of Turin, Italy
Dept. of Anaesthesia, Intensive Care and Emergency - 'Città della Salute e della Scienza' Hospital, Turin, Italy
luca.brazzi@unito.it

Gabriele Sales, Dept. of Anaesthesia, Intensive Care and Emergency - 'Città della Salute e della Scienza' Hospital, Turin, Italy
gabriele.sales86@gmail.com

Giorgia Montrucchio, Dept. of Anaesthesia, Intensive Care and Emergency - 'Città della Salute e della Scienza' Hospital, Turin, Italy
g.montrucchio@gmail.com

Andrea Costamagna, Dept. of Anaesthesia, Intensive Care and Emergency - 'Città della Salute e della Scienza' Hospital, Turin, Italy
andrea.costamagna@hotmail.it

Peer Revision 1

Consolación Rosado Rubio, PhD MD, Service of Nephrology of the Ávila Hospital SACYL Ávila, Spain
crosadorubio@hotmail.com

Peer Revision 2

Dra. Elena Domínguez-Garrido, Unidad Diagnóstico Molecular, Fundación Rioja, Logroño, La Rioja, Spain
edominguez@riojasalud.es