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Post intravitreal bevacizumab recurrent Burkholderia cepacia endophthalmitis treated with clear lens extraction in an African

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ABSTRACT

Purpose: To report the successful treatment of post intravitreal bevacizumab recurrent Burkholderia cepacia endophthalmitis managed with a clear lens extraction and posterior capsulectomy.

Observation: A 34-year-old female African, known SC hemoglobinopathy patient, presented with bilateral blur in vision and floaters of a week duration; worse in her right eye. Her visual acuity was right eye 6/9 (20/30) and left eye 6/6 (20/20). Her anterior segment examination was normal in both eyes. On fundus examination, she had a right eye vitreous hemorrhage and bilateral active Sea-fan neovascular proliferation in the retina periphery. Following the administration of bilateral simultaneous intravitreal bevacizumab, she presented 4 days later with a right eye infective endophthalmitis. She suffered multiple recurrences despite adequate treatment, including a vitrectomy with silicone oil injection. Multiple microbiological assessment of intraocular extracts confirmed persistent Burkholderia cepacia infection. A wide ring-shaped opaque plaque was noticed on the posterior capsule of her clear lens. A decision was taken to perform a lensectomy and posterior capsulectomy. This resulted in immediate resolution of hypopyon and all intraocular inflammation. Vision improved from Hand Motion to 6/18 (20/60).

Conclusion and importance: This report suggests than in some cases of recurrent, difficult to treat, Burkholderia cepacia endophthalmitis, since the organism may have colonized the posterior lens capsule, the eye and vision can be salvaged by timely removal of a clear lens and capsulectomy. Clear lens removal has not been previously reported for treating recurrent Burkholderia cepacia endophthalmitis.

1. Introduction

Burkholderia cepacia is a gram-negative bacillus found in soil and water; and a dreaded contaminant of pharmaceutical and medical devices.[1,2] It is a cause of postoperative infective endophthalmitis and is associated with recurrent disease.[3] It has gained prominence in recent years because of its resistance to treatment, which often results in poor visual outcomes. Besides, it has a high capacity for rapid mutation, inherent resistance to antibiotics and antiseptics, can survive under nutrient-limited conditions, and can use some antimicrobials as its source of carbon.[1] It has been reported to account for 1.8% of cases of postoperative endophthalmitis.[2] B. cepacia endophthalmitis like other gram-negative infections is associated with a poor prognostic outcome.[2] In a review of eight reported cases of post-operative B. cepacia endophthalmitis, 41% of cases had a visual outcome of less than 6/60 (20/200), and recurrence after initial treatment was a common clinical presentation, reported in 4 out of the 8 reports.[3]

While post intravitreal injection (IVI) endophthalmitis is well reported,[4,5] and commonly due to gram-positive organisms, there is atleast one report of B. cepacia infection after IVI.[6] Treatment of reported cases of IVI endophthalmitis consists of intravitreal, topical, and local administration of antibiotics and steroids, and in some cases vitrectomy. Reviewing existing literature, there has been no report of resolution of intraocular infection following the removal of a clear lens in a case of recurrent endophthalmitis due to B. cepacia infection. We report a case.

Abbreviations: PVD, Posterior Vitreous Detachment.; IVI, Intravitreal Injections.; IVB, Intravitreal Bevacizumab.; EVS, Endophthalmitis Vitrectomy Study.; VH, Vitreous Hemorrhage.

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2. Case report

A 34-year-old female African, known hemoglobinopathy SC patient presented with bilateral blur in vision and floaters, worse in her right eye of one-week duration. Her visual acuity was right eye (RE) 6/9 (20/30) and left eye (LE) 6/6 (20/20). Intraocular pressure was 10 mmHg in both eyes. On dilated fundus examination there was an attached retina and vitreous hemorrhage (VH) in the RE (Fig. 1a and b), and bilateral active sea fan neovascularization in the fundus periphery. After clinical workup, including fundus fluorescein angiography, optical coherence tomography (OCT), and angiography (OCTA) she was diagnosed to have bilateral proliferative sickle cell retinopathy (PSCR) with a RE complicating VH. Bilateral simultaneous injection of 1.25mg/0.05 cc intravitreal Bevacizumab (IVB) was given, with a plan to follow up with bilateral peripheral scatter retinal laser photocoagulation for the treatment of avascular peripheral retinae.

She was seen on post IVB day one and her vision was 6/9 (20/30) RE and 6/6 (20/20) LE. Other ocular findings were as before the intravitreal injection. She then presented on the 4th day post IVB having noticed a worsening of the blur in RE vision for a few hours before the presentation and ocular pain of about one-day duration. On examination, vision in her RE was reduced to counting fingers (CF), while LE was still 6/6 (20/20). RE conjunctiva was congested. There was fibrin and a 3 mm hypopyon in the RE anterior chamber, and a grey fundal reflex (Fig. 2). LE findings were entirely normal. A RE ultrasound B scan done on the same day revealed intense echogenicity within the vitreous cavity, and an attached retina. These findings were suggestive of a RE post IVB endophthalmitis and she was managed as such.

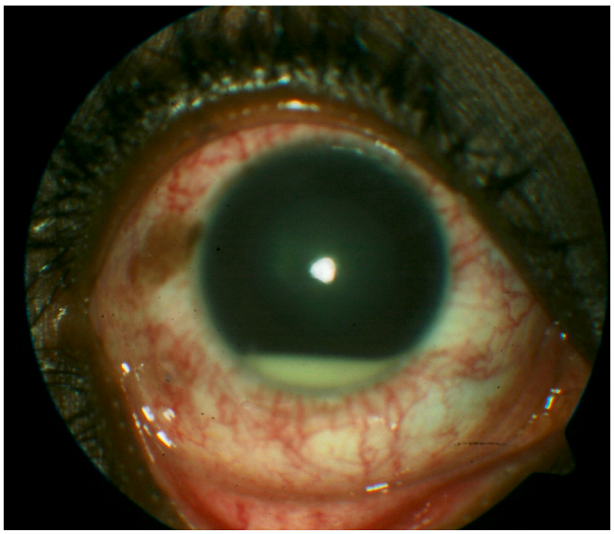

Fig. 2. Right eye showing conjunctival injection and a 3 mm hypopyon present at the occurrence of post intravitreal bevacizumab endophthalmitis. Note that there is absence of red reflex. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

On the 4th day post IVB she received RE frequent topical antibiotic & steroid (gutt. 0.5% Gatifloxacin & gutt. 0.1% Dexamethasone) every 30mins, and then tapered to hourly after a week, gutt. 2% Homatropine every 2 hours and tapered to four hourly after a week, Tabs. Moxifloxacin 400mg daily for 1 week and Tabs. Prednisolone 20mg daily for 1 week. Intravitreal antibiotics (Vancomycin 1mg/0.1 cc & Ceftazidime 2.25mg/0.1 cc) as per the endophthalmitis vitrectomy study (EVS) protocol was also administered on the 5th day post IVB.[7] Her symptoms improved when she was reviewed in the clinic by the 7th day post IVB as evidenced by resolution of the hypopyon and appearance of a dull red reflex, though RE vision was Hand Motion. Topical medications (gutt. 0.5% Gatifloxacin and gutt. 0.1% Dexamethasone) were further tapered after one week of hourly dosing to 2 hourly by the 17th day post IVB. Then, there was a recurrence of inflammation with worsening of her symptoms and return of hypopyon when she was reviewed on the 20th day post IVB. Vision in the RE was still Hand Motion (HM), and there were keratic precipitates present on the cornea endothelium.

A repeat ultrasound B scan done on the 20th day post IVB showed findings suggestive of a retinal detachment, Fig. 3. Therefore, a decision

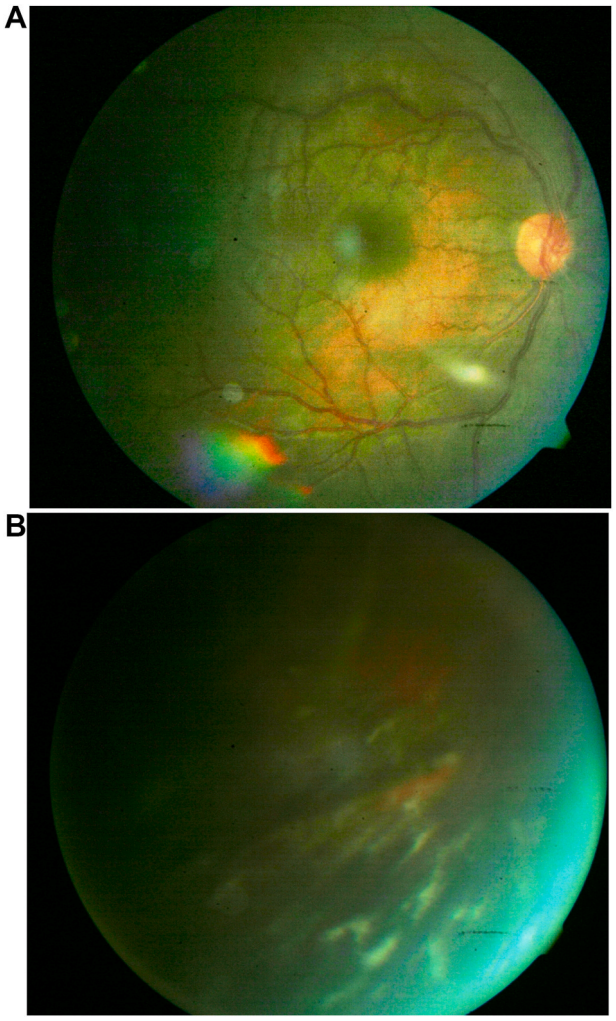

Fig. 1. 1a. Pre intravitreal injection fundus photograph. 1b. Vitreous hemorrhage in the inferior, peripheral fundus.

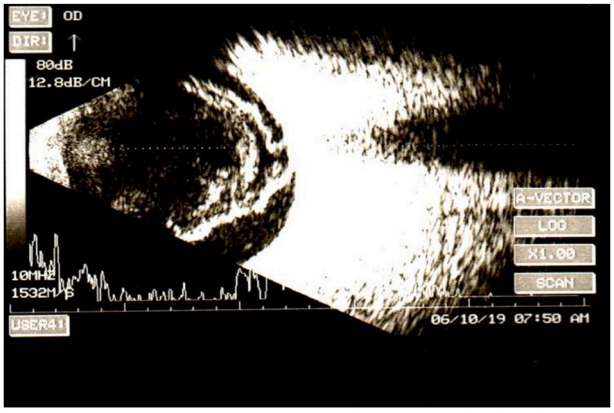

Fig. 3. Right eye B scan ultrasound demonstrating retinal detachment and echogenic vitreous; a partial PVD is present.

to perform a vitrectomy with silicone oil tamponade was taken and surgery was performed successfully on the 21st day post IVB. Posterior vitreous detachment (PVD) extension to the periphery was performed and silicone oil which is known to have an antimicrobial effect,[8,9] was injected as tamponade after surgery. Microbiological assessment including culture of vitrectomy extracts yielded Burkholderia cepacia which was sensitive to Ceftazidime & Sulfamethoxazole/Trimethoprim.

Intravitreal Ceftazidime 2.25mg/0.1 cc (which had been administered at the onset of treatment as per EVS guidelines) was again given into the silicone oil after vitrectomy. There was an initial post vitrectomy resolution of hypopyon as frequent topical Gatifloxacin and Dexamethasone were continued at every 30 minutes dosing. Also, her vision improved to Counting Fingers. As medications were subsequently tapered down to hourly dosing, there was another recurrence of inflammation, with a return of hypopyon by the 30th day post IVB. This necessitating a return to an increased frequency of topical medications to every 30 minutes dosing and another dose of intravitreal 2.25mg/0.1 cc Ceftazidime (third dose) was given. Also, oral 750mg Sulfamethoxazole/150mg Trimethoprim was administered twice daily for 1week. By the 38th day post IVB her vision had improved to 6/60 (20/200) on hourly eye drops, and oral Sulfamethoxazole/Trimethoprim was discontinued. At her review on the 45th day post IVB she had a recurrence of cells in the anterior chamber and hypopyon. Her vision was also reduced to Counting Fingers. The frequency of topical medications administration was therefore increased to every 30 minutes. She had multiple recurrences each time the frequency of topical Gatifloxacin and Dexamethasone was reduced.

At the 45th day post IVB a circular opaque plaque was noted to appear on the posterior capsule of the clear lens as seen in Fig. 4 (a red reflex was now present; Fig. 4). It was thought that this plaque was the site of fresh recurrence. The plaque continued to increase in size. A decision was therefore taken to remove the silicone oil and perform a lensectomy & posterior capsulectomy and this was discussed with the patient who consented to the procedure. Surgery was performed on the 50th day post IVB. At the conclusion of this surgery, intravitreal and intracameral Ceftazidime 2.25mg/0.1 cc and Vancomycin 1mg/0.1 cc (as per EVS guidelines) were again administered. Also, Ceftazidime and Vancomycin were given into the subconjunctival space. Following the silicone oil removal, posterior capsulectomy, and lensectomy, the culture of silicone oil and vitreous cavity extracts still yielded a heavy growth of Burkholderia cepacia with antibiotic sensitivities similar to the previous microbiological study i.e. sensitive to Ceftazidime & Sulfamethoxazole/Trimethoprim.

With post-operative use of topical 0.5% Gatifloxacin hourly, and topical steroid changed to topical 1% Prednisolone Acetate (Pred Forte) hourly, and oral 750mg Sulfamethoxazole/150mg Trimethoprim administered twice daily for 1 week, there was a complete resolution of the endophthalmitis and all intraocular inflammation (Fig. 5). By the 57th day post IVB topical Gatifloxacin and Prednisolone could be tapered to 2 hourly as there was no hypopyon and anterior chamber was devoid of cells. By the 4th month (120th day) post IVB her topical medications were stopped. The insertion of a posterior chamber intraocular lens, which was performed at the 6th month (180th day) post IVB improved her visual acuity from HM to 6/24(20/80) at the 1st-month post-op. Her retina in the RE was fully attached with a moderate degree of optic disc pallor (Fig. 6). Clinical assessment by the 9th month post IVB did not show any features of macular edema and all medications have been stopped by this time and vision maintained at 6/18 (20/60).

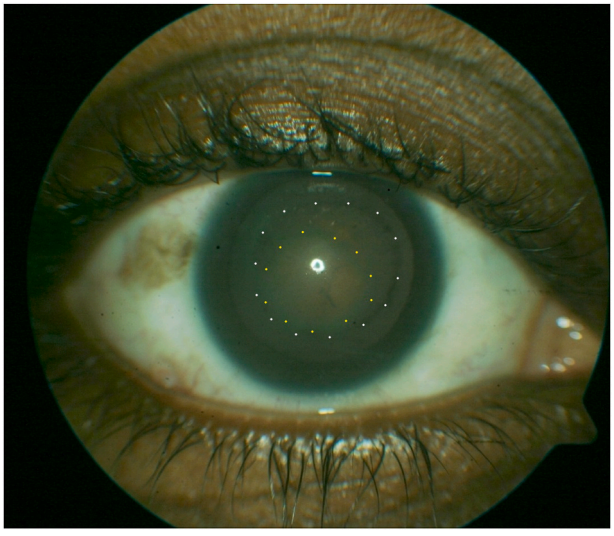

Fig. 4. Ring-shaped plaque on the posterior capsule can be seen against the background of some red reflex; boarders are highlighted with yellow dots. This plaque is surrounded by a wider ring of dark pigment which is also seen on the posterior capsule of the crystalline lens, the boarders of this ring is highlighted with white dots. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3. Discussion

Infective endophthalmitis is a known complication of IVI & can have devastating consequences on the eye & vision. Typically, gram-positive organisms especially Streptococcal and Staphylococci isolates are the predominant infectious agents associated with this form of endophthalmitis following the injection of vascular endothelial growth factor (VEGF) inhibitors such as Bevacizumab and Ranibizumab.[10]However, there are other less common organisms such as gram-negative species, B. cepacia being an example. B. cepacia has been reported by several authors as a cause of postoperative endophthalmitis.[3,11,12] There is at least one case report of post IV Ranibizumab endophthalmitis due to B. cepacia.[6] It is associated with frequent episodes of damaging recurrent inflammation and persistence of infection.[3,13] When intraocular infection occurs, the aim of treatment is to eradicate the infective organism and control intraocular inflammation.

B. cepacia endophthalmitis recurrence is due in part to the persistence of the microbe within the eye. Reasons for this persistence include the organisms well described multidrug resistance which is due to a rough lipopolysaccharide which encases the organism.[14] The organism is known to produce lipopolysaccharide and beta-lactamase that renders the antibiotics ineffective against it.[15] It is also known to mutate rapidly

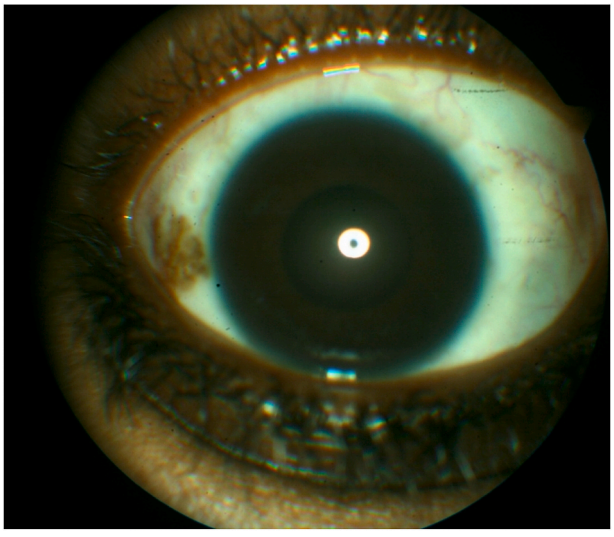

Fig. 5. Complete resolution of intraocular inflammation with a white conjunctiva and clear cornea.

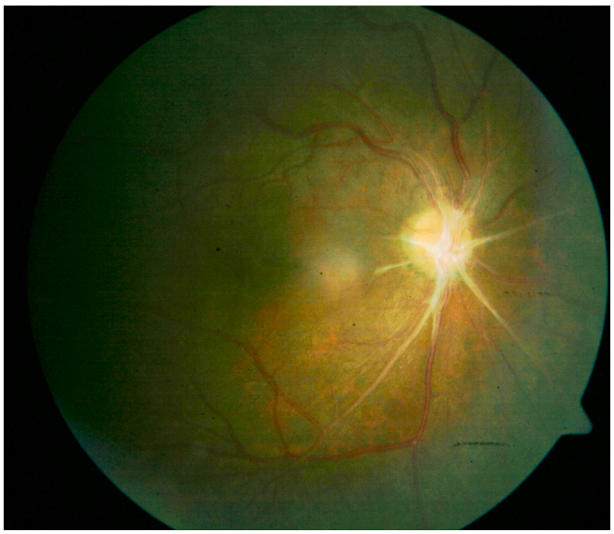

Fig. 6. Post treatment appearance of the fundus. Optic disc pallor can be seen.

and can use antimicrobials as its source of carbon.[1] Furthermore, as described in this case report, persistence and recurrence may be associated with the microbe's ability to colonize intraocular structures such as the crystalline lens or intraocular lens, lens zonules, ciliary body, and protecting itself from the effect of sensitive antimicrobials.[1,16,17] Despite the repeated use of intravitreal Ceftazidime which microbiology assessment revealed the B. cepacia was sensitive to, yet a heavy yield was cultured at the second sampling. The persistence of B. cepacia, in this case, could be as a result of the colonization of intraocular structures, since it succumbed when the lens was removed, without any change in antibiotic treatment. Ceftazidime generally has demonstrated in vitro efficacy for gram-negative organisms causing endophthalmitis and should be used when this group of organisms are suspected or isolated.[7]

Silicone oil has been shown to have an antimicrobial effect and therefore beneficial in endophthalmitis cases.[18–20] Due to the perceived inhibitory effect of silicone oil on microbes, its use as a tamponade post vitrectomy for infective endophthalmitis is often welcomed. This inhibitory effect of silicone oil on microbes has been demonstrated on the following common endophthalmitis causing microbes including *Staphylococcus aureus*, Staphylococcus epidermidis, *Escherichia coli*, *Pseudomonas aeruginosa*, and Candida albicans.[21] This antimicrobial effect of silicone oil is not effective against B. cepacia as reported in a series of silicone oil-related endophthalmitis in which B. cepacia was isolated as the culprit.[21] B. cepacia's resistance to silicone oil use was demonstrated in this case report since silicone oil could not prevent the further growth and recurrence of B. cepacia.

In several instances' physicians' have no choice but to resort to treating post-operative and post IVI endophthalmitis using the EVS guidelines before establishing a microbiological cause and obtaining specific antibiotic sensitivity patterns.[7] Therefore, in our case intravitreal Ceftazidime and Vancomycin were the initial antibiotics used. Our patient still experienced the persistence of B. cepacia due to the colonization of the posterior lens capsule and the crystalline lens. There are cases of chronic endophthalmitis in which intraocular persistence of the microbe is associated with microbial sequestration and colonization of the posterior lens capsule and the intraocular lens.[22,23] In such chronic endophthalmitis cases a pattern of apparent response to topical corticosteroids followed by relapse each time corticosteroids are tapered is common, particularly in chronic bacterial post-cataract endophthalmitis. Our case, though acute in onset also experienced this pattern of relapse each time topical antibiotics and steroids were tapered. An example of such chronic endophthalmitis is post-cataract surgery chronic endophthalmitis due to Propionibacterium Acnes (P. acnes), in which sequestration of the P. acnes into the capsular bag occurs.[24] Treatment of this form of endophthalmitis usually is by eradication of the P. acnes by employing a surgical posterior capsulectomy and Intraocular lens removal approach.[24]

In several eyes receiving IVI, especially amongst the younger age patients, a clear crystalline lens is present, as seen in our 34-year-old patient. This category of eyes will still have a clear crystalline lens should the unfortunate complication of post-IVI endophthalmitis occur. The mechanism of recurrent endophthalmitis seen in this case report involves colonization of the clear crystalline lens. This clinical situation should be recognized and could present as an opaque plaque on the posterior capsule. Though B. cepacia endophthalmitis post-IVI is rare, this clinical presentation and recurrent pattern of intraocular infection may be associated with other endophthalmitis causing gram-negative as well as gram-positive microbes. Therapy for such forms of endophthalmitis, therefore, includes the conventional endophthalmitis treatment protocol and a timely decision to remove the clear lens and perform surgical posterior capsulectomy, as was done in this case. Recognition of this clinical situation is important to avoid delay and permanent damage to the eye from persistent severe intraocular inflammation.

Lastly, this case report may suggest that eyes having a VH could be at some increased risk of post-IVI endophthalmitis compared to non-VH eyes. Since the same IVB was given to both eyes, but only the VH eye developed a full-blown endophthalmitis. The hemoglobin in the VH may serve as a culture medium to promote microbial growth.

In summary, lessons from this case report include the following; that B. cepacia is a cause of post IVB endophthalmitis. The only other case report on this is that of intraocular infection following treatment of macular degeneration using IV Ranibizumab.[6]

B. cepacia as previously reported, can be associated with multiple recurrences of endophthalmitis despite aggressive treatment (which could include vitrectomy and intravitreal antibiotics). In some cases of recurrence, B. cepacia may be noticed as a plaque on the posterior capsule of a clear lens. Removal of the infected capsule and the lens should be considered to ensure the removal of the source of recurrent endophthalmitis. Aggressive timely treatment of post IVB endophthalmitis due to B. cepacia can result in a return of good vision. Eyes with VH could be at a higher risk of endophthalmitis compared to non-VH eyes, if iatrogenic inoculation of microbes into the vitreous cavity occurs.

4. Conclusion

The visual outcome following the treatment of endophthalmitis in part depends on the infective organism. Gram-negative organisms are known to have a poor prognosis compared to more common causes such as gram-positive microbes e.g. Staph. Epidermidis. Therefore, there is a need for a more aggressive approach to management, including the possible removal of the clear crystalline lens, in some cases of recurrent infection when the lens may be colonized by the infecting microbe.

Patient consent

The patient gave written informed consent before all surgeries were performed and gave verbal consent to the publication of this case report. Also, all efforts have been made towards the anonymity of the patient.

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Credit author statement

Ogugua N Okonkwo: Conceptualization, Methodology, Writing Original Draft. Dennis Sibanda: Writing- Original draft preparation,

Reviewing, and Editing. Toyin Akanbi: Conception, Supervision, and Writing - Reviewing & Editing. Adekunle O. Hassan: Supervision, Resources, Writing- Reviewing and Editing.

Declaration of competing interest

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