Curr Infect Dis Rep (2014) 16:398
DOI 10.1007/s11908-014-0398-9

Therapeutic Ultrasound as a Treatment Modality for Chronic Rhinosinusitis

Jim Bartley · Noureddin Nakhostin Ansari · Soofia Naghdi

Published online: 26 February 2014

Abstract Chronic rhinosinusitis (CRS) is a chronic infective, inflammatory upper respiratory disease. While the current medical treatment of CRS focuses on the systemic and topical use of steroids and/or antibiotics, many bacteria residing on mucosal surfaces of patients with CRS exist in a biofilm state, making them resistant to most systemic antibiotics. Alternative therapeutic strategies that include blocking bacterial molecular communication, inhibiting biofilm matrix production and breaking down bacterial biofilms are all being explored. Physical therapies such as therapeutic ultrasound (US) have been advocated and utilized as a treatment modality for CRS for many years. US may have antiinflammatory actions and can also be used for the local delivery of drugs through the skin. Therapeutic US, which has been shown in clinical studies to be an effective treatment for both acute rhinosinusitis and CRS, offers significant potential in CRS management.

Keywords Biofilm · Inflammation · Rhinosinusitis · Sinusitis · Ultrasound

Introduction

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the sinonasal mucosa [1•]. The reasons for this inflammation remain poorly understood, and a variety of potential etiologies have been proposed [1•]. Complex polymicrobial communities exist on most, if not all, mucosal surfaces [2]. Current research is focused on the differences in the sinonasal microbiome between CRS patients and healthy individuals. CRS patients appear to have a reduced sinonasal bacterial diversity and an increased abundance of certain bacteria, particularly *Staphylococcus aureus* [3, 4]. This bacterial load is thought to contribute to the maintenance of the inflammatory response [3].

The current medical treatment of CRS focuses on the systemic and topical use of steroids and/or antibiotics [5]. While steroids are effective in managing the underlying chronic inflammation, the underlying causes are not addressed. In the short term, antibiotics reduce bacterial diversity even more and allow colonization with microbiota that are less susceptible to the prescribed antibiotics [6, 7]. Many bacteria residing on mucosal surfaces exist in a biofilm state, making them resistant to most antibiotics. This resistance has been attributed to a transport barrier created by the biofilm, binding of antibiotics to the exopolysaccharide in the biofilm and the bacteria in mature biofilms being metabolically dormant, and thus not taking up and/or metabolizing antibiotics [8••, 9–12]. Alternative therapeutic strategies such as blocking molecular communication (quorum sensing) between bacteria, inhibiting biofilm production and disrupting bacterial biofilms have been proposed. In industry, interventions against biofilms include biocides, chelating agents, scraping, enzymatic digestion, high-pressure spraying and ultrasound (US) [9]. Increasing evidence indicates that therapeutic US has a role in the management of bacterial biofilms. Therapeutic US may also have antiinflammatory actions [13]. Researchers have shown that therapeutic US is effective in treating patients with CRS. Therapeutic US thus offers significant potential in CRS management. In this review we present the evidence supporting the application of therapeutic US as a CRS therapy.

This article is part of the Topical Collection on *Respiratory Infections*

J. Bartley (✉)
Department of Surgery, University of Auckland, 10 Owens Road, Auckland 1023, New Zealand
e-mail: jbartley@ihug.co.nz

N. N. Ansari · S. Naghdi
School of Rehabilitation, Tehran University of Medical Sciences, Tehran, Iran

Basic Ultrasound Physics

Therapeutic US is produced by a transducer composed of a piezoelectric crystal, which converts electric energy into alternating compression and rarefaction of sound waves at a frequency greater than 20 kHz. The amplitude of the US wave is proportional to the displacement of the US transducer head during each half cycle. The amplitude represents the wave energy. The US wave frequency corresponds to the number of times that the transducer tip is displaced per second. Other important variables include treatment time and the US duty cycle (time ratio that the US is on), commonly termed either "continuous" or "pulsed". US pulsing decreases thermal effects by allowing time for heat to dissipate from the coupling medium during treatment. US frequencies range from 20 kHz to 10 GHz [14]. Medical applications (both diagnostic and therapeutic) employ frequencies between 1 MHz and 15 MHz, with most physiotherapy machines using frequencies of either 1 MHz or 3 MHz [15].

The longitudinal mechanical waves generated are transmitted at right angles to the transducer head. This causes the underlying tissues to alternatively contract and expand. As the US wave passes through tissue, the energy levels within the wave diminish exponentially [14]. The velocity of the US wave depends on the compressibility and the density of the tissue through which it passes. At a frequency of 1 MHz and a velocity of about 1,500 m/s, the wavelength in the tissues will be one-millionth of 1,500 m or 1.5 mm.

US has three effects on tissues: thermal effects, cavitation and acoustic streaming [15, 16]. Thermal effects are minimal with pulsed as opposed to continuous US [15]. Cavitation refers to the formation of microbubbles or cavities from dissolved gases, their growth and subsequent collapse in tissues and body fluids in extremely small time intervals (milliseconds) [14, 17••, 18]. Large quantities of energy are released. Very high local temperatures (of the order of 1,000–5,000 K) and pressures (100–50,000 bar) are generated [17••, 18]. Stable cavitation, which is defined as the pulsation of cavitation bubbles over many acoustic pressure cycles without collapse, occurs at therapeutic US doses. Transient (unstable) cavitation, which is not a feature of therapeutic US, refers to the rapid and uncontrolled growth of cavitation bubbles over several pressure cycles, and their eventual collapse into smaller bubbles [14]. This rapid collapse releases a large amount of energy, which may be detrimental to surrounding tissues.

Acoustic streaming refers to the small-scale eddying of fluids near vibrating structures, such as cell membranes and the surface of stable cavitation gas bubbles. This phenomenon produces shear stresses, which affect membrane diffusion and permeability. Sodium ion permeability is altered resulting in changes in cell membrane potential [15, 16, 19]. Calcium ion transport is modified, which in turn leads to an alteration in the enzyme control mechanisms of various metabolic processes, especially protein synthesis and cellular secretions [15, 16, 19]. Protein and calcium are important components of the biofilm matrix [20]. The result of the combined effects of stable cavitation and acoustic streaming is that the cell membrane becomes 'excited' (upregulated), thus increasing the activity levels of the whole cell [15, 16, 19].

The Influence of Ultrasound Frequency and Intensity

US frequency is usually fixed, because the maximum transfer efficiency of electrical to mechanical energy occurs only when the transducer is driven at its resonating frequency. At a constant irradiation, the resonant radius of cavitation bubbles has an inverse relationship with the applied US frequency [21], but the cavity collapse is more rapid at higher US frequencies, which leads to an increase in the magnitude of the collapse pressure. The smaller bubbles produced at higher frequencies require fewer acoustic cycles before they reach the requisite resonant size; a greater number of gas bubbles reach resonance size more quickly at higher frequencies [17••]. Cavitation bubbles are also subject to pressure and convective forces that can cause translational motion or interactions between bubbles [22].

Therapeutic US typically uses intensities of either 1 or 0.5 W/cm^2, whereas industry uses intensities of up to 300 W/cm^2. Altering either the overall energy or the area over which the energy is applied changes the intensity. The maximum size attained by a cavity during its growth phase increases with an increase in intensity. This increase in the maximum size is initially large (about 30 %) for the increase in intensity, but after certain intensities this increase is not substantial (<10 %). The complex physics relating US frequency and intensity to cavitation have been reviewed recently by Gogate [17••].

Action of Ultrasound on Bacterial Biofilms

At high energy levels, US treatment is capable of killing bacteria [23, 24]. In this situation bacterial killing is usually attributed to cavitation in or on the bacteria [24], or to the generation of free radicals [17••], which subsequently kill the bacteria. At a lower energy, sufficiently low that US does not kill bacteria, US has a synergistic effect with antibiotics (Table 1). This has been defined as the bioacoustic effect [25]. US may increase antibiotic effectiveness by increasing the rate of antibiotic transport to bacteria [26]. Electron spin resonance spectroscopy has shown that US at 70 kHz enhances the transport of hydrophobic molecules through the cell membrane [27]. US can also damage the bacterial cell wall. This in turn leads to increased energy requirements for repair [20]. US may increase the metabolic activity and the demand for oxygen

Table 1 Published studies on the bioacoustic effect of US

Reference	US frequency	Bacteria	Comment
[30]	67 kHz	*P. aeruginosa*, *E. coli*, *S. epidermidis*, *S. aureus*	*P. aeruginosa*, *E. coli* viability reduced when combined with gentamicin
[31]	70 kHz, 500 kHz, 2.25 MHz, 10 MHz	*P. aeruginosa*	Lower frequencies more effective when combined with gentamicin
[48]	70 kHz, 500 kHz	*E. coli*	Lower frequencies more effective against *E. coli*
[49]	28.48 Hz, 100 and 300 mW/cm^2	*E. coli*	300 mW/cm^2 in combination with gentamicin reduced bacterial count
[50]	28.48 kHz	*E. coli*	Pulsed US combined with gentamicin reduced bacterial viability
[26]	28.48 kHz, pulsed 500 mW/cm^2, 24 h vs 48 h	*S. epidermidis*	48 h more effective than 24 h
[32]	28.48 kHz, pulsed 500 mW/cm^2, 24 h and 48 h	*P. aeruginosa*, *E. coli*, on implants	US effective against *E. coli* only
[51]	28.48 Hz pulsed 500 mW/cm^2, 24–72 h after surgery	*E. coli*	Reduction in viability of biofilms when combined with gentamicin
[33]	46.5 kHz, 167 mW/cm^2	*E. coli*, *S. aureus*, coagulase-negative staphylococci, *P. aeruginosa*	Reduction in biofilm viability when gentamicin combined with US
[52]	40 kHz	*E. coli*	US enhanced activity of fluoroquinolones

and other nutrients [28]. US may damage the biofilm matrix. One confocal scanning laser microscopy study has shown that the structure does not change [29]; however, another study has shown that calcium can be lost from the biofilm matrix, which leads to decreased biofilm stability [20].

Different bacteria appear to have different US susceptibilities. Under identical conditions, US at 67 kHz combined with gentamicin was effective against cultures of Gram-negative *Pseudomonas aeruginosa* and *Escherichia coli,* but not against Gram-positive *S. epidermidis* or *S. aureus* [30]. The simultaneous application of US and gentamicin has been shown to reduce the viability of *P. aeruginosa* biofilms by several orders of magnitude. A lower US frequency (70 kHz) was significantly more effective than a higher frequency in reducing bacterial viability within the biofilm [31]. The duration of US treatment also appears to be important. Treatment of *E. coli* biofilms in vivo was only successful when treatment time was extended to 48 h; similar therapy was unable to reduce viable bacteria in *P. aeruginosa* biofilms [26, 32]. Carmen and colleagues have shown that *S. epidermidis* biofilms respond favorably to combinations of US (28.48 kHz) and vancomycin, but longer treatment times were required for this Gram-positive organism than for a Gram-negative species [26]. Ensing and colleagues have also shown that a prolonged US treatment time (40 h) with gentamicin-loaded bone cement reduces the planktonic and biofilm bacterial viability of *E. coli, P. aeruginosa, S. aureus* and coagulase-negative staphylococci [33]. Experimental laboratory evidence indicates that US has an important role in breaking down bacterial biofilms, especially when it is combined with antibiotics.

Phonophoresis (Sonophoresis)

For many decades, US has been utilized to deliver therapeutic compounds through the skin (phonophoresis). US can be applied either as a skin pretreatment prior to drug application, or with a coupling medium containing the drug or permeant [14]. The former is used where US has the potential to degrade the drug or other active ingredients. Historically, high frequencies (frequencies ≥0.7 MHz) were used for local corticosteroid delivery [34]. For transdermal drug delivery, low-frequency US (LFUS) increases skin permeability to a greater extent than high-frequency US (HFUS) [35, 36]. Therapeutic drug levels can be achieved using topical medication without the need for additional US. Lower frequencies (20 kHz) appear to be up to three times more effective than higher frequencies (1 MHz) [34–36]. The mechanisms of enhanced skin permeability between LFUS and HFUS appear to be different [14].

Several mechanisms of skin permeability enhancement in phonophoresis have been investigated. These include convection, lipid extraction, an increase in the solution–membrane interfacial transfer rate, thermal effects and mechanical or radiation pressure effects [14]. With LFUS, Mitragotri and colleagues have shown that cavitation within the skin is the primary mechanism of skin permeability enhancement [34]. Cavitation occurs within cavities near the corneocytes of the stratum corneum. The direct interaction of the oscillating cavitation bubbles is thought to induce disorder in the stratum corneum lipid bilayers, causing the observed increase in skin permeability [34]. HFUS has been utilized to deliver low molecular weight drugs (<1,000 Da) in a number of situations. Unlike HFUS, LFUS is not restricted severely by the size of

the molecules that it can deliver. Proteins and vaccines have been shown to be deliverable by LFUS [14]. US might have a role in local antibiotic delivery. Ansari and colleagues have reported the successful use of erythromycin phonophoresis to treat a patient with refractory CRS [37].

Anti-Inflammatory Actions of Ultrasound

Low-intensity US is used in musculoskeletal medicine. Low-intensity US reduces postoperative pain and swelling [38]. Animal studies have indicated that low-intensity US reduces inflammatory markers in the synovium via a reduction in inflammatory cell infiltrate [13]. Low-intensity US reduces joint pain in human osteoarthritis patients [39]. In surgically removed nasal polyps, LFUS treatment significantly decreased the number of inflammatory cells in the subepithelial and stromal layers [40].

Ultrasound as a Treatment for Rhinosinusitis

LFUS using a nasal solution and a handpiece inserted into the nasal vestibule has been studied. No damage to the underlying epithelium was noted [41]. In surgically removed nasal polyps treated with LFUS the reticular pattern of the connective tissue web remained intact, and no signs of vascular damage or leukocyte disintegration could be detected [40].

Recent clinical studies have indicated that therapeutic US may have a role in the management of rhinosinusitis (Table 2). Høsøien and colleagues [42•] treated 48 patients (a therapeutic group and a control group each of 24 patients) with clinically diagnosed acute sinusitis in a primary care setting. The therapeutic US group received four consecutive days of US, while the control group received amoxicillin 500 mg three times a day for 10 days. The clinical outcomes were similar in both groups in terms of patient satisfaction, number of side effects and relapses. The US group was more likely than the antibiotic group to prefer US to manage a further attack.

In a case-series, Ansari and colleagues [43] treated 57 CRS patients with low-intensity pulsed US. Most major and minor symptoms showed significant changes after US therapy ($p<0.05$). The "percent improvement" in symptoms was 81 %. Naghdi and colleagues [44] treated 30 adult CRS patients with ten sessions of continuous US. The "percent improvement" was 74 % at the end of treatment. One month after treatment, 72 % of patients reported continued improvement. Young and colleagues [45] treated 22 CRS patients who were being considered for endoscopic sinus surgery with six treatments of low-intensity pulsed US. Two patients were unable to complete the study protocol. After the sixth session, 18 patients had experienced improvement in symptoms, while two patients noted a worsening of symptoms. The median

Table 2 Studies testing the effect of therapeutic US on rhinosinusitis

Reference	No. of patients	Treated condition	Type of study	Results	Comment
[42•]	48	Acute rhinosinusitis	Randomized controlled trial with concealed allocation	No difference between therapeutic US and antibiotics	Experimental group preferred ultrasound
[46••]	20	Chronic rhinosinusitis	Single-blind randomized controlled trial	The US group (87 %) was significantly better than the control group (37 %; $p=0.007$)	A powerful result with such small numbers
[43]	57	Chronic rhinosinusitis	Case series	Most symptoms improved ($p<0.05$). Symptom improvement 81.3 %	Low-intensity pulsed ultrasound effective
[44]	30	Chronic rhinosinusitis	Case series using continuous US	74 % improvement in symptoms ($p<0.05$) largely maintained at 1 month	
[45]	22	Chronic rhinosinusitis	Case series	20-item Sino-Nasal Outcome Test score improved by 34 % ($p<0.0001$)	
[47]	40	Chronic rhinosinusitis	Randomized controlled trial comparing pulsed and continuous US	Sinus symptom scores with pulsed US slightly better than with continuous US but result not statistically significant ($p=0.09$)	

percentage improvement in the total overall symptom score was 16 % ($p<0.001$). The 20-Item Sino-Nasal Outcome Test score improved by 34 % ($p<0.001$).

Ansari and colleagues [46••] treated 20 CRS patients (a US group and a control group each of 10 patients) with continuous US in a randomized single-blind, placebo-controlled study. Following treatment, the mean "percent improvement" in the US group (87 %) was significantly higher than in the control group (37 %; $p=0.007$). At 1 month follow-up the US-treated group reported continued improvement. Ansari and colleagues [47] also treated 40 CRS patients with continuous or pulsed US in a randomized study. The improvement in CRS symptoms was similar in the two groups.

Conclusions

An optimal treatment for CRS should reduce the inflammatory response and the bacterial load, particularly *S. aureus,* without reducing the bacterial diversity of the sinonasal microbiome. In vivo studies have indicated that therapeutic US is able to reduce the inflammatory response, kill bacteria and destroy bacterial biofilms. This has been confirmed in in vivo clinical studies. The recognition that bacteria exist in complex communities called biofilms has led to a significant shift in our understanding of bacterial diseases. The resistance of bacteria within biofilms to conventional antibiotics means that new treatment strategies need to be developed. Current research is directed towards direct intranasal application of US [41], which might be more effective both in removing bacterial biofilms and in intranasal drug delivery. US offers potential as a sinusitis treatment modality.

Compliance with Ethics Guidelines

Conflict of Interest Jim Bartley, Nouredin Nakhostin Ansari and Soofia Naghdi have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.• Tomassen P, Van Zele T, Zhang N, et al. Pathophysiology of chronic rhinosinusitis. Proc Am Thorac Soc. 2011;8:115–20. *A recent review of the proposed etiologies of chronic rhinosinusitis.*

2. Suzaki H, Watanabe S, Pawankar R. Rhinosinusitis and asthma – microbiome and new perspectives. Curr Opin Allergy Clin Immunol. 2013;13:45–9.

3. Boase S, Foreman A, Cleland E, et al. The microbiome of chronic rhinosinusitis: culture, molecular diagnostics and biofilm detection. BMC Infect Dis. 2013;13:210.

4. Feazel LM, Robertson CE, Ramakrishnan VR, Frank DN. Microbiome complexity and Staphylococcus aureus in chronic rhinosinusitis. Laryngoscope. 2012;122:467–72.

5. Fokkens W, Lund V, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl. 2012;23:1–298.

6. Liu C, Soldanova K, Nordstrom L, et al. Medical therapy reduces microbiota diversity and evenness in surgically recalcitrant chronic rhinosinusitis. Int Forum Allergy Rhinol. 2013;3:775–81.

7. Jervis-Bardy J, Wormald P. Microbiological outcomes following mupirocin nasal washes for symptomatic Staphylococcus aureus – positive chronic rhinosinusitis following endoscopic sinus surgery. Int Forum Allergy Rhinol. 2012;2:111–5.

8.•• Costerton JW. Bacterial biofilms: a common cause of persistent infections. Science. 1999;284:1318–22. *An important review of bacterial biofilms.*

9. Dunne WM. Bacterial adhesion: seen any good biofilms lately? Clin Microbiol Rev. 2002;15:155–66.

10. Al-Mutairi D, Kilty SJ. Bacterial biofilms and the pathophysiology of chronic rhinosinusitis. Curr Opin Allergy Clin Immunol. 2011;11:18–23.

11. Costerton W. The application of biofilm science to the study and control of chronic bacterial infections. J Clin Invest. 2003;112:1466–77.

12. Hall-Stoodley L, Costerton JW, Stoodley P. Bacterial biofilms: from the natural environment to infectious diseases. Nat Rev Microbiol. 2004;2:95–108.

13. Chung J, Barua S, Choi B, et al. Anti-inflammatory effect of low intensity ultrasound (LIUS) on complete Freund's adjuvant-induced arthritis synovium. Osteoarthr Cartil. 2012;20:14–22.

14. Polat BE, Hart D, Langer R, Blankschtein D. Ultrasound-mediated transdermal drug delivery: mechanisms, scope, and emerging trends. J Control Release. 2011;152:330–48.

15. Watson T. The role of electrotherapy in contemporary physiotherapy practice. Man Ther. 2000;5:132–41.

16. Watson T. Ultrasound in contemporary physiotherapy practice. Ultrasonics. 2008;48:321–9.

17.•• Gogate P. Some aspects of the design of sonochemical reactors. Ultrason Sonochem. 2003;10:325–30. *A good review of ultrasound frequency and intensity to cavitation.*

18. Gogate P. Application of cavitational reactors for water disinfection: current status and path forward. J Environ Manage. 2007;85:801–15.

19. Dinnot MA, Dyson M, Young S, et al. The significance of membrane changes in the safe and effective use of therapeutic and diagnostic ultrasound. Phys Med Biol. 1989;34:1543–52.

20. Broekman S, Pohlmann O, Beardwood ES, de Meulenaer Cordemans E. Ultrasonic treatment for microbiological control of water systems. Ultrason Sonochem. 2010;17:1041–8.

21. Gaertner W. Frequency dependence of ultrasonic cavitation. J Acoust Soc Am. 1954;26:977–80.

22. Leighton T, Walton A, Pickworth M. Primary Bjerknes forces. Eur J Phys. 1990;11:47–50.

23. Heges M, Lewis J, Lunec J, Cramp W. The effect of ultrasound at 1.5 MHz on Escherichia coli. Int J Radiat Biol. 1980;37:103–8.

24. Scherba G, Weigel R, O'Brien W. Quantitative assessment of the germicidal efficacy of ultrasonic energy. Appl Environ Microbiol. 1991;57:2079–84.

25. Qian Z, Sagers R, Pitt W. Investigation of the mechanism of the bioacoustic effect. J Biomed Mater Res. 1999;44:198–205.

26. Carmen J, Roeder B, Nelson J, et al. Ultrasonically enhanced vancomycin activity against Staphylococcus epidermidis biofilms in vivo. J Biomater Appl. 2004;18:237–45.

27. Rapoport N, Smirnov A, Timoshin A, et al. Factors affecting the permeability of Pseudomonas aeruginosa cell walls toward lipophilic compounds: effects of ultrasound and cell age. Arch Biochem Biophys. 1997;344:114–24.
28. Pitt W, Ross S. Ultrasound increases the rate of bacterial cell growth. Biotechnol Prog. 2003;19:1038–44.
29. Qian Z, Stoodley P, Pitt W. Effect of low-intensity ultrasound upon biofilm structure from confocal scanning laser microscopy observation. Biomaterials. 1996;17:1975–80.
30. Pitt W, McBride M, Lunceford J, et al. Ultrasonic enhancement of antibiotic action on gram-negative bacteria. Antimicrob Agents Chemother. 1994;38:2577–82.
31. Qian Z, Sagers R, Pitt W. The effect of ultrasonic frequency upon enhanced killing of P. aeruginosa biofilms. Ann Biomed Eng. 1997;25:69–76.
32. Carmen J, Roeder B, Nelson J, et al. Treatment of biofilm infections on implants with low-frequency ultrasound and antibiotics. Am J Infect Control. 2005;33:78–82.
33. Ensing GT, Neut D, Horn JR, Mei HC, Busscher HJ. The combination of ultrasound with antibiotics released from bone cement decreases the viability of planktonic and biofilm bacteria: an in vitro study with clinical strains. J Antimicrob Chemother. 2006;58:1287–90.
34. Mitragotri S, Edwards D, Blankschtein D, Langer R. A mechanistic study of ultrasonically-enhanced transdermal drug delivery. J Pharm Sci. 1995;84:697–706.
35. Mitragotri S, Blankschtein D, Langer R. Ultrasound-mediated transdermal protein delivery. Science. 1995;269:850–3.
36. Mitragotri S, Blankschtein D, Langer R. Transdermal drug delivery using low frequency sonophoresis. Pharm Res. 1996;13:411–20.
37. Ansari NN, Fathali M, Naghdi S, et al. Treatment of chronic rhinosinusitis using erythromycin phonophoresis. Physiother Theory Pract. 2013;29:159–65.
38. Pilla A, Mont M, Nasser P, et al. Non-invasive low-intensity pulsed ultrasound accelerates bone healing in the rabbit. J Orthop Trauma. 1990;4:246–53.
39. Rutjes A, Nuesch E, Sterchi R, Juni P. Therapeutic ultrasound for osteoarthritis of the knee or hip. Cochrane Database Syst Rev. 2010: CD003132.
40. Karosi T, Sziklai I, Csomor P. Low-frequency ultrasound for biofilm disruption in chronic rhinosinusitis with nasal polyposis: in vitro pilot study. Laryngoscope. 2013;123:17–23.
41. Patel Z, Hwang PH, Chernomorsky A, et al. Low-frequency ultrasound in the nasal cavity and paranasal sinuses: a feasibility and distribution study. Int Forum Allergy Rhinol. 2012;2:303–8.
42.• Høsøien E, Lund AB, Vasseljen O. Similar effect of therapeutic ultrasound and antibiotics for acute bacterial rhinosinusitis: a randomised trial. J Physiother. 2010;56:27–32. *An important study showing ultrasound is as effective as antibiotics in the treatment of acute sinusitis.*
43. Ansari NN, Naghdi S, Farhadi M, Jalaie S. A preliminary study into the effect of low-intensity pulsed ultrasound on chronic maxillary and frontal sinusitis. Physiother Theory Pract. 2007;23:211–8.
44. Naghdi S, Ansari N, Farhadi M. A clinical trial on the treatment of chronic rhinosinusitis with continuous ultrasound. J Phys Ther Sci. 2008;20:233–8.
45. Young D, Morton R, Bartley J. Therapeutic ultrasound as treatment for chronic rhinosinusitis: preliminary observations. J Laryngol Otol. 2010;124:495–9.
46.•• Ansari NN, Naghdi S, Farhadi M. Physiotherapy for chronic rhinosinusitis: the use of continuous ultrasound. Int J Ther Rehabil. 2007;14:306–10. *Single-blind study showing that ultrasound is an effective treatment for chronic rhinosinusitis.*
47. Ansari N, Fathali M, Naghdi S, et al. A randomized, double-blind clinical trial comparing the effects of continuous and pulsed ultrasound in patients with chronic rhinosinusitis. Physiother Theory Pract. 2012;28:85–94.
48. Johnson L, Peterson R, Pitt W. Treatment of bacterial biofilms on polymeric biomaterials using antibiotics and ultrasound. J Biomater Sci Polym Ed. 1998;9:1177–85.
49. Rediske A, Roeder B, Brown M, et al. Ultrasonic enhancement of antibiotic action on Escherichia coli biofilms: an in vivo model. Antimicrob Agents Chemother. 1999;43:1211–4.
50. Rediske A, Roeder B, Nelson J, et al. Pulsed ultrasound enhances the killing of Escherichia coli biofilms by aminoglycoside antibiotics in vivo. Antimicrob Agents Chemother. 2000;44:771–2.
51. Ensing GT, Roeder BL, Nelson JL, et al. Effect of pulsed ultrasound in combination with gentamicin on bacterial viability in biofilms on bone cements in vivo. J Appl Microbiol. 2005;99:443–8.
52. Liu B, Wang D-J, Liu B-M, et al. The influence of ultrasound on the fluoroquinolones antibacterial activity. Ultrason Sonochem. 2011;18:1052–6.