Acute and chronic radiodermatitis: clinical signs, pathophysiology, risk factors and management options

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Radiodermatitis (RD) is a cutaneous reaction that occurs as a side-effect of radiotherapy during cancer treatment or sometimes after interventional radiology. There are two forms of RD depending on the time the skin reaction occurs. Acute skin reactions develop a few hours to weeks after the first exposure to radiation, whereas chronic RD can develop months, years or even decades after radiation. Both acute and chronic RD can substantially affect the patients' quality of life and cosmetic outcome. Therefore, a proper prevention and treatment strategy for RD is needed. However, the scientific evidence for effective management options for RD is still lacking. In this paper, we review the most recent literature on the epidemiology, clinical signs, pathophysiology, risk factors and prevention and treatment options for acute and chronic RD caused by radiotherapy and interventional radiology.

Keywords:
acute radiodermatitis, cancer, chronic radiodermatitis, fluoroscopy-guided interventions, interventional radiology, radiotherapy, skin, supportive care

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Introduction

In medicine, ionizing radiation, in the form of electromagnetic waves (γ or radiographs) or particles (neutrons, β or α), is used for both diagnostic and therapeutic goals [1]. Radiographs can be used for imaging purposes in computed tomography scans or during a fluoroscopy-guided intervention (FGI) (e.g. angiograms, barium radiography, insertion of stents, catheters and so on) [2]. On the other hand, ionizing radiation is also used as part of a cancer treatment, to destroy remaining cancer cells by radiotherapy (RT) [3].

The biologic effect of ionizing radiation on the human cell is based on either direct cellular damage or indirect cellular damage by the formation of reactive oxygen species (ROS). Ionizing radiation essentially damages the cell's ability to divide and multiply. Therefore, immature, undifferentiated and actively proliferating cells (e.g. stem cells, basal cells of the epidermis, mucosal cells, bone marrow cells) are the most radiosensitive [4].

Despite the developing RT and radiation-based imaging techniques in order to minimize the damage to healthy cells, patients still develop several complications. One of the most important side-effects is radiodermatitis (RD), a cutaneous reaction to the inflicted cellular injury [5]. Radiation-induced skin injuries are deterministic effects, which implies that they occur once the threshold level of exposure has been exceeded. The severity and progression of the skin reactions varies widely between patients depending on both treatment-related and patient-related risk factors. RD can occur as an acute (early) effect, developing within the first hours to weeks after radiation exposure, or as a 'late' effect (chronic), occurring months or years after the intervention [6].

In this review, an overview is given of the epidemiology, clinical signs, pathophysiology, risk factors and prevention and treatment options for acute and chronic RD caused by RT and FGI.

Epidemiology

Radiotherapy-induced skin reactions

There were 14.1 million new cancer cases worldwide estimated in 2012 [7]. RT is an important modality in modern cancer treatment. Approximately 50% of the cancer patients are treated with RT alone or in combination with other modalities (e.g. surgery, chemotherapy, immunotherapy and/or hormone therapy) [8]. Up to 95% of the cancer patients treated with RT will develop some degree of skin reaction in the treated area [4]. RD is most common in patients treated for breast, head and neck, anal and vulvar cancer [9]. This higher incidence is due to the fact that the irradiation target in these anatomical regions is closer to the skin and therefore it receives a high RT dose [9].

Fluoroscopy-guided intervention-induced skin reactions

Skin reactions due to FGI are either still rare or underreported. Up to now, only data are available of individual case reports in the radiology and dermatology literature [10–18]. However, the possible risk of the general patient population for exposure to a minimum radiation dose causing a skin injury has increased over the years. The reason for this is the increasing number of FGI, and thereby these interventions are often more complex and longer-lasting leading to a higher acute skin dose [2,19].

Clinical signs

Acute radiotherapy-induced radiodermatitis

Early skin effects occur within 2–4-weeks after the initiation of RT. Acute RD can be graded on the basis of the criteria of the Radiation Therapy Oncology (RTOG) as shown in Table 1 [20]. Acute RD starts with red rashes and dry desquamation (grade 1). A grade 2 skin reaction is characterized by a bright erythema combined with patchy moist desquamation located in the skin folds. When RD worsens, confluent moist desquamation outside the skin folds (grade 3) develops. In some rare cases, necrosis with hemorrhage and eventually ulceration can occur (grade 4) [20,23–25]. In particular, grade 2 to grade 4 RD can be very painful and affects greatly the patients' quality of life. Patients have to cope with problems during their daily life (e.g. washing practices, getting dressed, household activities, hobbies) [26]. In severe cases of acute RD, premature interruption of RT might be necessary, which will eventually affect the treatment outcome and overall patient survival [27]. Usually, acute skin reactions heal within a month after completion of RT [6].

Chronic radiotherapy-induced radiodermatitis

Late skin effects can develop months to years after the exposure to RT. The main cutaneous reactions that characterize chronic RD are skin atrophy, fibrosis, pigmentation changes, telangiectasia, necrosis and secondary malignant skin tumours (Table 1) [28].

Skin atrophy is related to a decreased number and activity of dermal fibroblasts and the reabsorption of collagen, resulting in a fragile and thin skin [29]. Remaining dermal fibroblasts are pathologically activated by growth factors [e.g. transforming growth factor-β (TGF-β)] into myofibroblasts. This is typically seen within the context of wound healing. However, in the scenario of chronic RD, this happens also even though no active wound is present, resulting in an excessive, unstoppable accumulation of collagen and extracellular matrix components leading to skin fibrosis. Radiotherapy-induced fibrosis (RIF) is clinically characterized by induration, thickening of the dermis and even a reduced range of motion [30]. Different types of pigmentary changes can be observed: the focal depletion of melanocytes in combination with focal melanocytic hyperactivity owing to the underlying chronic inflammatory process results in the typical dyspigmentation. This is clinically seen as a combination of areas with hyperpigmentation in between areas with hypopigmentation. Furthermore, owing to the continuous wound healing response within the skin and the resulting neovascularization, visible telangiectasia are also a typical clinical finding in the late RT skin reaction. Skin areas affected by chronic RD are also at high risk for secondary malignant skin tumours years after RT [29,31,32]. It is imperative to have a regular dermatological follow-up for patients affected by chronic RD. In contrast to acute RD, late skin reactions are irreversible and progressive, which substantiality affect the patients' quality of life and cosmetic outcome [28].

Fluoroscopy-guided intervention-induced radiodermatitis

FGI-induced skin reactions can range from prompt, early, mid-term to long-term effects depending on the time of onset after a single delivery of radiation (Table 2). The single-site acute skin dose mainly determines the severity of the skin reaction, with higher doses resulting in more severe skin injuries. Prompt skin reactions develop within 2 weeks after radiation. These are characterized by a transient erythematous reaction, which can occur from a few hours up to 24 h after exposure to a radiation dose of more than 2 Gy. Early skin reactions develop 2–8 weeks after exposure to radiation. With an increasing single-site acute skin dose, the skin reactions may vary from epilation, erythema, dry desquamation to eventually moist desquamation. During a 6–52-week period after radiation, mid-term skin reactions can still persist. These are characterized by dusky-mauve erythema and/or full-thickness or partial-thickness dermal necrosis. Finally, on the long-term skin reactions can still withstand 40 weeks after radiation exposure, which include dermal atrophy leading to a thin and weakened skin and/or telangiectasia. An overview of the dose–time relationship of FGI-induced skin reactions developed by Balter *et al.* [2] is shown in Table 2.

Pathogenesis

The pathogenesis of RD is rather complex and comprises a combination of direct radiation tissue injury followed by an inflammatory reaction. Radiation causes damage to the basal cells of the epidermis and the vascular endothelium via direct DNA damage or secondary owing to the creation of ROS [29].

Acute radiodermatitis

Early effects result from damage to the mitotic ability of the stem cells within the basal layer of the epidermis, which leads to a disruption in the self-renewing property of the skin. The degree to which skin reactions develop

Table 1. Radiation Therapy Oncology Group radiation morbidity scoring for radiotherapy-induced skin injuries [20–22]

	Grade				
Onset	0	1	2	3	4
Acute	No change over baseline	Follicular, faint or dull erythema; epilation; dry desquamation; decreased sweating	Tender or bright erythema; patchy moist desquamation; moderate oedema	Confluent, moist desquamation other than skin folds; pitting oedema	Ulceration; haemorrhage; necrosis
Chronic	None	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration

Table 2. Radiation effects on the skin and hair from a single delivery of radiation during a fluoroscopically guided intervention [2]

Band	Dose* (Gy)	RTOG grade	Approximate time of onset			
			Prompt (<2 weeks)	Early (2–8 weeks)	Mid-term (6–52 weeks)	Long-term (>40 weeks)
A1	0–2	NA	No observable effects expected	No observable effects expected	No observable effects expected	No observable effects expected
A2	2–5	1	Transient erythema	Epilation	Recovery from hair loss	No observable effects expected
B	5–10	1	Transient erythema	Erythema and epilation	Recovery; after higher doses, prolonged erythema and permanent partial epilation expected	Recovery; after higher doses, dermal atrophy and induration expected
C	10–15	1–2	Transient erythema	Erythema and epilation; possible dry or moist desquamation; recovery from desquamation	Prolonged erythema; permanent epilation	Telangiectasia; dermal atrophy and induration; skin expected to be weak
D	>15	3–4	Transient erythema; after very high doses, oedema and acute ulceration expected, with surgical intervention most likely required in longer term	Erythema and epilation; moist desquamation	Dermal atrophy; secondary ulceration due to failure of moist desquamation to heal, with surgical intervention most likely required	Possible late skin breakdown; wound might persist and progress to a deeper lesion, with surgical intervention most likely required

NA, not applicable; RTOG, Radiation Therapy Oncology Group.
*Single-site acute skin dose. Note that this is the actual skin dose, including backscatter and should not be confused with the reference point air kerma (kinetic energy released per unit mass) (Ka,r). Skin dosimetry is unlikely to be more accurate than ±50%.

depends on the survival of actively proliferating basal cells in the epidermis [31].

In the first phase, an erythematous skin reaction develops caused by an increased vascular permeability and vasodilation. This is followed by an inflammatory response leading to a secondary erythematous reaction. During this inflammatory reaction, keratinocytes, fibroblasts and endothelial cells stimulate resident and circulating immune cells. These irradiated skin cells produce a wide array of cytokines and chemokines [e.g. interleukin (IL)-1α, IL-1β, tumour necrosis factor (TNF)-α, TGF-β, IL-6, IL-8, C-C motif chemokine ligand (CCL)-4, C-X-C motif chemokine ligand-10 and CCL2]. These molecules upregulate the expression of adhesion molecules such as intercellular adhesion molecule-1 on keratinocytes and endothelial cells, as well as vascular cell adhesion molecule and E-selectin on endothelial cells.

The upregulation of these adhesion molecules plays a major role in the transendothelial migration of circulatory immune cells to the irradiated skin, which is a 'hallmark' of radiation-induced skin injury. The inflammatory response that is caused by RT not only occurs immediately but it builds up at each fraction of RT leading to a greater recruitment of immune cells and subsequently more tissue damage (i.e. fractionated inflammatory insult) [9,33,34].

At a higher RT dose, the skin tries to compensate the damage by increasing its rate of mitosis in the basal epidermal cell layer. However, as the turnover of new cells is faster than the shedding of the old cells, this leads to a thickened, dry, scaly skin (i.e. dry desquamation). Finally, moist desquamation arises if all the stem cells in the basal layer are destroyed. Consequently, the skin is unable to replace the damaged tissue by new cells, which leads to a broken epidermis, skin blisters filled with a serous exudate and substantial pain. These different phases of tissue injury will negatively affect the skin's barrier and immune function, leading to increased risk of infection [4,29,31,32].

Further, RT can also cause damage the sebaceous glands and hair follicles in the dermis, resulting in dryness and epilation. In some cases, hyperpigmentation can occur when the epidermal melanocytes are stimulated by the ionizing radiation [4].

Chronic radiodermatitis

The underlying mechanism behind chronic skin reactions is based on an extended inflammatory reaction that starts after the first RT session and is prolonged for months to years afterwards. Inflammatory cytokines (e.g. IL-1α, IL-6, TNF-α) are responsible for this reaction. In addition, TGF-β and platelet-derived growth factor are upregulated in irradiated skin. These cytokines enhance tissue fibrosis by activating fibroblasts and inducing synthesis of extracellular matrix proteins and metalloproteinases, as well as the formation of telangiectasia. The prolonged inflammatory reaction induces skin atrophy and necrosis via the accumulation and activation of leucocytes at the irradiated area [28].

Risk factors

The risk of developing RD depends on various therapy-related and patient-related factors. Treatment-related factors that influence the severity of the skin reactions include the radiation dose during a single delivery, the total dose, the duration of exposure, the volume of the treated area and the combination with other therapies (e.g. chemotherapy and/or targeted therapy). Furthermore, the cumulative effect of radiation implies that tissue damage builds up with every single delivery of radiation. This is demonstrated by the fact that patients develop more severe forms of RD at the end of their RT or after multiple imaging and interventional procedures using radiographs [35].

Patient-related factors include high BMI, overlapping skin folds, the sensitivity of the exposed skin region, smoking and nutritional status, pre-existing skin conditions (e.g. psoriasis) and genetic susceptibility [4,6,31,36,37].

Prevention and treatment

Acute radiotherapy-induced radiodermatitis

Management of acute RD is an important aspect of the RT department. RD may be distressing or painful for the patient, which may affect their general well-being. Therefore, a proper management of RD is necessary to improve the patients' quality of life [6,32].

Up to now, a comprehensive, evidence-based consensus for the prevention treatment of RD has not been published. As a consequence, each RT department uses a different intervention to prevent and/or manage acute RD. However, the Multinational Association for Supportive Care in Cancer (MASCC) has published some general clinical guidelines [38].

Concerning preventive measures for acute RD, the MASCC panel makes a strong recommendation for daily hygiene practices such as gentle washing with water, with or without a mild soap, and the use of deodorants. In order to reduce discomfort and itchiness caused by the skin reactions, the panel makes a strong recommendation for the prophylactic use of potent topical steroids [39,40]. Next to the preventive measures, the MASCC panel only shows poor evidence for the use of silver sulfadiazine cream in patients with established acute RD. There is insufficient evidence to support or refuse the use of the other agents for the prevention and management of acute RD according the MASCC guidelines [6,32,38,41]. Therefore, it is necessary to perform more randomized controlled clinical trials (RCT) to investigate the use of other prevention and treatment modalities for acute RD [6,31,32,42,43].

Photobiomodulation therapy: photobiomodulation therapy (PBMT), also named low-level laser therapy, is a noninvasive treatment option that is used to stimulate wound healing, reduce inflammation and relieve pain [44–50]. At the 2014 joint conference of the North American Association for Laser Therapy [51] and World Association for Laser Therapy, PBMT was defined as 'a light therapy that utilizes nonionizing light sources,

including lasers, light-emitting diodes (LEDs) and broad-band light, in the visible and red or near-infrared spectrum [52]. The light is absorbed by endogenous chromophores eliciting nonthermal, photophysical and photochemical events at various biological scales leading to physiological changes' [51].

Schindl *et al.* [53–55] was the first to study the clinical effect of PBMT on RD in patients. The study showed that PBMT was effective in the induction of wound healing in RT-induced skin ulcers after mastectomy in a small group of breast cancer patients.

More recently, two studies evaluated the efficacy of LED in the prevention of RD [56,57]. LED is another type of PBMT that has approximately the same characteristics as laser diodes but it uses noncoherent light. In a study by DeLand *et al.* [57], LED treatment significantly reduced the incidence and the severity of RD in breast cancer patients. On the other hand, Fife *et al.* [56] did not find a significantly reduced incidence or severity of RD after LED treatment in breast cancer patients. These conflicting results may be attributed to a variety of factors (e.g. type radiation technique, non-blinded versus blinded scoring of skin reactions and setup of the LED treatment).

Recently, Censabella *et al.* [58] investigated the efficacy of PBMT as a treatment for RD in breast cancer patients. During this prospective study, two successive groups of breast cancer patients undergoing identical RT regime (33 daily fractions of RT) post lumpectomy were compared. The control group (CTRL group, $N=41$) received the institutional skin care protocol, whereas the experimental group (laser therapy group, $N=38$) was treated with this protocol plus biweekly with PBMT (six sessions) starting at fraction 20 of RT. PBMT was delivered to the patients by a diode laser in the infrared range (808–905 nm) with a fixed energy density (4 J/cm^2). The severity of RD was evaluated according to the criteria of the RTOG [20]. Before the start of PBMT (i.e. at RT dose of 40Gy) the distribution of the RTOG grades was comparable between both groups, with most of the patients presenting RTOG grade 1. At the end of RT (RT dose of 66Gy), the severity of RD was significantly different between the two groups, with more presence of grade 2 in the CTRL group when compared with the laser-treated group. Furthermore, there was a significant intensification of the skin reactions in the CTRL group, whereas it remained stable in the laser therapy group. Future RCTs are necessary to further investigate the beneficial effect of PBMT in the prevention and management of acute RD.

Chronic radiotherapy-induced radiodermatitis

For the management of chronic RD, the available scientific data are limited. In this review, the focus lies on the treatment of telangiectasia, fibrosis, and ulceration and necrosis.

Telangiectasia

Up to now, even though clinical experience with the treatment of telangiectasias is more than three decades old, there is only limited evidence of three clinical trials investigating the use of pulsed dye laser (PDL) therapy for the management of telangiectasia in the context of chronic RD [38]. In a study by Lanigan *et al.* [59], eight female breast cancer patients who developed telangiectasia within 1 year after RT were treated by Candela SPTLIB PDL (585 nm, 450 ls pulse, 7 mm spot, 6 J/cm). All treated patients showed complete clearance of vessels after their PDL treatment. Another study compared the use of long pulsed-dye laser (LPDL) with intense pulsed light (IPL) in a randomized split-lesion trial. Thirteen female patients with telangiectasia underwent three treatments at a 6-week interval. The left or right side of the affected skin area was treated with PDL [(V-beam Perfecta; Candela Laser Corporation, Wayland, Massachusetts, USA) 595 nm] and the other side with IPL (Ellipse Flex; Danish Dermatologic Development A/S, Hørsholm, Denmark). Results showed that both treatment options were effective in reducing telangiectasia. However, LPDL was a more effective treatment option with a 90% vessel clearance, whereas it was 50% in the skin area treated with IPL. In addition, patient satisfaction was higher for LPDL than IPL, and LPDL was associated with a lower pain score. However, the study compared three passes with LPDL with one single pass with the IPL, and should hence be taken with caution regarding the comparison of the two techniques [60]. Finally, in a retrospective study by Rossi *et al.* [61], 11 patients were treated with PDL. There was clinical improvement in all the cases after an average of four PDL sessions. The average laser fluence was 4.2 (585 nm platform) and 7.8 (595 nm) J/cm^2 (4–8 J/cm^2). The average percentage of reduced vessels was 72.7 (50–90%). Furthermore, some patients also described an increased sense of confidence and satisfaction after their final PDL session. On the basis of these data, the MASCC panel made a weak recommendation for the use of LPDL for telangiectasia [38].

Fibrosis

The management of RIF is quite difficult. There are several options available ranging from physiotherapy, pharmacotherapy, hyperbaric oxygen to laser therapy. However, the scientific evidence for these options is limited. In order to avoid a diminished quality of life of patients with RIF, supportive care consisting of pain management, psychological support and wound care is necessary [28].

Physiotherapy: one of the most important treatment options for RIF is physical therapy, which includes deep massage and a range of motion exercise. These can improve the mobility of the affected area and prevent the development of contractures [28]. In a randomized, prospective study by Bourgeois *et al.* [62], the use of the LPG technique in 20 women who developed RIF after RT and surgery for breast cancer was investigated. The LPG technique is a technique of mechanical massage that allows skin mobilization by folding/unfolding. Ten patients underwent LPG treatment three times a week for 1 month, whereas the other 10 patients were only placed under medical supervision. Results of this study showed that the LPG treatment was able to

significantly reduce erythema, pain, pruritus and the feeling of induration of the skin.

Pharmacotherapy: a limited number of studies investigated the use of pentoxifyline (PTX) alone or in combination with tocopherol (vitamin E) to prevent or treat RIF [63–68]. PTX is a methylxanthine derivative that has a multitude of inflammatory effects. It can upregulate polymorphonuclear leucocyte and monocyte phagocytic activity, inhibit TNF-α and TNF-β synthesis, decrease granulocyte–macrophage colony-stimulating factor and interferon γ and inhibit the TGF-β expression [68–70]. Vitamin E, on the other hand, reduces the ROS concentration [71].

The available data of several small, randomized trials show contrasting results, with little to no benefit over the placebo treatment [66,67]. On the other hand, Delanian *et al.* [65] did show a beneficial effect of the combination of PTX with tocopherol in the treatment of RIF. In their latest study, they compared the effects of a long-term (24–48 months) versus short-term treatment (6–12 months) with PTX and tocopherol in 44 breast cancer patients. Their results showed that a long treatment of PTX-vitamin E (average 24 months) was necessary to reduce RIF with an average of 68%. There was a rebound effect when patients stopped their treatment before the 12-month period. Larger, RCTs are necessary to confirm these results and to estimate the optimal drug dose and duration.

Hyperbaric oxygen: in chronic RD, hyperbaric oxygen therapy can have beneficial effects by inducing re-epithelialization and reducing pain, oedema, erythema or lymphoedema. However, the scientific evidence for the reduction of RIF by hyperbaric oxygen is weak [72–74].

Laser therapy: the use of laser therapy for the management of RIF is new and has recently been introduced in the field. In a study by Tran *et al.* [75], three Vietnamese children who developed chronic RD after RT for haemangioma were treated with PDL and/or fractional laser in combination with skin grafting. Patients showed softened and repigmented skin with an increase in flexibility after. These positive results need to be further investigated in larger clinical trials.

Ulceration and necrosis

For the management of ulcerations and necrotic wounds in chronic RD, the general wound care guidelines are the most important. These include the application of wound dressings that absorb the wound exudate and protect the wound from environmental damage and bacteria to prevent secondary infections. For patients with very moist wounds, hydrogel or hydrocolloid dressings can be used. These dressings do not adhere to wounds, are absorbent and can easily be replaced. Studies have shown that these dressings are upregulating the wound healing process and improve the patients' comfort. For infected wounds, silver-containing dressings can be used. Chronic ulcerations need to undergo selective and careful debridement in order to clean the wound and stimulate the healing process [6,38]. In some severe cases, surgical interventions are necessary in which skin-flaps are used [76]. A more innovative technique in the management of skin ulcers is PBMT. A case report by Schindl *et al.* [54,55] showed that PBMT was able to improve the wound healing process and to increase the vascularization of RT-induced skin ulcers in breast cancer patients.

Fluoroscopy-guided intervention-induced skin reactions

Prevention

The best method to prevent the development of FGI-induced skin reactions is based on the minimization of the acute skin dose and on monitoring the patients after the radiological intervention. In order to avoid that patients will be exposed to an excessive radiation dose, a proper dose management before and during the intervention is a necessity. Before each intervention, the patient's individual risk needs to be determined, on the basis of their personal characteristics and previous exposures to radiation. This will influence the patient's risk of developing skin injury after the FGI. In addition, the procedure needs to be carefully planned and a trained interventionalist needs to be assigned to execute it. During the intervention, the imaging parameters have to be optimal in order to match the appropriate image quality with the lowest possible dose. Each patient should also receive advice from the interventionalist in order to make them aware of the possible development of skin reactions after the procedure. Thereby, a physician, who is trained in diagnosing radiation-induced skin injuries, needs to follow-up patients who were exposed to a high radiation dose [2,19,77].

Treatment

There is no standard treatment for patients with FGI induced skin injuries. Most of the time the treatment of these injuries is quite complex and demand a multi-disciplinary team of dermatologists, wound care specialists and in some cases plastic surgeons. First of all, it is important that the treatment team is informed about a possible radiogenic origin of the skin reaction in order to make a correct diagnosis. The available treatment options for FGI induced skin reactions depend on the severity of the injury. The same possible solutions that were described above for the RT-induced skin reactions can also be applied for acute and chronic FGI induced skin injuries [77].

Conclusion

Acute and chronic radiation-induced side-effects can seriously affect the patients' quality of life. To date, there are several preventive and therapeutic options in the management of RD. However, the scientific evidence for a general consensus is still missing. Therefore, more RCTs need to be performed in order to increase the applicability of new and developing solutions.

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Conflicts of interest

There are no conflicts of interest.

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