A review of retained placenta in bovines - risks, diagnosis, treatment, and control

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Abstract

Retained placenta (RP) is a syndrome that affects all species of domestic animals, including bovines. Retained placenta can lead to life-threatening complications and is considered an emergency in theriogenology practice. Various factors underlie the occurrence of RP, including defects in the immunological rejection of the placenta, disorders in myometrial contractions, infections, disorders in the release or function of proteolytic enzymes in the placenta, induction of parturition, preterm birth, abortion, stillbirth, excessive body weight, senility, bacterial and fungal toxins, inbreeding, abnormal hormonal environment at peri-parturition, injuries of the placenta, elective caesarean, environmental stressful conditions, nutritional deficiencies, metabolic disturbances, and breed. Depending on the underlying cause(s), different measures have been suggested to prevent RP, such as feeding a balanced ration, proper immunisation against diseases, supplying a dry and clean environment for parturition, using breeds with a low incidence of dystocia or RP. There are several methods for treating the disease, including manual removal of membranes, injection of collagenase into the umbilical arteries of the retained membranes, uterine lavage, hormone therapy, antibiotic therapy and others. This review highlights the effective means of management of RP in cattle.

Key words: *retained placenta; cattle; diagnosis; treatment; control*

Introduction

The placenta is a temporary organ that joins the mother and foetus. The functions of the placenta are similar among mammals. The placenta plays a critical role in facilitating nutrient, gas, and waste exchange between the physically separated maternal and foetal circulations, and is an important endocrine organ that produces hormones, mainly progesterone, oestrogen, corticotrophin-releasing hormone, relaxin, and lactogens that regulate both maternal and foetal physiological events during pregnancy and parturition. Normally, the foetal membranes are shed shortly after birth (within 8 hours of delivery). If the placenta is retained up to 12

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hours, this is called delayed removal and if retained for more than 24 hours of delivery, this it is called retention of the placenta. Aretained placenta (RP) becomes a breeding ground for the growth and proliferation of different types of microbes, resulting in inflammation of the uterus in various degrees, fever, weight loss, reduced milk production, increased calving intervals, increased open days, and even death. Retained placenta can cause substantial economic losses, mainly due to the decrease in milk and calf production. The key factor in the pathogenesis of RP in cattle is the lack of timely breaking of the cotyledon-caruncle bond (Arumugasaamy et al., 2020; Mota-Rojas et al., 2020; Bowman et al., 2021).

In the present review article, the risks, symptoms, diagnosis, and treatment of RP in cattle are discussed in detail, and strategies to prevent and control the disease are proposed.

Incidence of RP

It has been reported in the range of 5–20% in cows (Dervishi et al., 2016; Carrera-Chavez et al., 2019; Mahnani et al., 2021; Rohmah et al., 2023).

Risks of RP

Expulsion of the foetal membranes usually takes less than 6 to 8 hours after delivery in cows (Han and Kim, 2005). In practice, the most commonly used definition of RP is the retention of foetal membranes 24 hours or longer postpartum in cows. Retained placenta is one of the main causes of endometritis in cattle and induces economic losses (Rajala and Grohn, 1998). Retained placenta is a risk factor for postpartum reproductive and metabolic disorders, which can affect the subsequent reproductive capability of cows (Larson et al., 1985). The risks of RP include:

Decreased milk production. It has been demonstrated that cows suffering RP following recent calving produce 7% less milk during the lactation period (Mahnani et al., 2021).

Increased interval between parturition and the first postpartum oestrus. The interval between parturition and the first postpartum oestrus is increased significantly in cows with RP compared to those without RP. Oestrus may be postponed even up to 150 days postpartum in cows with RP in the subsequent pregnancy (Gaafar et al., 2010; Patil et al., 2020; Mahnani et al., 2021).

Increased interval between parturition and mating/insemination. The interval between parturition and mating/insemination in cows with RP is increased significantly compared those without RP (Mahnani et al., 2021). In Fresian cows, the intervals in cows with and without RP were 47.2±0.6 days and 56.9±1.2 days, respectively ($p<0.05$, Gaafar et al., 2010).

Increased number of matings/inseminations per pregnancy. The number of services per pregnancy in cattle with RP is increased significantly in comparison to cattle without RP (Gaafar et al., 2010; Mahnani et al., 2021). The number of services per pregnancy in cows with RP in the previous calving compared to cows without RP was 3.5±0.1 vs 2.6±0.1, respectively ($P<0.05$, Gaafar et al., 2010).

Increased open days. Open days are increased significantly in cows with RP in the previous calving compared to cows without RP (Gaafar et al., 2010; Mahnani et al., 2021). Open days in cows that experienced RP in the previous calving compared those that did not 109.6±3.1 vs 92.7±1.6, respectively. ($P<0.05$, Gaafar et al., 2010).

Uterine infections and infertility. The prevalence of uterine infections and infertility is significantly higher in cows that experienced RP in the recent calving than in those that did not (Gaafar et al., 2010; Mahnani et al., 2021). The incidence of endometritis was higher in cows that experienced RP than in cows that did not in the subsequent calving (78.9% *vs*

31.6%, respectively, $P<0.01$; Han and Kim, 2005). The prevalence of postpartum metritis in cows with RP was higher than in cows that did not experience RP after the recent calving ($P=0.005$; Bruun et al., 2002).

Developed signs of tetanus. In some cases of RP, the bacterium *Clostridium tetani* grows in the anaerobic environment of the uterus and induces tetanus symptoms by releasing toxins (Islam et al., 2012; Gupta et al., 2018).

Increased culling rate of infected animals from the herd. RP increases the risk of postpartum diseases in cattle and can cause 25% of affected cows to be culled from the herd during the first two months post-calving (Gaafar et al., 2010; Hur et al., 2011; Mahnani et al., 2021).

Perforation of the uterine wall. In most cases, this is caused by inappropriate obstetric interventions and treatments, such as inappropriate intraplacental administration of collagenase (Eiler et al., 1997).

Peritonitis. The possibility of peritonitis in cows is increased in cases of RP, especially in cows suffering metritis and uterine infections following caesarean section (Eppe et al., 2021; Mahnani et al., 2021).

Displaced abomasum. The incidence of displaced abomasum in cows with RP is higher than in cows that do not experience RP post-calving. Metabolic disorders play an important role in reducing the activity of myometrium and abomasum muscles and in the occurrence of RP and displaced abomasum disorders. If RP leads to a uterine infection, microbial toxins can also interrupt the contraction of myometrium and muscles of the abomasum (Gaafar et al., 2010; Mahnani et al., 2021).

Mastitis. The main economic impact of RP seems to be decreased milk production as cows with RP are more prone to mastitis (Gaafar et al., 2010; Mahnani et al., 2021). A study on more than 57,000 cows showed that RP significantly increased the rate of clinical mastitis in dairy cows (Ghavi Hossein-Zadeh and Ardalan, 2011). There is an association between RP and mastitis in cows, and a common defect in the immune system may be the cause of both RP and mastitis (Schukken et al., 1988).

Laminitis. The results of a study showed that the prevalence of lameness in cows that have suffered from RP is higher than in cows that have not suffered from RP in their recent calvings (Gunnink, 1984).

Uterine prolapse. This is more common in cows with RP than in those without, as the uterine atony and weight of the placenta are triggers for uterine prolapse in cases of RP (Correa et al., 1992; Alamaary and Ali, 2020).

Sepsis, endotoxemia, and septicaemia. The prevalence of metritis, sepsis, endotoxemia, and septicaemia in cows with RP is higher than in cows that do not experience RP post-calving (Piccinno et al., 2022).

Hypovolemic shock. This occurs as a result of internal bleeding due to the rupture of uterine and/or ovarian blood vessels, commonly as a result of uterine prolapse (Potter, 2008; Dasari and Maramulla, 2021).

Death. Internal bleeding, especially in cases of uterine prolapse or severe uterine infections, can be fatal (Wilson et al., 2022).

Symptoms of RP

Degenerated, discoloured, and ultimately fetid membranes hanging from the vulva. The retained membranes, and in some cases the retained foetus(es), may remain within the uterus cavity, though this may not be readily apparent. In these cases, retained membranes may be signalled by a foul-smelling or purulent vaginal discharge (Zhang et al., 2021).

Systemic illness. Fever, neglect of offspring, weakness, lethargy, dehydration, anorexia, depression, and tachycardia related to toxaemia or septicaemia may be seen (Paiano et al., 2020; Zhang et al., 2021).

Colitis. A cow with RP may show symptoms of colitis such as decreased feed intake, straining to defecate, abdominal distention, increased heart and respiratory rates, and teeth grinding (Azawi et al., 2007).

Bloody or a fetid watery red-brown uterine discharge. The stench is created as a result of the microbial decomposition of the remnants of the placenta (Paiano et al., 2020; Jeong and Kim, 2022).

Delay in postpartum uterine involution. In cows with RP, compared to cows that do not suffer from RP post-calving, involution of the uterus is significantly postponed (50 vs 39 days, respectively; Abou-Aiana et al., 2019; Amin et al., 2021).

Agalactia. The incidence of clinical mastitis and agalactia in cows with RP is significantly higher than in cows that did not suffer RP in the subsequent calving (Ostergaard et al., 2003; Ghavi Hossein-Zadeh and Ardalan, 2011). It has been suggested that a deficiency in the immune system is responsible for the occurrence of either RP or clinical mastitis in cows (Schukken et al., 1988; Kimura et al., 2002).

Diagnosis

The following methods can be used for diagnosis of RP:

History and clinical signs. If after 16 hours of delivery, the foetal membranes are still inside the uterus, the cow is considered to be suffering of RP (Asgari Safdar and Moradi Kor, 2014). It is often easy to diagnose the disease because the remnants of the placenta are usually hanging from the back of the animal. In complications associated with RP, such as metritis and clinical mastitis fever, increased heart and respiratory rates, anorexia, reduced movements of the rumen, weakness, dehydration, and a foul-smelling discharge from the vulva are seen (Mahnani et al., 2021).

Rectal palpation and vaginal examination. **These** can be used to find remnants of the placenta in the uterus and vagina (Konigsson et al., 2001; Ahmed et al., 2009).

Ultrasonographic examination of the reproductive system. This can be used to observe the remnants of the placenta in the uterus (Ahmed et al., 2009).

Thorough exploration of the expelled placenta. This may be done to ensure the placenta has been completely expelled (Gormley, 2019).

Microscopic appearance of the vulvar discharge. The discharge is normally non-inflammatory. An overtly inflammatory discharge, with full fields of degenerative PMNs are seen in pathological conditions of RP (Dubuc et al., 2010).

Blood tests. Blood tests, including complete blood count, biochemistry, erythrocyte sedimentation rate, measurement of C-reactive protein, and fibrinogen, are used to assess the health status of the animal to judge if any of the complications associated with RP have occurred (Moretti et al., 2015; Perumal et al., 2020).

Treatment

Due to its life-threatening nature, RP is considered an emergent condition requiring immediate attention and treatment. The main aims of treatment are to hasten the separation and expulsion of the placenta from the uterine cavity, and to eliminate toxic and inflammatory products from the uterus (Đuričić et al., 2011; Amin et al., 2021).

Treatment of RP includes the following:

Manual removal of the membranes. This is contraindicated in many cases because uterine infections are more frequent and more severe after this form of intervention, even when antibiotics are used. It should not be attempted unless the placenta can be detached without

causing irritation and haemorrhage, or if there is a danger of leaving remnants attached to the endometrium. The procedure should be performed aseptically. The procedure can increase the chance of absorption of septic/toxic materials, suppress phagocytic activity of the uterine leukocytes, and delay uterine involution. Possible complications include haemorrhage, uterine invagination, pulmonary embolus, permanent damage to the endometrium, vulvar haematoma, and perineal, vaginal, and cervical tears (Imhof et al., 2019). It is strictly forbidden to remove the retained placenta manually in a febrile cow or when the animal appears toxaemic.

Injection of collagenase into the umbilical arteries of the retained foetal membranes. This targets the lack of proteolysis process and might facilitate separation of the placenta from the uterus. Bacterial collagenase, 200,000 IU, plus 40 mg calcium chloride and 40 mg sodium bicarbonate dissolved in one litre of saline is used. Bacterial collagenase obtained from *Clostridium histolyticum* is used because it can degrade several types of collagen (Eiler and Hopkins, 1993; Abdisa, 2018). Oxytetracycline (100 mg) for intravenous injection can be added to the solution if an antibiotic is desired.

Uterine lavage. This helps to remove bacteria and cell debris from the uterine cavity, stimulates uterine contractility, and attracts neutrophils to the lumen of the uterus (Baqir et al., 2021). Uterine lavage can be performed one to three times a day using a large volume (10–20 litres) of sterile lactated ringer's solution, isotonic saline, or tap water. Uterine lavage is usually repeated until the returning fluid is clear. Some authors recommend the use of antiseptics in the fluid, though this may cause severe uterine irritation. Uterine lavage should not be performed on animals that have had a caesarean section, due to the potential risk of leakage of uterine fluids into the peritoneal cavity and consequently the risk of peritonitis. Uterine lavage is also useful in cases in which a partial section of foetal membranes is retained (Abdullah et al., 2014; Warankulasooriya et al., 2018; Piccinno et al., 2022).

***Hormone therapy*:**

Prostaglandin f2 alpha and its analogues are frequently used for the treatment of RP. It is well known that PGF2α serves as a pro-inflammatory mediator and induces inflammatory symptoms by increasing leukocyte infiltration into the tissues and increasing the expression and release of numerous cytokines (Xu et al., 2015). Retained placenta associated with uterine atony is comfortably treated with these products, as they support the inborn uterine contractions that play a major role in detachment process of the placenta (El-Hawary et al., 2019). Dosage is determined based on the type of drug (e.g., Cloprostenol; 500 mcg, IM; Rezende et al., 2020). Administration of PGF2α can cause colic (Hirsbrunner et al., 2003).

*Oxytocin and oxytocic drugs (ergometrine and methylergometrine)***.** Oxytocin is an uterotonic hormone that induces uterine contractions leading to the expulsion of RP (Magata et al., 2021). Oxytocin is used with a dose of 20–100 IU, IM per cow, three to four times a day. Higher doses of oxytocin are ineffective for expelling foetal membranes. It is hypothesised that high doses of oxytocin induce uterine spasms instead of intermittent contractions of uterine muscles (Bjorkman et al., 2017; Warankulasooriya et al., 2018). The uterus of the cattle is no longer responsive to oxytocin 24 hrs post-calving (Abdisa, 2018). The use of oxytocin and PGF2α after a caesarean section is recommended to prevent uterine bleeding and RP (Peters and Laven, 1996; England and Allen, 1998; Warankulasooriya et al., 2018). Administration of oxytocin may cause colic.

*Oestradiol and its analogues (stilboestrol and oestradiol benzoate)***.** These drugs can have beneficial effects in two ways: firstly by increasing uterine tone, particularly by increasing the myometrial response to

oxytocin, and secondly by increasing the uterine blood flow and phagocytic activity of PMNs of the reproductive tract (Rasmussen et al., 1996). Oestradiol benzoate can be used in the of 5–10 mg, IM (Khudhair et al., 2020). It should be noted that in cases where the uterus is infectious, oestrogen should not be used because it will worsen the condition. The infection may spread to the ovaries and peritoneal cavity, and more toxins will be absorbed as blood flow to the uterus is increased (Rasmussen et al., 1996; Khudhair et al., 2020).

Minerals. Calcium and magnesium therapy can be applied to help myometrial contractions (Baqir et al., 2021; Jayaganthan et al., 2022).

Antibiotic therapy. This is used to prevent or treatment of uterine infections. Antibiotics can be applied by an intrauterine or parenteral route. Oxytetracycline 5%, sulfonamides, and ceftiofur sodium can be used intrauterinely, but are not always recommended because intrauterine infusion of antibiotics can interrupt the activity of uterine neutrophils, and by killing the microbes, the process of decaying and decomposition of the retained membranes is delayed (Abdisa, 2018; Brahmanand and Sharm, 2020). It has been reported that intrauterine treatment with tetracyclines inhibits matrix metalloproteinase activity, and this in turn prevents the normal placental detachment processes (Kaitu'u et al., 2005). Local antibiotics, typically given as uterine infusions or boluses, cannot reduce the incidence of metritis or improve fertility in cows with RP compared to cows with RP that did not receive such treatment (Peters and Laven, 1996). Oxytetracycline, sulfonamides, ceftiofur sodium, amoxicillin, gentamicin, and marbofloxacin can be used parenterally. If cattle show no signs of a systemic disease, treatment can be postponed until 4–5 days postpartum (Abdisa, 2018). When the cow is febrile, systemic ceftiofur sodium is the most widely evaluated antibiotic and appears to be beneficial in reducing disease and aiding in the return to normal reproductive function.

Antiseptics. A variety of antiseptics such as chlorhexidine 0.1% and povidone-iodine 0.5% can be used intrauterinely (Liu et al., 2011; Thongrueang et al., 2022) to prevent and treat uterine infections alongside RP in cows. These compounds should be used with caution, especially iodine preparations because they can be extremely irritating (Liu et al., 2011).

Anti-inflammatory drugs. Non-steroid anti-inflammatory drugs (NSAIDs) are used in animals with RP because of their anti-inflammatory, analgesic, and anti-endotoxic effects. Meloxicam, flunixin meglumine, and phenylbutazone are routinely administered to cows with RP to prevent and alleviate the symptoms of the disease (Swartz et al., 2018). Cows treated with NSAIDs like flunixin meglumine post-caesarean section showed higher rates of RP compared to non-treated cows (P=0.01), which is believed to be mediated by way of reduction in prostaglandin synthesis (Waelchli et al., 1999).

Antihistamine drugs. Antihistamines such as diphenhydramine and promethazine can prevent or reduce the complications of RP in cows (Morrison et al., 1983).

Ozone therapy. Ozone is a strong disinfectant and activates uterine lymphocytes and monocytes, thereby supporting the secretion of cytokines. Ozone induces tissue regeneration, favours granulation and epithelialisation, and improves the local uterine metabolism. With ozone therapy, there is no bacterial resistance and no withdrawal period in milk and meat. Intrauterine application of ozone gas has been shown to improve reproductive indices, such as voluntary waiting period, calving to conception period, overall pregnancy rate, and services per conception, in cows involved in RP compared to cows that did not receive such treatment (Đuričić et al. 2012a; Đuričić et al. 2012b; Djuricic et al., 2012).

Immunisation against tetanus. A tetanus vaccine can be administered for cows with an unknown vaccination history or cows that are not routinely vaccinated. Otherwise, using tetanus toxoids is recommended (Islam et al., 2012; Boora et al., 2013).

Pentoxifylline. This can be used to prevent and alleviate the symptoms of the disease as it reduces the production of cytokines. The drug can be used at 10 mg/kg IV and multiple dose administrations may be required (Uney et al., 2019).

Fluid therapy. Intravenous fluids can be administered to combat dehydration and elimination of toxins in the patient (Atallah et al., 1999).

Transfusion. This should be done in the case of severe bleeding (Park et al., 2017; Crosby et al., 2022).

Laparotomy, hysterotomy, hysterectomy, or ovariohysterectomy. These procedures are options in complicated cases, if necessary, particularly if future pregnancies are not planned (Schonfelder and Sobiraj, 2006).

Prognosis

The prognosis is largely dependent upon how quickly the dam receives the treatment. With appropriate and timely treatment, the prognosis for survival and future fertility of the dam is excellent. Otherwise, the consequences are metritis, septic metritis, endometritis, peritonitis, salpingitis, oophoritis, infertility, sterility, and sometimes death (Chung et al., 2019; Faradillah and Agustina, 2023).

Prevention and control

The following proceedings can be taken to prevent and control RP in cows:

Reducing stress and feeding a balanced ration. This is particularly important in the peripartum period, to avoid hormonal imbalances, weakening of the immune system, and metabolic diseases, such as milk fever and fatty liver syndrome which can be predisposing factors for RP (Lu et al., 2020; Mahnani et al., 2021).

Vitamin and mineral supplementation. Vitamin and mineral deficiencies can impair general immunity. Vitamins A, E, D, selenium, molybdenum, zinc, and iodine supplementations can reduce the prevalence of RP in a herd (Molefe and Mwanza, 2020; Damarany, 2021). An IM injection of vitamin E (DL-tocopherol acetate, 1100 IU) and selenium (sodium selenite, 30 mg) 3 weeks prepartum, is used as a prophylactic dose to avoid RP in cattle. Note that over-supplementation with vitamin E and selenium increases the cases of RP in a herd (Gupta et al., 2005).

Proper immunisation against diseases. Immunisation for brucellosis, foot and mouth disease, haemorrhagic septicaemia, black quarter, theileriosis, infectious bovine rhinotracheitis, bovine viral diarrhoea, leptospirosis, salmonellosis, and blue tongue reduces the prevalence of RP in a herd (Kamel et al., 2022).

Proper body condition score (BCS) at the time of parturition. It has been shown that the rate of RP is increased in animals that are thin or obese at parturition. It is recommended that dairy cows have a BCS of 3–3.25 at the time of calving, based on a 5-point scale (Gillund et al., 2001; Roche et al., 2007). It is recommended that the BCS of beef cattle be 6 based on a 9-point scale at calving (DeRouen et al., 1994).

Dry and clean environment for parturition. This reduces the prevalence of RP by reducing the microbial load (Cattaneo et al., 2020).

Using breeds with a low incidence of dystocia and RP (if possible). Genetics is a determining factor in the incidence of dystocia and RP, and by choosing breeds with a low incidence of dystocia and RP, the incidence of these complications can be reduced in a herd. Selection of sires with suitable birth weight for the breed is necessary to protect the herd from calving problems (Mahnani et al., 2021).

Natural feeding of the neonate. Natural feeding at the first opportunity after parturition reduces the risk of RP by stimulating the secretion of oxytocin (Qureshi and Ahmad, 2008).

Conclusions

Retained placenta is a syndrome that affects all species of domestic animals. The disease is most common in dairy cows. Due to the complications and economic losses caused by retained placenta, the emphasis should be on prevention of the disease. Feeding animals a balanced diet, preventing obesity, providing immunisation against infectious diseases, and providing a clean environment for parturition, will reduce the incidence of the disease in a herd. Clinical examinations and paraclinical tests can be used to diagnose the disease. After diagnosis, monitoring and treatment should be started as soon as possible, as delaying treatment can threaten the life of the animal. The general principles of treatment include removing the retained membranes and draining the inflammatory and infectious material from the uterine cavity. Ecbolic drugs are used to stimulate uterine contractions. Several types of antibiotics are used intrauterine and parenteral to prevent and treatment of uterine infections. Nonsteroidal anti-inflammatory drugs and antihistamines are used to alleviate the symptoms of the disease. If the disease is diagnosed early and treatment is started at the earliest opportunity, the prognosis for the survival and subsequent fertility of the animal is good.

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Zaostajanje posteljice u krava. Rizici, dijagnoza, liječenje i kontrola - pregledni članak

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Zaostajanje posteljice (RP) je sindrom koji se javlja u svih vrsta domaćih životinja, uključujući krave. RP može dovesti do po život opasnih komplikacija pa je terapija spomenutog stanja hitna u teriogenologiji. Različiti čimbenici osnova su za pojavnost RP-a, uključujući defekte u imunološkom odbacivanju posteljice, poremećaje miometrijalnih kontrakcija, infekcije, poremećaje oslobađanja ili funkcioniranja proteolitičkih enzima u posteljici, induciranje porođaja, prijevremeni porođaj, pobačaj, mrtvorođenje, debljinu, senilnost, bakterijske i fungalne toksine, parenje blisko srodnih životinja, abnormalno hormonalno okruženje u peripartalnom razdoblju, ozljede posteljice, elektivni carski rez, stresne uvjete u okolišu, pothranjenost, metaboličke poremećaje, pasminu, itd. Ovisno o temeljnom uzroku/uzrocima RP-a, predloženi su različiti načini za sprječavanje RP-a poput hranidbe uravnoteženom hranom, pravilne imunizacije protiv bolesti, osiguravanja suhog i čistog okruženja za porođaj, odabira pasmina s niskom stopom pojavnosti distocije ili RP-a, itd. Nekoliko je metoda za liječenje bolesti, uključujući ručno uklanjanje membrana, injektiranje kolagena u pupčane arterije zaostalih membrana, ispiranje maternice, hormonalnu terapiju, terapiju antibioticima, itd. Ovaj pregled naglašava učinkovite načine upravljanja RP-om u goveda.

Ključne riječi: *zaostajanje posteljice, goveda, dijagnoza, liječenje, kontrola*