ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2015 January 16; 3(1): 1-88

Published by Baishideng Publishing Group Inc

WJCC

World Journal of Clinical Cases

A peer-reviewed, online, open-access journal of Clinical Cases

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2012-2016

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World Journal of Clinical Cases

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Monthly Volume 3 Number 1 January 16, 2015

World Journal of Clinical Cases
Volume 3 Number 1 January 16, 2015

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Monthly

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PUBLICATION DATE
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DOI: 10.12998/wjcc.v3.i1.1

World J Clin Cases 2015 January 16; 3(1): 1-9
ISSN 2307-8960 (online)

REVIEW

Minimally invasive procedures on the lumbar spine

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Received: July 28, 2014
Peer-review started: July 29, 2014
First decision: September 16, 2014
Revised: October 29, 2014
Accepted: October 31, 2014
Article in press: December 23, 2014
Published online: January 16, 2015

Abstract

Degenerative disease of the lumbar spine is a common and increasingly prevalent condition that is often implicated as the primary reason for chronic low back pain and the leading cause of disability in the western world. Surgical management of lumbar degenerative disease has historically been approached by way of open surgical procedures aimed at decompressing and/or stabilizing the lumbar spine. Advances in technology and surgical instrumentation have led to minimally invasive surgical techniques being developed and increasingly used in the treatment of lumbar degenerative disease. Compared to the traditional open spine surgery, minimally invasive techniques require smaller incisions and decrease approach-related morbidity by avoiding muscle crush injury by self-retaining retractors, preventing the disruption of tendon attachment sites of important muscles at the spinous processes, using known anatomic neurovascular and muscle planes, and minimizing collateral soft-tissue injury by limiting the width of the surgical corridor. The theoretical benefits of minimally invasive surgery over traditional open surgery include reduced blood loss, decreased postoperative pain and narcotics use, shorter hospital length of stay, faster recover and quicker return to work and normal activity. This paper describes the different minimally invasive techniques that are currently available for the treatment of degenerative disease of the lumbar spine.

Key words: Minimally invasive surgery; Spine surgery; Lumbar spine; Degenerative disease; Interbody fusion; Posterolateral fusion; Decompression; Indirect decompression techniques

Core tip: Degenerative disease of the lumbar spine is a common and increasingly prevalent condition that is often implicated as the primary reason for chronic low back pain and the leading cause of disability in the western world. Compared to the traditional open spine surgery, minimally invasive techniques require smaller incisions and decrease approach-related morbidity. The benefits of minimally invasive surgery over traditional open surgery include reduced blood loss, decreased postoperative pain and narcotics use, shorter hospital length of stay, faster recovery and quicker return to work and normal activity.

Skovrlj B, Gilligan J, Cutler HS, Qureshi SA. Minimally invasive

procedures on the lumbar spine. *World J Clin Cases* 2015; 3(1): 1-9 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i1/1.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i1.1

INTRODUCTION

Modern minimally invasive spine surgery (MIS) was introduced in the 1990s with the description of tubular retractors for access to the lumbar spine and the report of the first lumbar microendoscopic discectomy[1,2]. Since that time, advances in technology and surgical instrumentation have led to MIS developing into an important and rapidly growing filed of spine surgery. Today, MIS techniques and approaches are used in the treatment of a wide variety of spinal pathologies including degenerative disc disease, disc herniation, instability, deformity, fracture, infection and tumors[3]. Compared to the traditional open spine surgery, MIS was pursued as a means to reduce iatrogenic tissue trauma during surgery. The theoretical benefits of MIS over traditional open surgery include smaller incisions, less soft tissue damage, reduced estimated blood loss (EBL), decreased postoperative pain and narcotics use, shorter hospital length of stay (LOS), faster recover and quicker return to work and normal activity[4,5]. Traditional open spine surgery approaches often require extensive muscular and ligamentous disruption during the surgical approach to the spine resulting in decreased spinal stability and subsequent associated morbidities[6]. MIS minimizes approach-related morbidity by avoiding muscle crush injury by self-retaining retractors, preventing the disruption of tendon attachment sites of important muscles at the spinous processes, using known anatomic neurovascular and muscle planes, and minimizing collateral soft-tissue injury by limiting the width of the surgical corridor[7]. The decrease in the approach-related morbidity and indirect iatrogenic destabilization of the spine are important advantages of MIS over open spine surgery.

MIS approaches have been increasingly used in the treatment of degenerative diseases of the lumbar spine. As microsurgery, endoscopy and various percutaneous techniques advance and our rapidly aging population drives greater demand for spinal care, MIS will likely play an increasingly important role in the treatment of lumbar degenerative disease. This paper describes the different MIS techniques that are currently available for the treatment of degenerative disease of the lumbar spine.

MINIMALLY INVASIVE NON-FUSION PROCEDURES

MIS microdiscectomy

Lumbosacral nerve root compression or irritation secondary to an intervertebral disc herniation is a major cause of sciatica and low back pain. Patients with disc-related sciatica may be managed conservatively or *via* surgery when conservative treatment fails or symptoms worsen over time. It is estimated that over 250000 elective lumbar spine surgeries are performed in the United States each year for persistent symptoms of sciatica[8]. Of those, lumbar discectomy remains one of the most commonly performed procedures[9]. The goal of surgery is most commonly to remove intervertebral disc material and decompress the nerve root. Traditionally, the standard surgical treatment of lumbosacral disc herniation has been open microdiscectomy, however, with the rapid advances in surgical techniques and technology, there has been a growing trend towards MIS microdiscectomy.

An MIS microdiscectomy involves the use of serial tubular retractors to dilate the paraspinous musculature without stripping it off the spinous processes, and an endoscope or surgical microscope to visual the surgical field[10]. While the benefits of minimal soft tissue disruption appear to favor MIS microdiscectomy over open microdiscectomy, there is a significant learning curve associated with performing the procedure safely. Although many innovative techniques in the treatment of lumbar disc herniation have been developed, open microdiscectomy remains the standard of care at the current time[11].

A recent meta-analysis of controlled trials that compared outcomes of MIS and open microdiscectomy in patients with sciatica evaluated 29 studies (16 randomized controlled trials and 13 non-randomized studies) with a total of 4472 patients[11] (Table 1). Regarding clinical outcomes, the study found a moderate to low quality evidence of no differences between MIS and open microdiscectomy. Regarding perioperative outcomes, there was low to moderate evidence of no difference between MIS and open microdiscectomy; this was particularly notable for complications and reoperation rates. The study also found no significant difference in quality-adjusted life years (QALYs) or total costs from a societal perspective during the first year following treatment. The authors found low quality evidence that MIS took 10-15 min longer, resulted in a 52 cc reduction in EBL and reduced mean LOS by 1.5 d. The increased surgical time with MIS may be explained by the learning curve associated with MIS, variability in the techniques used and differences in how operative times were defined[11].

Currently, there is evidence from several comparative studies of MIS and open microdiscectomy suggesting that clinical outcomes between the two groups are similar. As surgeons become more proficient with MIS techniques and investigators conduct well-powered, randomized controlled trials, the indications favoring MIS microdiscectomy will be better defined.

MIS direct decompression

Lumbar spinal stenosis is the most common indication for spine surgery in patients older than 65, and its prevalence in the United States is expected to rise 59% by the year 2025[12]. Age-related degenerative changes

Table 1 Differences between outcomes of minimally invasive *vs* open surgical techniques

MIS techniques	Ref.	Differences in outcome compared to open techniques
Non-fusion techniques		
MIS microdiscectomy	Kamper *et al*[11]	Moderate to low evidence of no differences between MIS and open microdiscectomy
		No significant differences in QUALYs or total costs
		MIS took 10-15 min longer, resulted in 52 cc reduction in EBL and reduced mean LOS by 1.5 d
MIS direct decompression (Laminectomy/laminotomy)	Rahman *et al*[16]	Decreased EBL compared to open technique
		MIS procedures were 37-47 min shorter
		Decreased LOS by 2.52 d in patients undergoing decompression at ≤ 2 levels
		MIS had fewer complications (7.9% *vs* 16.1%)
	Anderson *et al*[17]	No significant differences in terms of ODI, Short-Form-12, and VAS
	Khoo *et al*[18]	Longer operative times in MIS group (109 min *vs* 88 min)
		Decreased EBL and postoperative stay in MIS group
	O'Toole *et al*[21]	0.10% surgical site infection rate
		Authors concluded that MIS technique may reduce SSI rate by 10-fold
MIS indirect decompression (Interspinous process devices)	Kuchta *et al*[26]	Statistically significant improvement in symptom severity and physical functioning throughout 2-yr follow-up period
	Bowers *et al*[27]	85% failure rate and 38% complication rate
	Brussee *et al*[28]	Poor outcome in 68.9% of patients
	Kim *et al*[29]	Cost analysis study found devices to be extremely costly and questioned cost-effectiveness
Fusion techniques		
Intertransverse onlay fusion	-	No literature available comparing MIS versus open posterolateral onlay fusion
Percutaneous pedicle screw fixation	Lehmann *et al*[34]1	EBL and muscle damage markers significantly lower in MIS group
		Compartment pressure, blood flow and EMG readings similar between both groups
		Radiation exposure greater in MIS group
MIS transforaminal lumbar interbody fusion	Seng *et al*[51]	Statistically increased fluoroscopic times (55.2 s *vs* 16.4 s) and operative times (185 min *vs* 166 min) in MIS group
		MIS had less EBL than open (127 cc *vs* 405 cc)
		Postoperative morphine use less in MIS group (8.5 mg *vs* 24.2 mg)
		Shorter LOS in MIS group (3.5 d *vs* 5.9 d)
	Parker *et al*[55]	MIS associated with reduction in mean hospital cost of $1758, indirect cost of $8474, total 2-yr social cost of $9295
		Similar 2-yr direct health care cost and QALYs gained
MIS direct lateral interbody fusion	Villavicencio *et al*[73]	Lower complication rate in MIS versus open (8.2% *vs* 16.7%)
	Rodgers *et al*[74]	Significantly lower complication rate in MIS cohort (7.5% *vs* 60%)
		Decreased EBL, lower transfusion rate and shorter LOS
	Deluzio *et al*[75]	Average LOS in MIS group 49% shorter
		Average cost savings for MIS group at 45 d of $2536/patient

[1]Animal study. MIS: Minimally invasive surgery; LOS: Length of stay; EBL: Estimated blood loss; ODI: Oswestry Disability Index; VAS: Visual analog scale; SSI: Surgical site infection; EMG: Electromyography; cc: Centimeter cubed; QALY: Quality adjusted life year.

in the lumbar spine such as hypertrophy of the facet joints with or without synovial cyst formation, foraminal stenosis due to decrease in the intervertebral disc height or osteophyte formation, ligamentum flavum thickening causing central and lateral recess compression and bulging or herniation of the intervertebral disc are all potential contributors to lumbar spinal stenosis. Surgery has been shown to decrease pain and improve functional status in patients with lumbar spinal stenosis[13]. Traditionally, an open midline approach involving a wide, bilateral laminectomy with medial facetectomy with or without foraminotomy has been the standard technique for surgical treatment of lumbar spinal stenosis. However, lumbar decompression surgery is increasingly being performed using tubular decompression, a MIS technique. This procedure utilizes a small paramedian incision and through the use of serial tubular dilators to reduce multifidus muscle injury while providing sufficient exposure of the surgical decompression site and allowing for bilateral decompression through a single incision[14]. Decompressing the contralateral side through a single unilateral paramedian incision allows the surgeon to spare the spinous process, rostral and caudal supraspinous and interspinous ligaments as well as the contralateral lamina and facet joint, thereby minimizing iatrogenic destabilization of the spine while achieving sufficient decompression for symptomatic relief. Furthermore, the use of an intraoperative endoscope or microscope for magnification and lighting allows for adequate visualization of the spinal anatomy[15].

Multiple studies have described shorter operating room times, decreased EBL, shorter LOS, lower surgical site infection rates, fewer complications and faster recovery times in MIS compared to the open lumbar decompression for spinal stenosis[16-20].

Rahman *et al*[16] retrospectively reviewed the medical records and relevant imaging of 126 patients (38 MIS *vs* 88 standard open technique) who underwent bilateral surgical decompression for lumbar stenosis to determine intraoperative EBL, length of operation, LOS, and

number and nature of complications. On average, patients undergoing open procedures had 194 cc more EBL than patients undergoing MIS procedures, with the greatest difference in patients undergoing procedures involving ⩾ 3 levels. MIS procedures were 37-47 min shorter than open procedures. Looking at the hospital LOS, the authors found that patients undergoing decompression at ⩽ 2 levels had a LOS that was 2.52 d shorter in the MIS group. In terms of overall complications, the MIS group had fewer complications than the open group (7.9% *vs* 16.1%). However, one limitation of this study was that it did not evaluate long-term outcomes of the two procedures.

Anderson *et al*[17] performed a retrospective analysis of 110 patients in two matched cohorts to compare the tubular retractor approach and traditional midline approach to decompressive surgery for unilateral lumbar radiculopathy. The two approaches were evaluated based on patient reported outcomes using the Oswestry Disability Index (ODI), Short Form-12, and visual analog scale. The authors found no significant differences between the surgical approaches with respect to patient reported outcomes.

Khoo *et al*[18] compared 25 patients undergoing microendoscopic decompressive laminotomy to 25 patients undergoing open decompression for lumbar spinal stenosis. The authors found that effective circumferential decompression was achieved in the majority of patients in both groups. Surgery was longer for the MIS procedure group compared to the open group (109 min per single level *vs* 88 min per single level). EBL was reduced by 125 cc in the MIS group and postoperative stay was decreased 48 h, from 94 h in the open group to 42 h in the MIS group.

O'Toole *et al*[21] performed a retrospective review of prospectively collected data in 1274 patients undergoing MIS decompression and found a 0.10% rate of surgical site infection. The authors concluded that MIS techniques may reduce postoperative wound infections as much as 10-fold compared to open techniques.

At the current time, favorable complication profiles and patient outcome studies with MIS tubular decompression makes this technique an acceptable treatment option in the surgical management of lumbar spinal stenosis (Table 1). Studies assessing long-term outcomes and cost-utility of MIS *vs* open lumbar decompression are needed to further establish the value of MIS decompression.

MIS indirect decompression

Lumbar interspinous process devices (IPDs) are a MIS technology intended to unload the facet joints, restore foraminal height, lower intradiscal pressure, restricts overextension and provide motion-preserving stabilization[22]. IPDs are used in the treatment of degenerative lumbar spinal stenosis and intermittent neurogenic claudication where they provide indirect decompression to the neural structures[23]. They have also been used in the treatment of discogenic low back pain, facet syndrome, disc herniation and lumbar spinal instability[24]. In 2005, the United States Food and Drug Administration (FDA) approved the first ever IPD (X-STOP, Medtronic, Memphis, TN, United States) for the treatment of patients aged 50 or older suffering from neurogenic intermittent claudication secondary to a confirmed diagnosis of lumbar spinal stenosis. The device was indicated for those patients with moderately impaired physical function who experience relief in flexion from their symptoms of leg/buttock/groin pain, with or without back pain, and have undergone a regimen of at least 6 mo of non-operative treatment. The device may be implanted at one or two lumbar levels in patients in whom operative treatment is indicated at no more than two levels[25]. Since the FDA approval of the first IPD, a growing number of devices have been introduced to the spine implant market and used for a wide range of lumbar spinal pathologies, many of them outside of the intended indications.

Outcomes with the use of IPDs have thus far been inconsistent. Kuchta *et al*[26] reported on a single-center clinical outcomes of 175 patients with symptomatic lumbar spinal stenosis treated with X-STOP implantation and reported statistically significant ($P < 0.001$) improvements in symptom severity and physical functioning throughout the 2-year follow-up period. Bowers *et al*[27] reviewed complications associated with the use of X-STOP in 13 patients and found a 85% ultimate failure rate with patients requiring additional surgery for symptomatic relief. The authors also reported a 38% complications rate, including 3 spinous process fractures and 2 instances of new onset radiculopathy. Brussee *et al*[28] review 65 patients with neurogenic claudication who underwent placement of X-STOP device and found poor outcomes in 68.9% of patients.

Multiple studies have also reported high complication and reoperation rates following implantation of IPDs. Complication rates published in the literature range from 11.6% to 38% while reported reoperation rates range from 4.6% to 85%[26-31]. Epstein *et al*[23] reported on the cost of the treatment of 16 patients with a total of 31 X-STOP devices and found a total cost of $576407 charge for the devices alone plus an added $80944 charge for the operating/recovery room. The authors concluded that IPDs appear to be extremely costly and questioned the cost-effectiveness of these devices.

At the current time, there is evidence of poor long-term outcomes as well as high complication and reoperation rates following the use of IPDs for the treatment of degenerative lumbar conditions (Table 1). Studies on the cost-effectiveness and value of IPDs are currently lacking and are needed to determine the future faith of these devices.

MIS LUMBAR FUSION PROCEDURES

MIS posterolateral intertransverse onlay fusion without instrumentation

In the traditional posterior midline approach to the

lumbar spine, access to the intertransverse region requires extensive stripping of the paraspinal musculature to the tips of the transverse processes. This process results in significant destruction, postoperative atrophy and scarring of the multifidus muscles which has been associated with significant postoperative morbidity[32]. For this reason, a MIS paraspinal muscle-splitting technique (modified Wiltse approach) using an expandable tubular dilator has become an increasingly popular technique used for exposure of the transverse processes and intertransverse space. The use of an expandable tubular retractor allows for both of the transverse processes and the fusion bed to be simultaneously exposed.

The theoretical advantages of this MIS technique are decreased paraspinal muscle destruction, decreased surgical incision size, decreased EBL, decreased postoperative narcotic use and shorter LOS. However, there are no studies in the literature comparing outcomes or cost-effectiveness of lumbar intertransverse onlay fusion utilizing the MIS muscle-splitting approach compared to the traditional open approach (Table 1).

MIS percutaneous pedicle screw fixation

Pedicle screw fixation allows for the creation of a solid and biomechanically rigid construct that allows for fusion to occur at the intended levels. Traditionally, open midline incisions were utilized for exposure of the spine in preparation for pedicle screw placement. Open procedures require extensive tissue dissection to expose the entry points and provide adequate lateral-to-medial orientation for optimal screw trajectory. This dissection in turn may result in muscular denervation, facet capsule disruption, damage to the proximal facet joints and weakening of other ligamentous structures, resulting in prolonged post-operative pain and morbidity[33]. Open lumbar fusion procedures are associated with increased operative times, increased EBL and risk of postoperative surgical site infection[34]. LOS and cost of treatment are also adversely affected by open pedicle screw fixation and spinal fusion techniques[35]. Recently, MIS percutaneous pedicle screw fixation has become an increasingly popular MIS technique for lumbar spine fixation[36-38]. Percutaneous pedicle screw placement offers several distinct advantages over the traditional open approach. It eliminates the need for a midline incision and extensive paraspinal muscle dissection. Kim *et al*[38] revealed that percutaneous *vs* open instrumentation was associated with decreased multifidus muscle atrophy, a superior postoperative trunk muscle strength, lower blood loss and less postoperative narcotic use. However, the authors did not find an improved clinical outcome in terms of patient satisfaction and pain scores. Muscle damage is also related to direct compression by muscle retractors, which result in ischemia of the compressed muscle groups and can lead to postoperative muscle necrosis. Percutaneous pedicle screw placement allows the surgeon to more easily achieve an ideal lateral-to-medial trajectory, especially advantageous in obese patients. The advantage of a minimally traumatic access to the lumbar spine carries the disadvantages of longer operative times and increased radiation exposure, both dependent on surgeon experience and comfort level.

Several authors have demonstrated reduced intraoperative EBL, perioperative risk of transfusion, improved cosmesis, decreased post-operative pain and narcotic use, decreased LOS, faster return to activity and reduced overall costs[39-43]. To date, however, there exists no high-quality literature to support the notion that MIS pedicle screw instrumentation is superior to the traditional open technique. Most of the studies evaluating open *vs* percutaneous pedicle techniques do so in context of interbody fusion techniques with no study directly evaluating the two instrumentation techniques alone. Lehmann *et al*[34] compared open *vs* percutaneous pedicle screw insertion in a sheep model and found that EBL and muscle damage markers were significantly lower in the percutaneous group while radiation time was significantly longer in the percutaneous group. In terms of compartment pressure, blood flow and electromyography measurements at different time points during the operative procedure, no significant differences were revealed.

Many technical challenges unique to the percutaneous pedicle screw placement technique and a steep learning curve exists, requiring different technical, psychomotor and cognitive skills. Mobbs *et al*[44] noted several challenges in percutaneous screw placement including changing direction of screw placement following initial pedicle cannulation, L5/S1 screw head proximity, cannulation of small pedicles, skin incision selection and insertion of rod for multi-segmental fixation, and difficult Jamshidi placement in hard pedicles. Surgeon experience plays a key role in perioperative outcomes of MIS techniques. It is recommended that surgeons have adequate experience with open techniques before attempting MIS fixation techniques and that they begin with simple MIS procedures[44].

Despite all the encouraging clinical data (Table 1), prospective outcomes studies with long-term follow up comparing percutaneous instrumented fusion to conventional open instrumented fusion are required to determine the safety, effectiveness and clinical benefit of MIS spinal fixation.

MIS transforaminal lumbar interbody fusion

The TLIF is a versatile surgical procedure modified from the posterior lumbar interbody fusion (PLIF) and pioneered by Harms and Rolinger in 1982[45]. Transforaminal lumbar interbody fusion (TLIF) utilizes the principles of load sharing to provide a circumferential fusion consisting of an anterior column support and a posterior tension band. It is designed to restore lumbar lordosis, widen neural foramina, restore disc height and indirectly relieve spinal stenosis. TLIF has been effective in the treatment of lumbar spondylosis with or without spondylolisthesis and has also been used successfully

in the treatment of lumbar degenerative disc disease, recurrent lumbar disc herniation and complex lumbar stenosis. One of the main disadvantages to TLIF is the significant postoperative morbidity due to the extensive paraspinal muscle and soft tissue dissection and retraction required in order to provide access to the vertebral column. This approach-related morbidity can potentially affect short- and long-term patient outcomes due to increased postoperative pain, delayed rehabilitation and impaired spinal function.

MIS TLIF was first described by Foley *et al*[46] in 2003 and has since become an increasingly popular MIS method to achieve lumbar arthrodesis[47-50]. MIS TLIF has been shown to have short- and long-term clinical outcomes comparable to open TLIF with the additional benefits of decreased postoperative pain, decreased EBL, faster recovery times, reduced postoperative narcotic use, faster postoperative ambulation and shorter LOS[51-54] (Table 1).

Seng *et al*[51] retrospectively analyzed 40 cases of MIS TLIF compared to 40 open TLIFs and compared fluoroscopic times, operative times, EBL, LOS, postoperative narcotic use, complication rates and patient outcomes. The authors found a statistically significant increase in fluoroscopic times in the MIS TLIF group (MIS: 55.2 s, open 16.4 s, $P < 0.001$) as well as a statistically insignificant increase in operative times for the MIS TLIF group (MIS: 185 min, open: 166 min, $P = 0.085$). MIS had less EBL than open (127 cc *vs* 405 cc, $P < 0.001$). Postoperative morphine use for the MIS group was significantly less than the open group (8.5 mg *vs* 24.2 mg, $P = 0.006$). The authors also found that patient in the MIS TLIF group ambulated on average 1.5 d earlier ($P < 0.001$) and had an overall shorter LOS (MIS: 3.6 d, open: 5.9 d, $P < 0.001$). The overall complication rate was 15% for the MIS group and 20% for the open group, however this did not reach statistical significance ($P = 0.774$). Fusion rates, assessed by the Bridwell classification, showed that grade 1 fusion was achieved in 97.5% of both groups at 5 years. Both groups showed significant improvement in ODI, neurogenic symptom score, back and leg pain and SF-36 scores at follow-ups of 6 mo up to 5 years with no significant differences between them.

Parker *et al*[55] prospectively evaluated 100 patients undergoing TLIF (50 MIS *vs* 50 open) for back-related medical resource use, missed work, and QALY. The authors found that LOS and time to return to work were less for MIS compared to open TLIF ($P = 0.006$ and $P = 0.03$, respectively). MIS and open TLIF patients demonstrated similar improvements in patient-reported outcomes assessed. MIS was associated with a reduction in mean hospital cost of $1758, indirect cost of $8474, and total 2-year social cost of $9295 ($P = 0.03$), but similar 2-year direct health care cost and QALYs gained. The authors concluded that while both MIS and open TLIF are effective treatments for degenerative spondylolisthesis, MIS TLIF may represent a valuable and cost-saving advancement from a societal and hospital perspective.

Disadvantages of the MIS TLIF are related to the decreased visualization of the surgical field and a steep learning curve for the procedure resulting in increased fluoroscopic times and operative times which may be more significant in less experienced surgeons.

MIS direct lateral approaches

The lateral transpsoas, retroperitoneal approach, also known as extreme lateral interbody fusion (XLIF) or direct lateral interbody fusion (DLIF) is a minimally invasive technique that has become an increasingly common method to achieve fusion in the lumbar spine. This MIS approach was intially described in by Pimenta[56] (DLIF) in 2001, and later by Ozgur *et al*[57] (XLIF) in 2006. The MIS direct lateral approach differs from the traditional anterior lumbar interbody fusion (ALIF) and open posterior interbody fusion techniques in several important ways. In addition to being an MIS technique, the direct lateral approach requires the patient to be in the lateral decubitus position. The technique utilizes specialized retractors allowing for direct visualization of the surgical approach corridor. Continual neurophysiologic monitoring and fluoroscopic guidance during the approach phase of the procedure is necessary as the psoas splitting technique exposes the lumbar plexus and predisposes it to injury, which can result in psoas muscle weakness and thigh numbness[58,59].

Initial studies evaluating the safety and postoperative results of the MIS transpsoas approach concluded that the MIS technique was safe and allowed for exposure of the lumbar spine without mobilization of the great vessels or sympathetic plexus[60,61].

Smith *et al*[62] compared the long term outcome of XLIF compared to ALIF in a group of 202 patients (115 XLIF *vs* 87 ALIF) and found that the overall general surgical complication rate was significantly lower for XLIF compared to ALIF (8.2% *vs* 16.7%). Rodgers *et al*[63] described the complications in a large prospective series of 600 patients who underwent XLIF. The authors found the overall incidence of perioperative complications was 6.2% (1.5% in-hospital surgery-related, 2.8% in-hospital medical events, 1.0% out-of-hospital surgery-related, and 0.8% out-of-hospital medical events). There were no wound infections, no vascular injuries, no intraperitoneal visceral injuries and a 0.7% transient postoperative neurologic deficit rate. These complication rates compared favorably to the ALIF risk of vascular injury (1.9%-3%)[64-66]. Another major risk of open ALIF approach is retrograde ejaculation, occurring in 0.6%-4.5% of men[67]. There are currently no reports of retrograde ejaculation following %g MIS lateral interbody fusion which can be attributed to the fact that the sympathetic plexus is not mobilized during the transpsoas approach. Motor deficits after MIS lateral interbody fusion have been reported to range from 0.3%-2.9% with the majority of cases resolving spontaneously within three months[63,68,69]. These rates are comparable to the

reported motor deficit rates after PLIF (1.0%-6.1%) and MIS TLIF (4.1%) procedures[70-73].

Rodgers *et al*[74] retrospectively compared lumbar fusion outcomes in geriatric patients over 80 years of age who underwent XLIF or open PLIF. The authors observed a significantly lower complication rate in the XLIF group compared to the open TLIF group (7.5% *vs* 60%) we well as less blood loss (hemoglobin change, 1.4 g *vs* 2.7 g), a lower transfusion rate (0% *vs* 70%) and shorter LOS (1.3 d *vs* 5.3 d). The authors also described a lower overall mortality rate in the lateral interbody group compared to the open PLIF group (2.5% *vs* 30%).

Deluzio *et al*[75] retrospectively reviewed 210 patients (109 MIS *vs* 101 open) who underwent 2-level lumbar spine fusion from L1-2 to L4-5. They found the average LOS in the MIS group to be 49% shorter than in the open group (1.2 d *vs* 3.2 d). The authors noted that the average cost for the entire perioperative period, including both surgical and post-surgical costs out to 45 d, showed an average savings of 9.6% or $2563/patient in the MIS group.

The MIS lateral interbody fusion appears to present a safe and effective technique for treating degenerative lumbar disorders (Table 1). Long-term outcome studies and cost-analysis and value studies are needed to further clarify the benefits of this MIS approach.

CONCLUSION

In the recent years, there has been a growing trend in MIS approaches for the treatment of degenerative diseases of the lumbar spine. Although traditional open approaches are still performed by the majority of spine surgeons, the body of evidence supporting the safety and efficacy of MIS approaches in appropriately selected patients is growing. MIS approaches for lumbar microdiscectomy, laminectomy, and lumbar interbody fusion by way of the transforaminal or direct lateral approach have shown favorable complication profiles and clinical outcomes compared to traditional open approaches. MIS interspinous process devices have shown poor long-term outcomes as well as high complication and reoperation rates.

While the disadvantages of MIS techniques are the steep learning curve, narrow operative corridor and diminished visual field, these are outweighed by the benefits of MIS techniques in many instances. Going forward, long-term outcome studies and cost-effectiveness studies will be needed to fully assess the benefits of MIS techniques for treating degenerative disease of the lumbar spine.

REFERENCES

1 **Faubert C**, Caspar W. Lumbar percutaneous discectomy. Initial experience in 28 cases. *Neuroradiology* 1991; **33**: 407-410 [PMID: 1749470 DOI: 10.1007/BF00598613]

2 **Foley KT**, Smith MM. Microendoscopic discectomy. *Tech Neurosurg* 1997; **3**: 301-307

3 **American Academy of Neurological Surgeons.** Minimally Invasive Spine Surgery (MIS). Patient Information. [accessed 2014 July 25]. Available from: URL: http: //www.aans.org/Patient Information/Conditions and Treatments/Minimally Invasive Spine Surgery MIS.aspx

4 **Society for Minimally Invasive Spine Surgery.** Benefits and Testimonials. [accessed 2014 June 24]. Available from: URL: http: //www.smiss.org/benefits-and-testimonials

5 **Barbagallo GM**, Yoder E, Dettori JR, Albanese V. Percutaneous minimally invasive versus open spine surgery in the treatment of fractures of the thoracolumbar junction: a comparative effectiveness review. *Evid Based Spine Care J* 2012; **3**: 43-49 [PMID: 23526905 DOI: 10.1055/s-0032-1327809]

6 **Snyder LA**, O'Toole J, Eichholz KM, Perez-Cruet MJ, Fessler R. The technological development of minimally invasive spine surgery. *Biomed Res Int* 2014; **2014**: 293582 [PMID: 24967347 DOI: 10.1155/2014/293582]

7 **Kim CW**, Siemionow K, Anderson DG, Phillips FM. The current state of minimally invasive spine surgery. *Instr Course Lect* 2011; **60**: 353-370 [PMID: 21553786]

8 **Atlas SJ**, Chang Y, Kammann E, Keller RB, Deyo RA, Singer DE. Long-term disability and return to work among patients who have a herniated lumbar disc: the effect of disability compensation. *J Bone Joint Surg Am* 2000; **82**: 4-15 [PMID: 10653079]

9 **Dewing CB**, Provencher MT, Riffenburgh RH, Kerr S, Manos RE. The outcomes of lumbar microdiscectomy in a young, active population: correlation by herniation type and level. *Spine* (Phila Pa 1976) 2008; **33**: 33-38 [PMID: 18165746 DOI: 10.1097/BRS.0b013e31815e3a42]

10 **Lau D**, Han SJ, Lee JG, Lu DC, Chou D. Minimally invasive compared to open microdiscectomy for lumbar disc herniation. *J Clin Neurosci* 2011; **18**: 81-84 [PMID: 20851604 DOI: 10.1016/j.jocn.2010.04.040]

11 **Kamper SJ**, Ostelo RW, Rubinstein SM, Nellensteijn JM, Peul WC, Arts MP, van Tulder MW. Minimally invasive surgery for lumbar disc herniation: a systematic review and meta-analysis. *Eur Spine J* 2014; **23**: 1021-1043 [PMID: 24442183 DOI: 10.1007/s00586-013-316-2]

12 **Bae HW**, Rajaee SS, Kanim LE. Nationwide trends in the surgical management of lumbar spinal stenosis. *Spine* (Phila Pa 1976) 2013; **38**: 916-926 [PMID: 23324922 DOI: 10.1097/BRS.0b013e3182833e7c]

13 **Atlas SJ**, Keller RB, Robson D, Deyo RA, Singer DE. Surgical and nonsurgical management of lumbar spinal stenosis: four-year outcomes from the maine lumbar spine study. *Spine* (Phila Pa 1976) 2000; **25**: 556-562 [PMID: 10749631 DOI: 10.1097/00007632-200003010-00005]

14 **Alimi M**, Hofstetter CP, Torres JM, Cong GT, Njoku I, Hartl R. Unilateral tubular approach for bilateral laminectomy: effect on ipsilateral and contralateral buttock and leg pain. *Global Spine J* 2014; **4:** 149 [DOI: 10.1055/s-0034-1376720]

15 **Rihn JA**, Currier BL, Phillips FM, Glassman SD, Albert TJ. Defining the value of spine care. *J Am Acad Orthop Surg* 2013; **21**: 419-426 [PMID: 23818029 DOI: 10.5435/JAAOS-21-07-419]

16 **Rahman M**, Summers LE, Richter B, Mimran RI, Jacob RP. Comparison of techniques for decompressive lumbar laminectomy: the minimally invasive versus the „classic" open approach. *Minim Invasive Neurosurg* 2008; **51**: 100-105 [PMID: 18401823 DOI: 10.1055/s-2007-1022542]

17 **Anderson DG**, Patel A, Maltenfort M, Vaccaro AR, Ratliff J, Hilibrand A, Harrop JS, Sharan AD, Ponnappan RK, Rihn J, Albert TJ. Lumbar decompression using a traditional midline approach versus a tubular retractor system: comparison of patient-based clinical outcomes. *Spine* (Phila Pa 1976) 2011; **36**: E320-E325 [PMID: 21178844 DOI: 10.1097/BRS.0b013e3181db1dfb]

18 **Khoo LT**, Fessler RG. Microendoscopic decompressive laminotomy for the treatment of lumbar stenosis. *Neurosurgery* 2002; **51**: S146-S154 [PMID: 12234442]

19 **Asgarzadie F**, Khoo LT. Minimally invasive operative

management for lumbar spinal stenosis: overview of early and long-term outcomes. *Orthop Clin North Am* 2007; **38**: 387-399; abstract vi-vii [PMID: 17629986 DOI: 10.1016/j.ocl.2007.02.006]

20 **Palmer S**, Turner R, Palmer R. Bilateral decompression of lumbar spinal stenosis involving a unilateral approach with microscope and tubular retractor system. *J Neurosurg* 2002; **97**: 213-217 [PMID: 12296681]

21 **O'Toole JE**, Eichholz KM, Fessler RG. Surgical site infection rates after minimally invasive spinal surgery. *J Neurosurg Spine* 2009; **11**: 471-476 [PMID: 19929344 DOI: 10.3171/2009.5.SPINE08633]

22 **Tian NF**, Zhang XL, Wu YS, Jiang LB, Xu HZ, Chi YL. Fusion after interspinous device placement. *Orthopedics* 2012; **35**: e1822-e1825 [PMID: 23218645 DOI: 10.3928/01477447-20121120-33]

23 **Epstein NE**. A review of interspinous fusion devices: High complication, reoperation rates, and costs with poor outcomes. *Surg Neurol Int* 2012; **3**: 7 [PMID: 22347676 DOI: 10.4103/2152-7806.92172]

24 **Bono CM**, Vaccaro AR. Interspinous process devices in the lumbar spine. *J Spinal Disord Tech* 2007; **20**: 255-261 [PMID: 17473649 DOI: 10.1097/BSD.0b013e3180331352]

25 **US Food and Drug Administration.** Medical Devices. X STOP® Interspinous Process Decompression System (XSTOP) – P040001. [accessed 2014 September 20]. Available from: URL: http: //www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm078378.htm

26 **Kuchta J**, Sobottke R, Eysel P, Simons P. Two-year results of interspinous spacer (X-Stop) implantation in 175 patients with neurologic intermittent claudication due to lumbar spinal stenosis. *Eur Spine J* 2009; **18**: 823-829 [PMID: 19387698 DOI: 10.1007/s00586-009-0967-z]

27 **Bowers C**, Amini A, Dailey AT, Schmidt MH. Dynamic interspinous process stabilization: review of complications associated with the X-Stop device. *Neurosurg Focus* 2010; **28**: E8 [PMID: 20568923 DOI: 10.3171/2010.3.FOCUS1047]

28 **Brussee P**, Hauth J, Donk RD, Verbeek AL, Bartels RH. Self-rated evaluation of outcome of the implantation of interspinous process distraction (X-Stop) for neurogenic claudication. *Eur Spine J* 2008; **17**: 200-203 [PMID: 17972111 DOI: 10.1007/s00586-007-0540-6]

29 **Kim DH**, Tantorski M, Shaw J, Martha J, Li L, Shanti N, Rencu T, Parazin S, Kwon B. Occult spinous process fractures associated with interspinous process spacers. *Spine* (Phila Pa 1976) 2011; **36**: E1080-E1085 [PMID: 21343860 DOI: 10.1097/BRS.0b013e318204066a]

30 **Verhoof OJ**, Bron JL, Wapstra FH, van Royen BJ. High failure rate of the interspinous distraction device (X-Stop) for the treatment of lumbar spinal stenosis caused by degenerative spondylolisthesis. *Eur Spine J* 2008; **17**: 188-192 [PMID: 17846801 DOI: 10.1007/s00586-007-0492-x]

31 **Barbagallo GM**, Olindo G, Corbino L, Albanese V. Analysis of complications in patients treated with the X-Stop Interspinous Process Decompression System: proposal for a novel anatomic scoring system for patient selection and review of the literature. *Neurosurgery* 2009; **65**: 111-119; discussion 119-120 [PMID: 19574832 DOI: 10.1227/01.NEU.0000346254.07116.31]

32 **Motosuneya T**, Asazuma T, Tsuji T, Watanabe H, Nakayama Y, Nemoto K. Postoperative change of the cross-sectional area of back musculature after 5 surgical procedures as assessed by magnetic resonance imaging. *J Spinal Disord Tech* 2006; **19**: 318-322 [PMID: 16826001 DOI: 10.1097/01.bsd.0000211205.15997.06]

33 **Stokes IA**, Gardner-Morse M, Henry SM, Badger GJ. Decrease in trunk muscular response to perturbation with preactivation of lumbar spinal musculature. *Spine* (Phila Pa 1976) 2000; **25**: 1957-1964 [PMID: 10908940]

34 **Lehmann W**, Ushmaev A, Ruecker A, Nuechtern J, Grossterlinden L, Begemann PG, Baeumer T, Rueger JM, Briem D. Comparison of open versus percutaneous pedicle screw insertion in a sheep model. *Eur Spine J* 2008; **17**: 857-863 [PMID: 18389291 DOI: 10.1007/s00586-008-0652-7]

35 **Foley KT**, Gupta SK. Percutaneous pedicle screw fixation of the lumbar spine: preliminary clinical results. *J Neurosurg* 2002; **97**: 7-12 [PMID: 12120655]

36 **Lowery GL**, Kulkarni SS. Posterior percutaneous spine instrumentation. *Eur Spine J* 2000; **9** Suppl 1: S126-S130 [PMID: 10766069]

37 **Teitelbaum GP**, Shaolian S, McDougall CG, Preul MC, Crawford NR, Sonntag VK. New percutaneously inserted spinal fixation system. *Spine* (Phila Pa 1976) 2004; **29**: 703-709 [PMID: 15014282]

38 **Kim DH**, Albert TJ. Update on use of instrumentation in lumbar spine disorders. *Best Pract Res Clin Rheumatol* 2002; **16**: 123-140 [PMID: 11987935]

39 **Weber BR**, Grob D, Dvorák J, Müntener M. Posterior surgical approach to the lumbar spine and its effect on the multifidus muscle. *Spine* (Phila Pa 1976) 1997; **22**: 1765-1772 [PMID: 9259789 DOI: 10.1097/00007632-199708010-00017]

40 **Harris EB**, Massey P, Lawrence J, Rihn J, Vaccaro A, Anderson DG. Percutaneous techniques for minimally invasive posterior lumbar fusion. *Neurosurg Focus* 2008; **25**: E12 [PMID: 18673041 DOI: 10.3171/FOC/2008/25/8/E12]

41 **Hsieh PC**, Koski TR, Sciubba DM, Moller DJ, O'Shaughnessy BA, Li KW, Gokaslan ZL, Ondra SL, Fessler RG, Liu JC. Maximizing the potential of minimally invasive spine surgery in complex spinal disorders. *Neurosurg Focus* 2008; **25**: E19 [PMID: 18673048 DOI: 10.3171/FOC/2008/25/8/E19]

42 **Assaker R**. Minimal access spinal technologies: state-of-the-art, indications, and techniques. *Joint Bone Spine* 2004; **71**: 459-469 [PMID: 15589424 DOI: 10.1016/j.jbspin.2004.08.006]

43 **Kerr SM**, Tannoury C, White AP, Hannallah D, Mendel RC, Anderson DG. The role of minimally invasive surgery in the lumbar spine. *Operative Techniques in Orthopaedics* 2007; **17**: 183-189 [DOI: 10.1053/j.oto.2007.04.005]

44 **Mobbs RJ**, Sivabalan P, Li J. Technique, challenges and indications for percutaneous pedicle screw fixation. *J Clin Neurosci* 2011; **18**: 741-749 [PMID: 21514165 DOI: 10.1016/j.jocn.2010.09.019]

45 **Harms J**, Rolinger H. [A one-stager procedure in operative treatment of spondylolistheses: dorsal traction-reposition and anterior fusion (author's transl)]. *Z Orthop Ihre Grenzgeb* 1982; **120**: 343-347 [PMID: 7113376 DOI: 10.1055/s-2008-1051624]

46 **Foley KT**, Holly LT, Schwender JD. Minimally invasive lumbar fusion. *Spine* (Phila Pa 1976) 2003; **28**: S26-S35 [PMID: 12897471 DOI: 10.1097/01.BRS.0000076895.52418.5E]

47 **Isaacs RE**, Podichetty VK, Santiago P, Sandhu FA, Spears J, Kelly K, Rice L, Fessler RG. Minimally invasive micro-endoscopy-assisted transforaminal lumbar interbody fusion with instrumentation. *J Neurosurg Spine* 2005; **3**: 98-105 [PMID: 16370298 DOI: 10.3171/spi.2005.3.2.0098]

48 **Jang JS**, Lee SH. Minimally invasive transforaminal lumbar interbody fusion with ipsilateral pedicle screw and contralateral facet screw fixation. *J Neurosurg Spine* 2005; **3**: 218-223 [PMID: 16235705 DOI: 10.3171/spi.2005.3.3.0218]

49 **Mummaneni PV**, Rodts GE. The mini-open transforaminal lumbar interbody fusion. *Neurosurgery* 2005; **57**: 256-261; discussion 256-261 [PMID: 16234672 DOI: 10.1227/01.NEU.0000176408.95304.F3]

50 **Ozgur BM**, Yoo K, Rodriguez G, Taylor WR. Minimally-invasive technique for transforaminal lumbar interbody fusion (TLIF). *Eur Spine J* 2005; **14**: 887-894 [PMID: 16151713 DOI: 10.1007/s00586-005-0941-3]

51 **Seng C**, Siddiqui MA, Wong KP, Zhang K, Yeo W, Tan SB, Yue WM. Five-year outcomes of minimally invasive versus open transforaminal lumbar interbody fusion: a matched-pair comparison study. *Spine* (Phila Pa 1976) 2013; **38**: 2049-2055 [PMID: 23963015 DOI: 10.1097/BRS.0b013e3182a8212d]

52 **Lee KH**, Yue WM, Yeo W, Soeharno H, Tan SB. Clinical and radiological outcomes of open versus minimally invasive transforaminal lumbar interbody fusion. *Eur Spine J* 2012; **21**: 2265-2270 [PMID: 22453894 DOI: 10.1007/s00586-012-2281-4]

53 **Peng CW**, Yue WM, Poh SY, Yeo W, Tan SB. Clinical and radiological outcomes of minimally invasive versus open transforaminal lumbar interbody fusion. *Spine* (Phila Pa 1976) 2009; **34**: 1385-1389 [PMID: 19478658 DOI: 10.1097/BRS.0b013e3181a4e3be]

54 **Adogwa O**, Parker SL, Bydon A, Cheng J, McGirt MJ. Comparative effectiveness of minimally invasive versus open transforaminal lumbar interbody fusion: 2-year assessment of narcotic use, return to work, disability, and quality of life. *J Spinal Disord Tech* 2011; **24**: 479-484 [PMID: 21336176 DOI: 10.1097/BSD.0b013e3182055cac]

55 **Parker SL**, Mendenhall SK, Shau DN, Zuckerman SL, Godil SS, Cheng JS, McGirt MJ. Minimally invasive versus open transforaminal lumbar interbody fusion for degenerative spondylolisthesis: comparative effectiveness and cost-utility analysis. *World Neurosurg* 2014; **82**: 230-238 [PMID: 23321379 DOI: 10.1016/j.wneu.2013.01.041]

56 **Pimenta L.** Lateral endoscopic transpsoas retroperitoneal approach for lumbar spine surgery. VIII Brazilian Spine Society Meeting. Brazil: Belo Horizonte, Minas Gerais, 2001

57 **Ozgur BM**, Aryan HE, Pimenta L, Taylor WR. Extreme Lateral Interbody Fusion (XLIF): a novel surgical technique for anterior lumbar interbody fusion. *Spine J* 2006; **6**: 435-443 [PMID: 16825052 DOI: 10.1016/j.spinee.2005.08.012]

58 **Knight RQ**, Schwaegler P, Hanscom D, Roh J. Direct lateral lumbar interbody fusion for degenerative conditions: early complication profile. *J Spinal Disord Tech* 2009; **22**: 34-37 [PMID: 19190432 DOI: 10.1097/BSD.0b013e3181679b8a]

59 **Benglis DM**, Vanni S, Levi AD. An anatomical study of the lumbosacral plexus as related to the minimally invasive transpsoas approach to the lumbar spine. *J Neurosurg Spine* 2009; **10**: 139-144 [PMID: 19278328 DOI: 10.3171/2008.10.SPI08479]

60 **Malham GM**, Ellis NJ, Parker RM, Seex KA. Clinical outcome and fusion rates after the first 30 extreme lateral interbody fusions. *Scientific World Journal* 2012; **2012**: 246989 [PMID: 23213282 DOI: 10.1100/2012/246989]

61 **Bergey DL**, Villavicencio AT, Goldstein T, Regan JJ. Endoscopic lateral transpsoas approach to the lumbar spine. *Spine* (Phila Pa 1976) 2004; **29**: 1681-1688 [PMID: 15284517 DOI: 10.1097/01.BRS.0000133643.75795.EF]

62 **Smith WD**, Christian G, Serrano S, Malone KT. A comparison of perioperative charges and outcome between open and mini-open approaches for anterior lumbar discectomy and fusion. *J Clin Neurosci* 2012; **19**: 673-680 [PMID: 22236486 DOI: 10.1016/j.jocn.2011.09.010]

63 **Rodgers WB**, Gerber EJ, Patterson J. Intraoperative and early postoperative complications in extreme lateral interbody fusion: an analysis of 600 cases. *Spine* (Phila Pa 1976) 2011; **36**: 26-32 [PMID: 21192221 DOI: 10.1097/BRS.0b013e3181e1040a]

64 **Sasso RC**, Best NM, Mummaneni PV, Reilly TM, Hussain SM. Analysis of operative complications in a series of 471 anterior lumbar interbody fusion procedures. *Spine* (Phila Pa 1976) 2005; **30**: 670-674 [PMID: 15770183 DOI: 10.1097/01.brs.0000155423.18218.75]

65 **Fantini GA**, Pappou IP, Girardi FP, Sandhu HS, Cammisa FP. Major vascular injury during anterior lumbar spinal surgery: incidence, risk factors, and management. *Spine* (Phila Pa 1976) 2007; **32**: 2751-2758 [PMID: 18007256 DOI: 10.1097/BRS.0b013e31815a996e]

66 **Brau SA**, Delamarter RB, Schiffman ML, Williams LA, Watkins RG. Vascular injury during anterior lumbar surgery. *Spine J* 2004; **4**: 409-412 [PMID: 15246301 DOI: 10.1016/j.spinee.2003.12.003]

67 **Sasso RC**, Kenneth Burkus J, LeHuec JC. Retrograde ejaculation after anterior lumbar interbody fusion: transperitoneal versus retroperitoneal exposure. *Spine* (Phila Pa 1976) 2003; **28**: 1023-1026 [PMID: 12768143 DOI: 10.1097/01.BRS.0000062965.47779.EB]

68 **Pumberger M**, Hughes AP, Huang RR, Sama AA, Cammisa FP, Girardi FP. Neurologic deficit following lateral lumbar interbody fusion. *Eur Spine J* 2012; **21**: 1192-1199 [PMID: 22130617 DOI: 10.1007/s00586-011-2087-9]

69 **Youssef JA**, McAfee PC, Patty CA, Raley E, DeBauche S, Shucosky E, Chotikul L. Minimally invasive surgery: lateral approach interbody fusion: results and review. *Spine* (Phila Pa 1976) 2010; **35**: S302-S311 [PMID: 21160394 DOI: 10.1097/BRS.0b013e3182023438]

70 **Okuda S**, Miyauchi A, Oda T, Haku T, Yamamoto T, Iwasaki M. Surgical complications of posterior lumbar interbody fusion with total facetectomy in 251 patients. *J Neurosurg Spine* 2006; **4**: 304-309 [PMID: 16619677 DOI: 10.3171/spi.2006.4.4.304]

71 **Krishna M**, Pollock RD, Bhatia C. Incidence, etiology, classification, and management of neuralgia after posterior lumbar interbody fusion surgery in 226 patients. *Spine J* 2008; **8**: 374-379 [PMID: 17433779 DOI: 10.1016/j.spinee.2006.09.004]

72 **Kim KT**, Lee SH, Lee YH, Bae SC, Suk KS. Clinical outcomes of 3 fusion methods through the posterior approach in the lumbar spine. *Spine* (Phila Pa 1976) 2006; **31**: 1351-1357; discussion 1358 [PMID: 16721298 DOI: 10.1097/01.brs.0000218635.14571.55]

73 **Villavicencio AT**, Burneikiene S, Bulsara KR, Thramann JJ. Perioperative complications in transforaminal lumbar interbody fusion versus anterior-posterior reconstruction for lumbar disc degeneration and instability. *J Spinal Disord Tech* 2006; **19**: 92-97 [PMID: 16760781 DOI: 10.1097/01.bsd.0000185277.14484.4e]

74 **Rodgers WB**, Gerber EJ, Rodgers JA. Lumbar fusion in octogenarians: the promise of minimally invasive surgery. *Spine* (Phila Pa 1976) 2010; **35**: S355-S360 [PMID: 21160400 DOI: 10.1097/BRS.0b013e3182023796]

75 **Deluzio KJ**, Lucio JC, Rodgers WB. Value and cost in less invasive spinal fusion surgery: Lessons from a community hospital. *SAS J* 2010; **4**: 37-40 [DOI: 10.1016/j.esas.2010.03.004]

P- Reviewer: Alimehmeti R, Landi A **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

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DOI: 10.12998/wjcc.v3.i1.10

World J Clin Cases 2015 January 16; 3(1): 10-19
ISSN 2307-8960 (online)

REVIEW

Evaluation of chronic kidney disease in chronic heart failure: From biomarkers to arterial renal resistances

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Received: July 30, 2014
Peer-review started: July 30, 2014
First decision: September 16, 2014
Revised: October 20, 2014
Accepted: October 28, 2014
Article in press: December 23, 2014
Published online: January 16, 2015

Abstract

Chronic kidney disease and its worsening are recurring conditions in chronic heart failure (CHF) which are independently associated with poor patient outcome. The heart and kidney share many pathophysiological mechanisms which can determine dysfunction in each organ. Cardiorenal syndrome is the condition in which these two organs negatively affect each other, therefore an accurate evaluation of renal function in the clinical setting of CHF is essential. This review aims to revise the parameters currently used to evaluate renal dysfunction in CHF with particular reference to the usefulness and the limitations of biomarkers in evaluating glomerular dysfunction and tubular damage. Moreover, it is reported the possible utility of renal arterial resistance index (a parameter associated with abnormalities in renal vascular bed) for a better assesment of kidney disfunction.

Key words: Heart failure; Biomarkers; Doppler; Renal resistance index; Chronic kidney disease

Core tip: In the clinical setting of chronic heart failure the evaluation of renal dysfunction is essential. This review revises the currently available markers of renal function in chronic heart failure for a better characterization of renal function. Moreover, it is discussed the potential utility of a Doppler derived parameter, the renal resistance index, which is associated with abnormalities in the kidney vascularization.

Iacoviello M, Leone M, Antoncecchi V, Ciccone MM. Evaluation of chronic kidney disease in chronic heart failure: From biomarkers to arterial renal resistances. *World J Clin Cases* 2015; 3(1): 10-19 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i1/10.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i1.10

INTRODUCTION

Subjects with chronic heart failure (CHF) often present

chronic kidney disease (CKD) as well as worsening of renal function (WRF), which are both responsible for a poor outcome[1-3]. Over the past few years interest in this link between the kidney and heart has increased as these organs share many pathophysiological mechanisms, and are therefore able to negatively affect each other. This reciprocal influence has recently been defined as cardiorenal syndrome[4].

In this clinical setting the pathophysiological background underlying renal impairment is, in part, different when acute and chronic heart failure are considered. In acute decompensated heart failure (ADHF) acute kidney injury (AKI) can often occur[5]. Both low cardiac output and venous congestion are the principal determinants of WRF. When cardiac output decreases, renal perfusion and, consequently, glomerular filtration rate are reduced. On the other hand, venous congestion is the cause of a rise in efferent arterioles and end glomerular capillary pressure thus inducing a decrease in net filtration pressure, an increase in interstitial pressure with damage to tubules[6].

In CHF patients, abnormalities in cardiac function lead to a gradual WRF rather than AKI and a steady decrease in renal perfusion due to low cardiac output which is associated with micro and macrovascular disease[5]. However, also the presence of increased central venous pressure in CHF can favour the occurrence of WRF[7,8]. Finally, neuro-hormonal activation further enhances pathophysiological mechanisms leading to WRF[1].

On the basis of these considerations it is clear that in ADHF and CHF patients the evaluation of kidney function is extremely relevant. The aim of this review is to revise the parameters currently used to evaluate renal function in the CHF clinical setting and discuss the usefulness and limitations of biomarkers in evaluating glomerular dysfunction and tubular damage. Moreover, it is reported the possible utility of renal arterial resistance index (a parameter associated with abnormalities in renal vascular bed) for a better assesment of kidney Dysfunction.

ESTIMATION OF GLOMERULAR FUNCTION

Glomerular filtration rate and serum creatinine

Currently glomerular filtration rate (GFR) is the most used index to assess kidney function. It measures kidney filtration capacity and all the guidelines on heart failure recommend its routine use in CHF patients[9,10]. GFR can be estimated using renal clearance of an exogenous substance (inulina or I-iothalamate), however, even though this approach is more accurate, it is limited as it is expensive and time consuming. Consequently, GFR estimation is generally performed using an endogenous marker, *i.e.*, serum creatinine[11]. Creatinine is produced in the muscles from creatine phosphate and it is removed by kidneys through glomerular filtration, but also by proximal tubular secretion.

The traditional method of measuring the clearance of creatinine requires a 24 h urine sample, which can be difficult for patients to perform and is often not done correctly. Therefore GFR is generally estimated by using serum creatinine levels[9]. For this purpose, Cockroft-Gault (CG), simplified Modification of Diet in renal disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) are the most widespread equations. These equations include creatinine serum levels, age, gender, race and, in CG, weight. However, they present an imperfect performance: GFR is underestimated by MDRD and CKD EPI and overestimated by CG, particularly at lower creatine serum levels[11].

Smilde *et al*[12] were the first to validate these creatinine based equations in a large cohort of CHF patients. In particular, they showed that GFR assessed by MDRD formula is underestimated in patients with normal and near normal values and overestimated in patients with worsening renal function. MDRD has a good prognostic significance, but is lower than that of the real GFR.

More recently the CKD EPI formula has been introduced. It is currently the equation most used to evaluate GFR in CKD as it has been found to be more accurate than MDRD in patients with a preserved renal function[13,14]. Moreover, the metanalysis by Matsushita *et al*[15] showed that CKD EPI formula allowed a better risk stratification for mortality and end stage renal disease in a general population and in patients with cardiovascular diseases.

Valente *et al*[16] first evaluated the role of this equation in the setting of CHF, showing that CKD EPI classifies KDOQI stages more accurately than the MDRD equation, especially in patients with a higher GFR. Furthermore, in the metanalysis of McAlister *et al*[17] the EPI formula was more accurate in estimating the risk of patients with CHF. According to these studies the CKD EPI formula is the preferred method to estimate GFR in CHF patients, particularly in those with preserved or moderately impaired renal function.

Creatinine serum levels and GFR are also used to estimate WRF. In CHF, WRF has generally been evaluated by assessing changes in creatinine[18]. In particular, an increase of > 0.3 mg/dL and/or > 25% between two time points[3] have been shown to be related to a worse outcome, hospitalizations for heart failure and higher mortality[19-23]. However, a rise in serum creatinine could be not associated with a significant reduction in GFR. A patient presenting higher baseline values of serum creatinine will show a less marked change in GFR than a patient with lower baseline values. Also the use of changes in GFR in order to assess WRF present some limitations due to the slight fluctuations in GFR which are common. For this reason current guidelines suggest that changes of 25% or more in estimated GFR should be considered as being associated with a change in GFR category[24].

Although creatinine serum levels and estimated GFR represent the corner stone in the evaluation of renal function and its worsening, several factors influencing the creatinine value and limiting its derived measures

should also be considered. Creatinine values show a significant between-person and within-person variability, they are influenced by age, diet, gender and body mass. Moreover, when kidney filtration capacity decreases, GFR can be overestimated because of creatinine tubular active secretion[25]. Finally, in CHF patients there are several factors that can affect the validity of equations used to estimate GFR, such as the hemodynamic component of renal dysfunction, drugs interfering with renal function and the loss of muscle mass that is frequent in the end stages of the disease[12].

It is also worth noting that the kidneys use only part of their filtering capacity. A normal GFR could subtend an impairment in this increasing filtration capacity, in other words it could be observed in kidneys with a reduced renal reserve[26].

In order to avoid the limitations of creatinine, new biomarkers estimating glomerular function, such as Cystatin C, have been introduced.

Cystatin C

This is a protein of cysteine proteinase inhibitor family (13 kdal) which is secreted by all cells with nucleus. It passes freely through the glomerular basement membrane and then it is reabsorbed, but not secreted in the tubules. As a consequence, it is an ideal marker of kidney filtration capacity. Moreover age, gender, food and body mass affect less its serum levels[27]. The only clinical conditions that can influence it are inflammatory status, the use of corticosteroids and thyroid diseases[28,29]. Several studies have shown that, in patients with moderate renal impairment, Cystatin C serum levels estimate GFR better than the equations based on creatinine serum levels[30,31].

In fact the KDIGO guidelines[32] for CKD management recommend assessing Cystatin C in patients with eGFRcr of 45-60 mL/min per 1.73 m^2 , on condition that they don't present other manifestations of CKD, such as albumin-creatinine ratio > 30 mg/g.

Formulas based on Cystatin C values have also been presented in order to obtain an estimate of GFR thus facilitating the clinical use of this marker. Moreover, equations based on combined creatinine-cystatin serum levels give a more accurate estimate of GFR than those based on each single level[33,34].

Cystatin C has also been demonstrated more accurate than creatinine in stratifying the risk of mortality and cardiovascular events in old subjects[35] and people with coronary artery disease[36]. High levels are also predictors of heart failure onset[37]. It is likely that the high Cystatin C levels reflect a mild or moderate decrease in renal function that is not detected by creatinine[33].

There are limited data on the role of Cystatin C in CHF[38-40]. Arimoto *et al*[38] showed the usefulness of Cystatin C in prognostic stratification of mild or moderate CHF. Moreover, Cystatin C has been found to better estimate the increased risk of cardiovascular death in elderly affected by CHF[39] as well as in patients with preserved renal function[40].

Although Cystatin C could be an interesting marker for an early assessment of renal function and for risk stratification in CHF, at present it is not widely used to estimate GFR. This is due to the widespread and consolidated use of creatinine, as well as to the fact that the Cystatin C measurement is more expensive, even if other markers, such as NT proBNP or troponin, have a similar cost[32].

Microalbuminuria

Albumin is the protein with the highest concentration in serum but has a low concentration in urine because of its large size, the selectivity of the glomerular filtration barrier and tubular reabsorption[11]. An increased albumin urinary excretion is a recognized early marker of kidney damage and its quantification is used for monitoring patients with CKD as well as for estimating the risk of kidney disease progression[24], as shown in Table 1. The urinary excretion of albumin is currently evaluated by calculating the albumin-to-creatinine ratio (UACR) in urine samples. An UACR < 30 mg/g is defined as normoalbuminuria, a UACR between 30 and 299 mg/g as microalbuminuria, and a UACR > 300 mg/g as macroalbuminuria[41].

Microalbuminuria has been shown to be associated not only with CKD progression, but also with an increased risk of cardiovascular death in the general population as well as in subjects with diabetes and hypertension[42].

The greater prevalence of microalbuminuria in CHF subjects than in the general population was demonstrated for the first time by Van der Wall[43]. In CHF albuminuria and reduced GFR can coexist, but sometimes only one of the conditions was found because they are caused by different pathophysiological mechanisms. Albuminuria can be the consequence of damage to the glomerular basement membrane secondary to endothelial dysfunction and inflammatory cytokine activation[44]. Moreover, it can be caused by hyperfiltration due to a reduction in the number of nephrons. This condition could occur in the event of a post glomerular ischemia which leads to hypoxia, oxidative stress and tubulointerstitial injury[45]. Other mechanisms involved in the genesis of microalbuminuria could be renal congestion[46,47] and reduced tubular reabsorption of albumin as a consequence of tubular dysfunction[48].

The large substudies from CHARM and GISSI HF trials[49,50] have confirmed the high prevalence of micro and macroalbuminuria in CHF patients (microalbuminuria was more common than macroalbuminuria) and its association with a worse outcome. HF patients with higher albumin urinary levels showed a greater mortality and an increased risk of HF hospitalizations. This prognostic value was independent from serum creatinine levels, eGFR and the comorbidities that worsen renal filtration function. Another important finding of these studies was that mortality risk increased with the increase in albumin excretion, even in the normal range (< 30 mg/g) suggesting that this parameter is a continuous measure of risk.

All of these studies showed that albumin urinary excretion is not affected by treatment with angiotensin

Table 1 Risk of chronic renal disease progression according to K/DOQI clinical practice guidelines[25]

Glomerular filtration rate categories			Microalbuminuria		
			A1 normal to mildly increased < 30 mg/g	A2 moderately increased 30-299 mg/g	A3 severely increased > 300 mg/g
1	Normal or high	> 90 mL/min	Low risk	Moderately increased risk	High risk
2	Mildly decreased	60-89 mL/min			
3a	Mildly to moderately decreased	45-59 mL/min	Moderately increased risk	High risk	Very high risk
3b	Moderately to severely decreased	30-44 mL/min	High risk	Very high risk	Very high risk
4	Severely decreased	15-29 mL/min	Very high risk	Very high risk	Very high risk
5	Kidney failure	< 15 or dialysis mL/min	Very high risk	Very high risk	Very high risk

receptor blockade, contrary to that observed in patients with diabetes, hypertension and renal disease. This may be due to the different pathophysiological mechanisms underlying albuminuria in CHF[51].

MARKERS OF TUBULAR DAMAGE

Different markers reflecting tubular damage have been studied in order to obtain a more accurate evaluation of renal function.

The Neutrophil gelatinase-associated lipocalin (NGAL) is a lipocalin protein (25 kdal), which is produced by the kidney, but also by other organs (the trachea, lung, stomach and colon). After being filtered through the glomerulus, NGAL is reabsorbed in the proximal tubule. When the proximal tubule is damaged, filtered NGAL can not be totally reabsorbed and its urinary levels increase[52]. Furthermore, during tubular damage NGAL mRNA is transcribed and overexpressed in loop of Henle and collecting duct and its plasma and urinary levels rise considerably[53,54]. NGAL plasma levels can also be increased by systemic diseases such as inflammation and cancer, but urinary levels are less influenced by these conditions[54].

The N-acetyl beta glucosaminidase (NAG) is a protein produced in the proximal tubular cells which is excreted into the urine when a tubular injury occurs[55]. Its urinary levels are increased in acute and chronic kidney disease[56] but also in diabetes and hypertension.

The Kidney injury molecule (KIM1) is a transmembrane glycoprotein and its expression in proximal tubule cells increases significantly after hypoxic or nephrotoxic tubular injury[57]. Its urinary levels are high also in patients with polycystic kidney[58] and renal cancer[59].

NAG, NGAL and KIM 1 have been widely studied in the setting of AKI (Acute Kidney Injury),where they have had a diagnostic and prognostic role, and show an increase 24 h prior to creatinine[60-63]. Recently, the utility of these markers in cardiorenal syndrome[25] has been evaluated by a number of studies, mainly involving patients with ADHF[64-67].

On the other hand, there are few studies which examine these markers in patients with CHF[68]. Damman *et al*[69] have shown a significant increase in urinary NGAL levels in these patients when compared to healthy controls, suggesting that renal dysfunction in CHF is characterised not only by a decrease in GRF and an increase in urinary albumin excretion but also by tubular damage. The renal perfusion decrease that occurs in CHF produces a GRF reduction and determines hypoxia leading to tubular damage.

Another study by Damman *et al*[70] showed that NGAL urinary levels were not correlated with prognosis, while urinary NAG and KIM1 were associated to a worse outcome (death, heart failure, hospitalisations and heart transplantation) and have an additional prognostic value compared to GRF. According to the authors, one explanation for this difference could be that NAG and KIM1 are produced in two different parts of the nephron and damage to the proximal part of the tubule may be more significant for the prognosis.

Finally, in a substudy of the GISSI HF trial[71] it has been confirmed that markers of tubular damage were strongly associated with HF hospitalizations and all cause mortality. In particular, NAG was the only marker remaining significantly correlated with a worse prognosis at multivariate analysis. This association was independent from estimated GFR and urinary protein excretion.

Markers of tubular function could be also related to WRF. In another substudy of the GISSI HF trial[47] patients with WRF had higher NGAL, NAG and KIM1 levels. These outpatients with WFR had a worse outcome. A possible explanation could be that the increase in these markers is caused by renal hypoxia, leading to a progressive deterioration of renal function that makes the kidney more vulnerable. At multivariate analysis KIM1 was the strongest independent predictor of WRF among all associated variables (eGFR and albuminuria included).

Beside NAG, NGAL and KIM 1, also other markers of tubular damage have been proposed.

IL 18 is a cytokine secreted by proximal tubular cells. When AKI occurs, it has been shown to increase more quickly than serum creatinine levels. It also increases in inflammatory status, therefore it is not highly specific[72,73]. Mallat *et al*[74] showed that, in ADHF, IL 18 plasma levels increased and were higher in patients who died during follow-up.

The fatty acid-binding proteins (FABPs) are proteins able to bind free fatty acids. Among the several tissue-specific isoforms, urinary levels of liver FABP (FABP-1)

and heart FABP (FABP-3) can reflect AKI, because excreted when an ischemic tubular injury occurs[25]. Moreover, serum FABP levels have been associated to worse outcome in CHF patients[75].

RENAL CIRCULATION AND RENAL RESISTANCE INDEX

Markers of GFR and tubular damage offer information about the status of nephrons. However, kidney circulation also plays a key role in renal function. Consequently, the evaluation of renal circulation could provide useful parameters to add to the information obtained from the above mentioned biomarkers.

Renal circulation

The kidney is a highly perfused organ, receiving 22% of cardiac output at rest[76]. After entering the hilum, the renal arteries divide into the interlobar, arcuate and interlobular arteries. Afferent arterioles originate from interlobular arteries, leading to the glomerular capillaries, and then to efferent arterioles. Efferent arterioles are followed by a second capillary network, *i.e.,* peritubular capillaries, and finally by the venous system. The regulation of renal blood flow (RBF) is not dependent on oxygen demand, but on reflex and neurohormonal mechanisms underlying the control of afferent and efferent arteriole tone. These mechanisms are not discussed in this review, however it is worth noting that arteriole tone changes are the main determinants of arterial renal resistance. The arteriolar tone is determined by reflex mechanisms, such as myogenic effect and tubular-glomerular feedback, and neurohormonal mechanisms. Of the neurohormonal systems, sympathetic and renin-angiotensin-aldosterone are those which most influence efferent arteriolar tone, determining vasoconstriction and increased water and sodium reabsorption. Endothelin, nitric oxide, prostaglandins, bradykinin and natriuretic peptides are also involved in the regulation of arteriolar tone.

The self-regulation of RBF allows renal perfusion to be kept constant through a wide range of arterial pressure (70-180 mmHg). On the other hand, changes in venous renal pressure could affect RBF more than those of arterial pressure. In 1931 Winton[77] evaluated the reduction of RBF by changing arterial and venous pressures in isolated kidneys. The results demonstrated that the changes were greater when renal venous pressure had been increased. More recent studies have confirmed the association between central venous pressure and renal function worsening in acute, as well as in chronic heart failure[77-79]. The mechanisms by which central venous pressure could affect RBF are different. In particular, it can increase both intra-abdominal pressure and renal venous pressure. This leads not only to an increase in capillary pressure and a reduction in artero-venous gradient but also to greater interstitial pressures and, consequently, greater arterial renal resistances.

Functional abnormalities of RBF and of renal resistances due to neurohormonal and hemodynamic changes could also lead to structural changes. Chade[76] demonstrated that the functional increase in renal vascular resistances could lead to ischemia, endothelial dysfunction, cytokine production and finally to fibrosis. This cascade of events causes a renal vascular rarefaction which could further induce CKD worsening.

On the basis of this pathophysiological background we can conclude that an increase in arterial renal resistances could represent an altered neuro-hormonal status, an increased central venous pressure, but it could also reflect the presence of parenchymal abnormalities and vascular rarefaction which favour CKD progression.

Arterial renal resistance index

Arterial renal resistance index (RRI) is a non-invasive measurement of renal arterial resistance which is easily evaluated by Doppler technique (Figure 1). It is calculated using Pourcelot's formula[80] since the peak systolic velocity and the end-diastolic velocity are obtained. Doppler evaluation of renal arteries is generally performed at the level of one or more interlobar arteries. In healthy adult subjects the RRI mean value is around 0.60 with no significant differences between the two kidneys[81]. An RRI greater than 0.70 is generally considered abnormal[82].

RRI has been found to be associated with renal parenchymal abnormalities. Platt e coll[83] first demonstrated the relationship between an increased RRI and parenchymal and vascular abnormalities assessed by renal biopsies. Later RRI has been found to be strongly associated with arteriolosclerosis, glomerulosclerosis, interstitial renal fibrosis and tubulo-interstitial lesions[84-88].

Our study group evaluated the independent predictors of RRI values in a large group of CHF outpatients with reduced ejection fraction. In a multivariate logistic regression model including univariate predictors, only age, systolic pulmonary pressure, central venous pressure, GFR, diabetes, logarithm of NT-proBNP, pulse arterial pressure and NYHA class remained significantly correlated to RRI. These results help to confirm the pathophysiological background responsible for the modification of RRI in CHF. In particular, RRI seems to carry information about renal artery abnormalities and/or alterations of arterial stiffness, as suggested by the correlation we found with the related parameters such as age, diabetes and pulse pressure. Moreover, the relationship between RRI and central venous pressure highlights the role of intra abdominal pressure and renal venous pressure in determining an increase in renal arterial resistances[89].

In a group of patients with CHF and preserved left ventricular ejection fraction, Ennezat *et al*[90] first demonstrated the significance of RRI in predicting prognosis. In our series of outpatients affected by CHF (mainly due to a reduced left ventricular ejection fraction), we have also demonstrated the prognostic significance of RRI[89]. The combined end-point that we considered was death, urgent heart transplantation or hospitalization due to heart failure worsening. RRI was associated with events in an univariate Cox regression model (HR

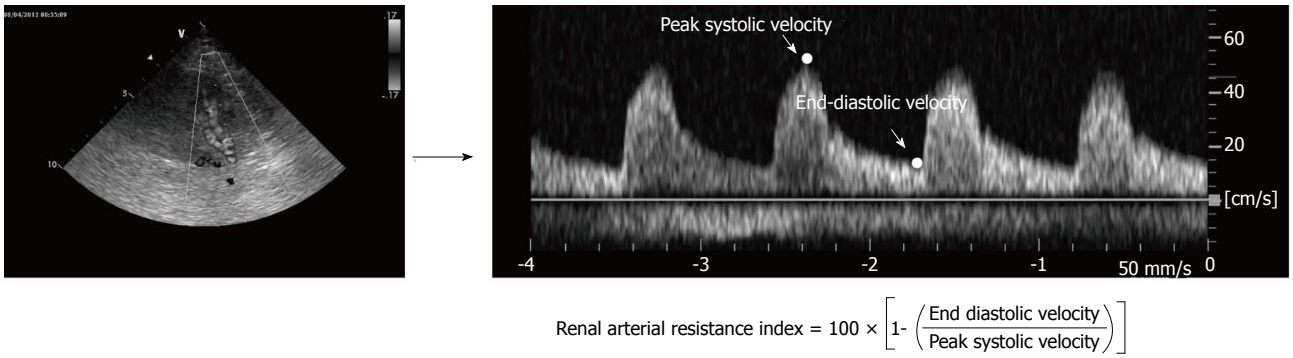

Figure 1 Calculation of Renal arterial Resistance Index. Renal arterial Doppler was performed using a 4 MHz probe, with the patient in the sitting position and using a posterior approach to visualise the kidney. The course of the right or left kidney segmental arteries is visualised by color Doppler flow and, at the middle tract level of the best one visualised, pulsed Doppler is performed. Peak systolic velocity and end diastolic velocity are used to calculate the renal arterial resistance index according to Pourcelot's formula.

= 1.14; 95%CI: 1.09-1.19; $P < 0.001$; C-index: 0.77), but also in a multivariate model (HR = 1.08; 95%CI: 1.02-1.13; $P = 0.004$; C-index: 0.86) correcting for the independent predictors, i.e. LVEF, GFR and logNT-proBNP. Moreover, with the addition of RRI, the reclassification model showed an important rise according to both category-free net reclassification improvement NRI (47%; 95%CI: 13%-80%; $P = 0.006$) and integrated discrimination improvement IDI (0.034; 95%CI: 0.006-0.061; $P = 0.016$). Likewise, in our series, RRI has been also found to be independently associated with an increased risk of death (at multivariate analysis: HR = 1.06; 95%CI: 1.01-1.12; $P = 0.023$; C-index = 0.783)[91].

The pathophysiological factors influencing RRI offer an explanation to the incremental prognostic value of this parameter when added to a model already including GFR. In addition to GFR, RRI could provide further information about renal function by reflecting not only glomerular function but also the other factors which influence the progression of kidney disease. Therefore, RRI could complete the information carried by GFR and allow a better characterization of renal dysfunction in CHF.

This is also supported by the fact that in our series RRI was able not only to predict heart failure progression but also worsening of renal function. At multivariate analysis a RRI > 70 was independently associated with an increase in creatinine > 0.3 mg/dL[92], regardless of baseline GFR values.

CONCLUSION

The evaluation of renal dysfunction is a cornerstone for CHF patients' management. GFR estimation is, at present, considered the best parameter to assess overall kidney function and it is recommended for routinely use. However, serum creatinine, traditionally used to estimate glomerular filtration rate, has several limitations. As a consequence the use of other parameters to evaluate hyperfiltration, tubular function and hemodynamic status could be useful in order to better define renal function. To this purpose RRI, an echo-Doppler derived parameter, which reflects abnormalities of the renal vascular bed, seems to be very promising as it carries an independent and incremental information to detect patients with worse prognosis and increased risk of WRF.

REFERENCES

1 **Hillege HL**, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 2000; **102**: 203-210 [PMID: 10889132]

2 **Smith GL**, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. *J Am Coll Cardiol* 2006; **47**: 1987-1996 [PMID: 16697315 DOI: 10.1016/j.jacc.2005.11.084]

3 **Damman K**, Jaarsma T, Voors AA, Navis G, Hillege HL, van Veldhuisen DJ. Both in- and out-hospital worsening of renal function predict outcome in patients with heart failure: results from the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH). *Eur J Heart Fail* 2009; **11**: 847-854 [PMID: 19696057 DOI: 10.1093/eurjhf/hfp108]

4 **Ronco C**, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008; **52**: 1527-1539 [PMID: 19007588 DOI: 10.1016/j.jacc.2008.07.051]

5 **Ronco C**, Ronco F. Cardio-renal syndromes: a systematic approach for consensus definition and classification. *Heart Fail Rev* 2012; **17**: 151-160 [PMID: 21197571 DOI: 10.1007/s10741-010-9224-0]

6 **Ronco C**, Di Lullo L. Cardiorenal syndrome. *Heart Fail Clin* 2014; **10**: 251-280 [PMID: 24656104 DOI: 10.1016/j.hfc.2013.12.003]

7 **Damman K**, Navis G, Smilde TD, Voors AA, van der Bij W, van Veldhuisen DJ, Hillege HL. Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. *Eur J Heart Fail* 2007; **9**: 872-878 [PMID: 17586090 DOI: 10.1016/j.ejheart.2007.05.010]

8 **Iacoviello M**, Puzzovivo A, Monitillo F, Saulle D, Lattarulo MS, Guida P, Forleo C, Gesualdo L, Favale S. Independent role of high central venous pressure in predicting worsening of renal function in chronic heart failure outpatients. *Int J Cardiol* 2013; **162**: 261-263 [PMID: 22805552 DOI: 10.1016/j.ijcard.2012.06.088]

9 **Stevens LA**, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. *N Engl J Med* 2006; **354**: 2473-2483 [PMID: 16760447]

10 **McMurray JJ**, Adamopoulos S, Anker SD, Auricchio A,

Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012; **14**: 803-869 [PMID: 22828712 DOI: 10.1093/eurjhf/hfs105]

11 **Ferguson MA**, Waikar SS. Established and emerging markers of kidney function. *Clin Chem* 2012; **58**: 680-689 [PMID: 22311920 DOI: 10.1373/clinchem.2011.167494]

12 **Smilde TD**, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. *Circulation* 2006; **114**: 1572-1580 [PMID: 17015793 DOI: 10.1161/CIRCULATIONAHA]

13 **Levey AS**, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604-612 [PMID: 19414839 DOI: 10.7326/0003-4819-150-9-200905050-00006]

14 **Stevens LA**, Schmid CH, Greene T, Zhang YL, Beck GJ, Froissart M, Hamm LL, Lewis JB, Mauer M, Navis GJ, Steffes MW, Eggers PW, Coresh J, Levey AS. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. *Am J Kidney Dis* 2010; **56**: 486-495 [PMID: 20557989 DOI: 10.1053/j.ajkd.2010.03.026]

15 **Matsushita K**, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, Polkinghorne KR, Shankar A, Smith DH, Tonelli M, Warnock DG, Wen CP, Coresh J, Gansevoort RT, Hemmelgarn BR, Levey AS. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA* 2012; **307**: 1941-1951 [PMID: 22570462 DOI: 10.1001/jama.2012.3954]

16 **Valente MA**, Hillege HL, Navis G, Voors AA, Dunselman PH, van Veldhuisen DJ, Damman K. The Chronic Kidney Disease Epidemiology Collaboration equation outperforms the Modification of Diet in Renal Disease equation for estimating glomerular filtration rate in chronic systolic heart failure. *Eur J Heart Fail* 2014; **16**: 86-94 [PMID: 23901055 DOI: 10.1093/eurjhf/hft128]

17 **McAlister FA**, Ezekowitz J, Tarantini L, Squire I, Komajda M, Bayes-Genis A, Gotsman I, Whalley G, Earle N, Poppe KK, Doughty RN. Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: impact of the new Chronic Kidney Disease-Epidemiology Collaboration Group formula. *Circ Heart Fail* 2012; **5**: 309-314 [PMID: 22441773 DOI: 10.1161/CIRCHEARTFAILURE.111.966242]

18 **Damman K**, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, van Veldhuisen DJ, Hillege HL. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. *J Card Fail* 2007; **13**: 599-608 [PMID: 17923350 DOI: 10.1016/j.cardfail.2007.04.008]

19 **Smith GL**, Shlipak MG, Havranek EP, Masoudi FA, McClellan WM, Foody JM, Rathore SS, Krumholz HM. Race and renal impairment in heart failure: mortality in blacks versus whites. *Circulation* 2005; **111**: 1270-1277 [PMID: 15769768 DOI: 10.116110.1161/01.CIR.0000158131]

20 **Akhter MW**, Aronson D, Bitar F, Khan S, Singh H, Singh RP, Burger AJ, Elkayam U. Effect of elevated admission serum creatinine and its worsening on outcome in hospitalized patients with decompensated heart failure. *Am J Cardiol* 2004; **94**: 957-960 [PMID: 15464689 DOI: 10.1016/j.amjcard.2004.06.041]

21 **Khan NA**, Ma I, Thompson CR, Humphries K, Salem DN, Sarnak MJ, Levin A. Kidney function and mortality among patients with left ventricular systolic dysfunction. *J Am Soc Nephrol* 2006; **17**: 244-253 [PMID: 16291840 DOI: 10.1681/ASN.2005030270]

22 **Krumholz HM**, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD, Horwitz RI. Correlates and impact on outcomes of worsening renal function in patients & gt; or =65 years of age with heart failure. *Am J Cardiol* 2000; **85**: 1110-1113 [PMID: 10781761]

23 **Metra M**, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, Fontanella B, Lombardi C, Milani P, Verzura G, Cotter G, Dittrich H, Massie BM, Dei Cas L. Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. *Eur J Heart Fail* 2008; **10**: 188-195 [PMID: 18279773 DOI: 10.1016/j.ejheart.2008.01.011]

24 **Stevens PE**, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013; **158**: 825-830 [PMID: 23732715 DOI: 10.7326/0003-4819-158-11-201306040-00007]

25 **Damman K**, Voors AA, Navis G, van Veldhuisen DJ, Hillege HL. Current and novel renal biomarkers in heart failure. *Heart Fail Rev* 2012; **17**: 241-250 [PMID: 21604178 DOI: 10.1007/s10741-011-9254-2]

26 **Bosch JP**. Renal reserve: a functional view of glomerular filtration rate. *Semin Nephrol* 1995; **15**: 381-385 [PMID: 8525139]

27 **Laterza OF**, Price CP, Scott MG. Cystatin C: an improved estimator of glomerular filtration rate? *Clin Chem* 2002; **48**: 699-707 [PMID: 11978596]

28 **Singh D**, Whooley MA, Ix JH, Ali S, Shlipak MG. Association of cystatin C and estimated GFR with inflammatory biomarkers: the Heart and Soul Study. *Nephrol Dial Transplant* 2007; **22**: 1087-1092 [PMID: 17210589 DOI: 10.1093/ndt/gfl744]

29 **Fricker M**, Wiesli P, Brändle M, Schwegler B, Schmid C. Impact of thyroid dysfunction on serum cystatin C. *Kidney Int* 2003; **63**: 1944-1947 [PMID: 12675875 DOI: 10.1046/j.1523-1755.2003.00925.x]

30 **Dharnidharka VR**, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis* 2002; **40**: 221-226 [PMID: 12148093 DOI: 10.1054/ajkd.2002.34487]

31 **Hoek FJ**, Kemperman FA, Krediet RT. A comparison between cystatin C, plasma creatinine and the Cockcroft and Gault formula for the estimation of glomerular filtration rate. *Nephrol Dial Transplant* 2003; **18**: 2024-2031 [PMID: 13679476 DOI: 10.1093/ndt/gfg349]

32 **Shlipak MG**, Mattes MD, Peralta CA. Update on cystatin C: incorporation into clinical practice. *Am J Kidney Dis* 2013; **62**: 595-603 [PMID: 23701892 DOI: 10.1053/j.ajkd.2013.03.027]

33 **Lassus J**, Harjola VP. Cystatin C: a step forward in assessing kidney function and cardiovascular risk. *Heart Fail Rev* 2012; **17**: 251-261 [PMID: 21431356 DOI: 10.1007/s10741-011-9242-6]

34 **Inker LA**, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; **367**: 20-29 [PMID: 22762315 DOI: 10.1056/NEJMoa1114248]

35 **Shlipak MG**, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS, Stehman-Breen C. Cystatin C and

the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 2005; **352**: 2049-2060 [PMID: 15901858 DOI: 10.1056/NEJMoa043161]

36 **Ix JH**, Shlipak MG, Chertow GM, Whooley MA. Association of cystatin C with mortality, cardiovascular events, and incident heart failure among persons with coronary heart disease: data from the Heart and Soul Study. *Circulation* 2007; **115**: 173-179 [PMID: 17190862 DOI: 10.1161/CIRCULATIONAHA.106.644286]

37 **Sarnak MJ**, Katz R, Stehman-Breen CO, Fried LF, Jenny NS, Psaty BM, Newman AB, Siscovick D, Shlipak MG. Cystatin C concentration as a risk factor for heart failure in older adults. *Ann Intern Med* 2005; **142**: 497-505 [PMID: 15809461 DOI: 10.7326/0003-4819-142-7-200504050-00008]

38 **Arimoto T**, Takeishi Y, Niizeki T, Takabatake N, Okuyama H, Fukui A, Tachibana H, Nozaki N, Hirono O, Tsunoda Y, Miyashita T, Shishido T, Takahashi H, Koyama Y, Kubota I. Cystatin C, a novel measure of renal function, is an independent predictor of cardiac events in patients with heart failure. *J Card Fail* 2005; **11**: 595-601 [PMID: 16230262 DOI: 10.1016/j.cardfail.2005.06.001]

39 **Alehagen U**, Dahlström U, Lindahl TL. Cystatin C and NT-proBNP, a powerful combination of biomarkers for predicting cardiovascular mortality in elderly patients with heart failure: results from a 10-year study in primary care. *Eur J Heart Fail* 2009; **11**: 354-360 [PMID: 19228797 DOI: 10.1093/eurjhf/hfp024]

40 **Tang WH**, Van Lente F, Shrestha K, Troughton RW, Francis GS, Tong W, Martin MG, Borowski AG, Jasper S, Starling RC, Klein AL. Impact of myocardial function on cystatin C measurements in chronic systolic heart failure. *J Card Fail* 2008; **14**: 394-399 [PMID: 18514931 DOI: 10.1016/j.cardfail.2008.01.006]

41 **Miller WG**, Bruns DE, Hortin GL, Sandberg S, Aakre KM, McQueen MJ, Itoh Y, Lieske JC, Seccombe DW, Jones G, Bunk DM, Curhan GC, Narva AS. Current issues in measurement and reporting of urinary albumin excretion. *Clin Chem* 2009; **55**: 24-38 [PMID: 19028824 DOI: 10.1373/clinchem.2008.106567]

42 **van der Velde M**, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, de Jong P, Gansevoort RT, van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey AS, de Jong PE, Gansevoort RT, Levey A, El-Nahas M, Eckardt KU, Kasiske BL, Ninomiya T, Chalmers J, Macmahon S, Tonelli M, Hemmelgarn B, Sacks F, Curhan G, Collins AJ, Li S, Chen SC, Hawaii Cohort KP, Lee BJ, Ishani A, Neaton J, Svendsen K, Mann JF, Yusuf S, Teo KK, Gao P, Nelson RG, Knowler WC, Bilo HJ, Joosten H, Kleefstra N, Groenier KH, Auguste P, Veldhuis K, Wang Y, Camarata L, Thomas B, Manley T. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011; **79**: 1341-1352 [PMID: 21307840 DOI: 10.1038/ki.2010.536]

43 **van de Wal RM**, Asselbergs FW, Plokker HW, Smilde TD, Lok D, van Veldhuisen DJ, van Gilst WH, Voors AA. High prevalence of microalbuminuria in chronic heart failure patients. *J Card Fail* 2005; **11**: 602-606 [PMID: 16230263 DOI: 10.1016/j.cardfail.2005.05.007]

44 **Niizeki T**, Takeishi Y, Sasaki T, Kaneko K, Sugawara S, Watanabe T, Kubota I. Usefulness of albuminuria as a prognostic indicator in patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 2013; **111**: 1180-1186 [PMID: 23351461 DOI: 10.1016/j.amjcard.2012.12.050]

45 **Kriz W**, LeHir M. Pathways to nephron loss starting from glomerular diseases-insights from animal models. *Kidney Int* 2005; **67**: 404-419 [PMID: 15673288 DOI: 10.1111/j.1523-1755.2005.67097.x]

46 **Gerstein HC**, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Hallé JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; **286**: 421-426 [PMID: 11466120 DOI: 10.1001/jama.286.4.421]

47 **Damman K**, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol* 2009; **53**: 582-588 [PMID: 19215832 DOI: 10.1016/j.jacc.2008.08.080]

48 **Damman K**, Masson S, Hillege HL, Voors AA, van Veldhuisen DJ, Rossignol P, Proietti G, Barbuzzi S, Nicolosi GL, Tavazzi L, Maggioni AP, Latini R. Tubular damage and worsening renal function in chronic heart failure. *JACC Heart Fail* 2013; **1**: 417-424 [PMID: 24621973 DOI: 10.1016/j.jchf.2013.05.007]

49 **Jackson CE**, Solomon SD, Gerstein HC, Zetterstrand S, Olofsson B, Michelson EL, Granger CB, Swedberg K, Pfeffer MA, Yusuf S, McMurray JJ. Albuminuria in chronic heart failure: prevalence and prognostic importance. *Lancet* 2009; **374**: 543-550 [PMID: 19683640 DOI: 10.1016/S0140-6736(09)61378-7]

50 **Masson S**, Latini R, Milani V, Moretti L, Rossi MG, Carbonieri E, Frisinghelli A, Minneci C, Valisi M, Maggioni AP, Marchioli R, Tognoni G, Tavazzi L. Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: data from the GISSI-Heart Failure trial. *Circ Heart Fail* 2010; **3**: 65-72 [PMID: 19850697 DOI: 10.1161/CIRCHEARTFAILURE]

51 **Damman K**, Hillege HL, van Veldhuisen DJ. Albuminuria in heart failure: a CHARMing new risk factor? *Lancet* 2009; **374**: 506-508 [PMID: 19683628 DOI: 10.1016/S0140-6736(09)61469-0]

52 **Schmidt-Ott KM**, Mori K, Li JY, Kalandadze A, Cohen DJ, Devarajan P, Barasch J. Dual action of neutrophil gelatinase-associated lipocalin. *J Am Soc Nephrol* 2007; **18**: 407-413 [PMID: 17229907 DOI: 10.1681/ASN.2006080882]

53 **Mori K**, Lee HT, Rapoport D, Drexler IR, Foster K, Yang J, Schmidt-Ott KM, Chen X, Li JY, Weiss S, Mishra J, Cheema FH, Markowitz G, Suganami T, Sawai K, Mukoyama M, Kunis C, D'Agati V, Devarajan P, Barasch J. Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. *J Clin Invest* 2005; **115**: 610-621 [PMID: 15711640 DOI: 10.1172/JCI200523056]

54 **Schmidt-Ott KM**, Mori K, Kalandadze A, Li JY, Paragas N, Nicholas T, Devarajan P, Barasch J. Neutrophil gelatinase-associated lipocalin-mediated iron traffic in kidney epithelia. *Curr Opin Nephrol Hypertens* 2006; **15**: 442-449 [PMID: 16775460 DOI: 10.1097/01.mnh.0000232886]

55 **Bazzi C**, Petrini C, Rizza V, Arrigo G, Napodano P, Paparella M, D'Amico G. Urinary N-acetyl-beta-glucosaminidase excretion is a marker of tubular cell dysfunction and a predictor of outcome in primary glomerulonephritis. *Nephrol Dial Transplant* 2002; **17**: 1890-1896 [PMID: 12401843 DOI: 10.1093/ndt/17.11.1890]

56 **Wellwood JM**, Ellis BG, Price RG, Hammond K, Thompson AE, Jones NF. Urinary N-acetyl- beta-D-glucosaminidase activities in patients with renal disease. *Br Med J* 1975; **3**: 408-411 [PMID: 1156788]

57 **Han WK**, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. *Kidney Int* 2002; **62**: 237-244 [PMID: 12081583 DOI: 10.1046/j.1523-1755.2002.00433.x]

58 **Meijer E**, Boertien WE, Nauta FL, Bakker SJ, van Oeveren W, Rook M, van der Jagt EJ, van Goor H, Peters DJ, Navis G, de Jong PE, Gansevoort RT. Association of urinary biomarkers with disease severity in patients with autosomal dominant polycystic kidney disease: a cross-sectional analysis. *Am J Kidney Dis* 2010; **56**: 883-895 [PMID: 20888104 DOI: 10.1053/j.ajkd.2010.06.023]

59 **Han WK**, Alinani A, Wu CL, Michaelson D, Loda M, McGovern FJ, Thadhani R, Bonventre JV. Human kidney

injury molecule-1 is a tissue and urinary tumor marker of renal cell carcinoma. *J Am Soc Nephrol* 2005; **16**: 1126-1134 [PMID: 15744000 DOI: 10.1681/ASN.2004070530]

60 **Haase M**, Bellomo R, Devarajan P, Ma Q, Bennett MR, Möckel M, Matalanis G, Dragun D, Haase-Fielitz A. Novel biomarkers early predict the severity of acute kidney injury after cardiac surgery in adults. *Ann Thorac Surg* 2009; **88**: 124-130 [PMID: 19559209 DOI: 10.1016/j.athoracsur.2009.04.023]

61 **Haase M**, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009; **54**: 1012-1024 [PMID: 19850388 DOI: 10.1053/j.ajkd.2009.07.020]

62 **Mishra J**, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, Ruff SM, Zahedi K, Shao M, Bean J, Mori K, Barasch J, Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 2005; **365**: 1231-1238 [PMID: 15811456 DOI: 10.1016/S0140-6736(05)74811-X]

63 **Parikh CR**, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, Edelstein CL, Devarajan P, Patel UD, Zappitelli M, Krawczeski CD, Passik CS, Swaminathan M, Garg AX. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. *J Am Soc Nephrol* 2011; **22**: 1748-1757 [PMID: 21836143 DOI: 10.1681/ASN.2010121302]

64 **Choudhary R**, Gopal D, Kipper BA, De La Parra Landa A, Aramin H, Lee E, Shah S, Maisel AS. Cardiorenal biomarkers in acute heart failure. *J Geriatr Cardiol* 2012; **9**: 292-304 [PMID: 23097660 DOI: 10.3724/SP.J.1263.2012.02291]

65 **Alvelos M**, Lourenço P, Dias C, Amorim M, Rema J, Leite AB, Guimarães JT, Almeida P, Bettencourt P. Prognostic value of neutrophil gelatinase-associated lipocalin in acute heart failure. *Int J Cardiol* 2013; **165**: 51-55 [PMID: 21872946]

66 **Dupont M**, Shrestha K, Singh D, Awad A, Kovach C, Scarcipino M, Maroo AP, Tang WH. Lack of significant renal tubular injury despite acute kidney injury in acute decompensated heart failure. *Eur J Heart Fail* 2012; **14**: 597-604 [PMID: 22505396 DOI: 10.1093/eurjhf/hfs039]

67 **Collins SP**, Hart KW, Lindsell CJ, Fermann GJ, Weintraub NL, Miller KF, Roll SN, Sperling MI, Sawyer DB, Storrow AB. Elevated urinary neutrophil gelatinase-associated lipocalcin after acute heart failure treatment is associated with worsening renal function and adverse events. *Eur J Heart Fail* 2012; **14**: 1020-1029 [PMID: 22733980 DOI: 10.1093/eurjhf/hfs087]

68 **Testani JM**, Tang WH. Biomarkers of acute kidney injury in chronic heart failure: what do the signals mean? *JACC Heart Fail* 2013; **1**: 425-426 [PMID: 24621974 DOI: 10.1016/j.jchf.2013.08.001]

69 **Damman K**, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Urinary neutrophil gelatinase associated lipocalin (NGAL), a marker of tubular damage, is increased in patients with chronic heart failure. *Eur J Heart Fail* 2008; **10**: 997-1000 [PMID: 18804416 DOI: 10.1016/j.ejheart.2008.07.001]

70 **Damman K**, Van Veldhuisen DJ, Navis G, Vaidya VS, Smilde TD, Westenbrink BD, Bonventre JV, Voors AA, Hillege HL. Tubular damage in chronic systolic heart failure is associated with reduced survival independent of glomerular filtration rate. *Heart* 2010; **96**: 1297-1302 [PMID: 20659949 DOI: 10.1136/hrt.2010.194878]

71 **Damman K**, Masson S, Hillege HL, Maggioni AP, Voors AA, Opasich C, van Veldhuisen DJ, Montagna L, Cosmi F, Tognoni G, Tavazzi L, Latini R. Clinical outcome of renal tubular damage in chronic heart failure. *Eur Heart J* 2011; **32**: 2705-2712 [PMID: 21666249 DOI: 10.1093/eurheartj/ehr190]

72 **Parikh CR**, Jani A, Melnikov VY, Faubel S, Edelstein CL. Urinary interleukin-18 is a marker of human acute tubular necrosis. *Am J Kidney Dis* 2004; **43**: 405-414 [PMID: 14981598]

73 **Parikh CR**, Mishra J, Thiessen-Philbrook H, Dursun B, Ma Q, Kelly C, Dent C, Devarajan P, Edelstein CL. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. *Kidney Int* 2006; **70**: 199-203 [PMID: 16710348 DOI: 10.1038/sj.ki.5001527]

74 **Mallat Z**, Heymes C, Corbaz A, Logeart D, Alouani S, Cohen-Solal A, Seidler T, Hasenfuss G, Chvatchko Y, Shah AM, Tedgui A. Evidence for altered interleukin 18 (IL)-18 pathway in human heart failure. *FASEB J* 2004; **18**: 1752-1754 [PMID: 15371332 DOI: 10.1096/fj.04-2426fje]

75 **Niizeki T**, Takeishi Y, Arimoto T, Nozaki N, Hirono O, Watanabe T, Nitobe J, Miyashita T, Miyamoto T, Koyama Y, Kitahara T, Suzuki S, Sasaki T, Kubota I. Persistently increased serum concentration of heart-type fatty acid-binding protein predicts adverse clinical outcomes in patients with chronic heart failure. *Circ J* 2008; **72**: 109-114 [PMID: 18159110]

76 **Chade AR**. Renal vascular structure and rarefaction. *Compr Physiol* 2013; **3**: 817-831 [PMID: 23720331 DOI: 10.1002/cphy.c120012]

77 **Winton FR**. The influence of venous pressure on the isolated mammalian kidney. *J Physiol* 1931; **72**: 49-61 [PMID: 16994199]

78 **Mullens W**, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* 2009; **53**: 589-596 [PMID: 19215833 DOI: 10.1016/j.jacc.2008.05.068]

79 **Jessup M**, Costanzo MR. The cardiorenal syndrome: do we need a change of strategy or a change of tactics? *J Am Coll Cardiol* 2009; **53**: 597-599 [PMID: 19215834 DOI: 10.1016/j.jacc.2008.11.012]

80 **Pourcelot L**. Velocimetrie ultrasonore Doppler. Seminaire INSERM. Paris, France: Edition INSERM, 1974: 213-240

81 **Parolini C**, Noce A, Staffolani E, Giarrizzo GF, Costanzi S, Splendiani G. Renal resistive index and long-term outcome in chronic nephropathies. *Radiology* 2009; **252**: 888-896 [PMID: 19528356 DOI: 10.1148/radiol.2523080351]

82 **Tublin ME**, Bude RO, Platt JF. Review. The resistive index in renal Doppler sonography: where do we stand? *AJR Am J Roentgenol* 2003; **180**: 885-892 [PMID: 12646425]

83 **Platt JF**, Ellis JH, Rubin JM, DiPietro MA, Sedman AB. Intrarenal arterial Doppler sonography in patients with nonobstructive renal disease: correlation of resistive index with biopsy findings. *AJR Am J Roentgenol* 1990; **154**: 1223-1227 [PMID: 2110732]

84 **Ikee R**, Kobayashi S, Hemmi N, Imakiire T, Kikuchi Y, Moriya H, Suzuki S, Miura S. Correlation between the resistive index by Doppler ultrasound and kidney function and histology. *Am J Kidney Dis* 2005; **46**: 603-609 [PMID: 16183414 DOI: 10.1053/j.ajkd.2005.06.006]

85 **Hanamura K**, Tojo A, Kinugasa S, Asaba K, Fujita T. The resistive index is a marker of renal function, pathology, prognosis, and responsiveness to steroid therapy in chronic kidney disease patients. *Int J Nephrol* 2012; **2012**: 139565 [PMID: 23304501 DOI: 10.1155/2012/139565]

86 **Sugiura T**, Nakamori A, Wada A, Fukuhara Y. Evaluation of tubulointerstitial injury by Doppler ultrasonography in glomerular diseases. *Clin Nephrol* 2004; **61**: 119-126 [PMID: 14989631]

87 **Sugiura T**, Wada A. Resistive index predicts renal prognosis in chronic kidney disease. *Nephrol Dial Transplant* 2009; **24**: 2780-2785 [PMID: 19318356 DOI: 10.1093/ndt/gfp121]

88 **Boddi M**, Cecioni I, Poggesi L, Fiorentino F, Olianti K, Berardino S, La Cava G, Gensini G. Renal resistive index early detects chronic tubulointerstitial nephropathy in normo- and hypertensive patients. *Am J Nephrol* 2006; **26**: 16-21 [PMID: 16401882]

89 **Ciccone MM**, Iacoviello M, Gesualdo L, Puzzovivo A, Antoncecchi V, Doronzo A, Monitillo F, Citarelli G, Paradies V, Favale S. The renal arterial resistance index: a marker of renal function with an independent and incremental role in predicting heart failure progression. *Eur J Heart Fail* 2014; **16**: 210-216 [PMID: 24464953 DOI: 10.1002/ejhf.34]

90 **Ennezat PV**, Maréchaux S, Six-Carpentier M, Pinçon C, Sediri I, Delsart P, Gras M, Mounier-Véhier C, Gautier C, Montaigne D, Jude B, Asseman P, Le Jemtel TH. Renal resistance index and its prognostic significance in patients with heart failure with preserved ejection fraction. *Nephrol Dial Transplant* 2011; **26**: 3908-3913 [PMID: 21421591 DOI: 10.1093/ndt/gfr116]

91 **Monitillo F,** Iacoviello M. Citarelli G, Leone M. Independent and incremental role of renal resistance index in predicting mortality among heart failure outpatients. *Eur J of Heart Fail* 2014; **16**: 126

92 **Citarelli G**, Iacoviello M, Monitillo F, Leone M. A high renal arterial resistance index is associated to one year worsening of renal function in heart failure outpatients. *Eur J of Heart Fail* 2014; **16**: 126

P- Reviewer: Artunc F, Schoenhagen P **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Clinical Cases

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DOI: 10.12998/wjcc.v3.i1.20

World J Clin Cases 2015 January 16; 3(1): 20-33
ISSN 2307-8960 (online)

REVIEW

Anthrax: A disease of biowarfare and public health importance

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Author contributions: Goel AK solely contributed in this paper.
Supported by Defence Research and Development Establishment, Defence Research and Development Organization, Ministry of Defence, Gwalior.

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Received: July 28, 2014
Peer-review started: July 30, 2014
First decision: August 28, 2014
Revised: October 23, 2014
Accepted: October 31, 2014
Article in press: December 23, 2014
Published online: January 16, 2015

Abstract

Bioterrorism has received a lot of attention in the first decade of this century. Biological agents are considered attractive weapons for bioterrorism as these are easy to obtain, comparatively inexpensive to produce and exhibit widespread fear and panic than the actual potential of physical damage. *Bacillus anthracis* (*B. anthracis*), the etiologic agent of anthrax is a Gram positive, spore forming, non-motile bacterium. This is supposed to be one of the most potent BW agents because its spores are extremely resistant to natural conditions and can survive for several decades in the environment. *B. anthracis* spores enter the body through skin lesion (cutaneous anthrax), lungs (pulmonary anthrax), or gastrointestinal route (gastrointestinal anthrax) and germinate, giving rise to the vegetative form. Anthrax is a concern of public health also in many countries where agriculture is the main source of income including India. Anthrax has been associated with human history for a very long time and regained its popularity after Sept 2001 incidence in United States. The present review article describes the history, biology, life cycle, pathogenicity, virulence, epidemiology and potential of *B. anthracis* as biological weapon.

Key words: Anthrax; *Bacillus anthracis*; Biological warfare; Epidemiology; Infection; Public health

Core tip: Anthrax is primarily a zoonotic disease which is caused by *Bacillus anthracis* (*B. anthracis*) and for human it has both, public health as well as biodefence importance. Anthrax has been known since ancient times; however it acquired attention as biological warfare disease after 2001 incidence in United States. *B. anthracis* is supposed to be the most potent BW agent because of its hardy spores, various modes of infection and high mortality rate. Understanding about the life cycle, virulence, pathogenicity and detection and diagnosis of *B. anthracis* is important to curb the disease.

Goel AK. Anthrax: A disease of biowarfare and public health importance. *World J Clin Cases* 2015; 3(1): 20-33 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i1/20.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i1.20

INTRODUCTION

Bacillus anthracis (*B. anthracis*), the causative organism

of anthrax is a Gram-positive spore forming bacillus commonly found in soil of endemic areas. Anthrax is a zoonotic disease which is mainly associated with herbivores and domestic animals. The disease occurs regularly in countries where widespread vaccination of animals is not practiced. Human anthrax is less common and usually spreads to human populations through close occupational proximity to infected livestock by handling infected domestic animals including cattle and goats or their products like skin, meat, hides and bones. This bacterium can infect humans by cutaneous, gastrointestinal, or respiratory routes[1]. *B. anthracis* exists in two forms, vegetative cells (inside the host) and spores for persistence in the soil or environment[2]. In the soil, *B. anthracis* is generally found in endospore form where it can remain viable for decades in this form. As *B. anthracis* forms spores that can be aerosolized and sprayed to spread disease, the potential use of this bacterium as a bioterrorism agent has long been suspected. However, the events in 2001 have confirmed that bioterrorism is no longer a threat but a reality[3]. Owing to its highly pathogenic nature and spore forming capability, *B. anthracis* is considered as one of the most important biological warfare agents[4,5].

There are two major virulence factors in *B. anthracis*, poly-γ-D-glutamic acid capsule and a tripartite toxin[6]. Pathogenic *B. anthracis* bacteria produce capsule which mimics the immune system of host by masking the bacteria from macrophages[7]. The tripartite toxin of anthrax consists of three independently secreted proteins, *i.e.,* protective antigen (PA), lethal factor (LF) and edema factor (EF)[8,9]. Anthrax toxin is a binary A-B toxin, where PA acts as the binding (B) domain and LF and EF act as active (A) domains individually to form the binary toxins lethal toxin (LTx) and edema toxin (ETx), respectively[10]. After ingestion or coming in contact with skin lesions, bacteria multiply and within a few days or weeks cause the death of human or animal host.

Anthrax is not a major issue of health in developed countries as only a few incidences are reported from such countries. However, for developing countries whose economy is mainly agriculture dependent, cutaneous anthrax is still a major concern of health. India ranks first in having the world's largest livestock population. Therefore, animal anthrax is common in several regions in India. However, only a few intermittent cases of human anthrax are reported from the Southern states[11]. Human cutaneous anthrax is a concern of public health in some states like Orissa and Andhra Pradesh[12].

HISTORY OF ANTHRAX

Anthrax, caused by *B. anthracis* is a highly contagious and fatal. Anthrax has a long association with human history and was known in Europe (1190-1491 BC) and China (3000 BC). Anthrax was described in the early literature of the Greeks, Romans and Hindus. The name anthrax was derived from the Greek word "anthrakis" which means coal because coal black skin lesions are formed in cutaneous form of anthrax. The description of fifth plague of Egypt, an epidemic of ancient Egypt in the book of Genesis (1491 BC), which exterminated the Egyptian livestock including cattle, sheep, goats, camels, horses and donkeys without affecting the Israelites livestock, may be due to anthrax. The disease described by Virgil (29 BC) in his third Georgics (selection of poems on agriculture and animal husbandry) seems to be anthrax in domestic and wild animals as it was an economically important agricultural disease in Europe during the 16th to the 18th centuries[13].

In 19th century, research on anthrax led to a lot of medical developments. In 1850, Pierre Rayer first described filiform bodies (small rods, about half the length of a red blood corpuscle) in the blood of sheep that had died due to anthrax. Casimir-Joseph Davaine in 1863 suggested that the "corpuscles" were the etiology of anthrax that could be transmitted to sheep, horses, cattle, guinea pigs, and mice by subcutaneous inoculation of infected blood[14]. Tiegel and Klebs in 1864 demonstrated that anthrax-infected blood, if filtered through a clay candle (bacterial filter), lost its infectivity, while the deposit on filter remained infective[15]. These observations in absence of culture of the organism strongly supported the concept that the causative agent of anthrax was a living organism that multiplied in the body, invaded the blood stream, and produced death by septicaemia. Robert Koch derived his three postulates for germ theory of disease considering anthrax as prototype. In 1876, he conclusively proved that *B. anthracis* was the etiological agent of anthrax by applying his postulates for the first time during his research in Wollstein, Germany[16]. Thus, anthrax was the first disease whose causative agent was established as microbial agent. After isolating the anthrax bacteria from skin lesions of sheep, he obtained the pure cultures by growing the bacilli on the aqueous humor of ox's eye, and injected the bacteria into healthy sheep. He performed another experiment by growing pure cultures of rods from the aqueous humor of an ox's eye. By studying, drawing and photographing these cultures, he recorded the multiplication of the bacilli and found that under unfavourable environmental conditions, especially under conditions of oxygen deprivation, they produced round spores within themselves. The spores return to bacilli when growth conditions are favourable, proving the spore formation as self-protective mechanism of *B. anthracis*. Thus, by now it was clear how certain pastures or agriculture areas became dangerous. When any animal dies from anthrax infection, the infected blood and body fluids comes out in soil from the natural orifices of animal. The bacteria, which are in the vegetative form in the blood, convert into spores on exposure to air. These spores are extremely resistant to natural conditions and could remain dormant in the soil for decades. These spores remain available to cause new infections among susceptible animals that graze in the field.

Pasteur *et al*[17] proved the buried cadavers of anthrax

infected animals as important origin of new infections. They further revealed that spores from buried soil could be transported to the upper surface by the activities of earthworms[18]. He also confirmed Koch's discovery of the anthrax germ. He found that chickens were immune to anthrax, and postulated that it was because of high body temperature (43 ℃-44 ℃) of chickens. On lowering the body temperature to 37 ℃, chickens became susceptible to anthrax. For vaccination, Pasteur heated the anthrax germs and inoculated 25 sheep. He used the heated anthrax bacteria to inoculate sheep and found that all sheep survived (only one pregnant sheep died due to some other complications), whereas all un-inoculated sheep died after one or two days of challenge with virulent *B. anthracis*. Pasteur proved that the weakened anthrax lost its virulence but still could confer immunity and this technique was termed as "vaccination". Thus, first live bacterial vaccine was developed for anthrax by Pasteur *et al*[17]. During 1876-1877, a devastating anthrax outbreak affected several sheep and cattle in France's livestock. By that time, rod-shaped *B. anthracis* was established as the causative agent of anthrax by Robert Koch. However, still many people believed that instead of bacterium itself, some toxic substance produced by *B. anthracis* was causing the disease. But, Pasteur finally proved that anthrax was caused by living *B. anthracis* and not by some toxic substance.

Anthrax was also known as woolsorters' disease. Prior to 1837, no specific disease had been associated with wool. However, after that a large number of cases occurred in and around Bradford, England and the name Bradford disease became synonymous with woolsorters' disease. In 1879, Bell proved that woolsorters' disease (now inhalational anthrax) was due to anthrax[19]. This led to institution of Bradford rules which in 1897 became law. Consequently, incidences of inhalation anthrax among sorters decreased significantly. In 1913, Eurich found that blood contamination was the important factor in woolsorters' disease[20]. Blood seemed to serve as a glue to bind anthrax spores to the raw product. Washing of wool removed soil, dried serum and blood but anthrax spores remained adherent. Elimination of inhalation anthrax as an industrial hazard followed passage of the Anthrax Prevention Act in 1919. This law mandated the construction of a decontamination station in Liverpool whereby all dangerous wool and hair products entering England were disinfected with formaldehyde[21].

During 1979-1980, the world's largest ever recorded outbreak of anthrax occurred in Zimbabwe during the civil war. In a two-year period, over 9400 cutaneous anthrax cases, including 182 fatalities were reported. Before the war, anthrax was endemic in Zimbabwe and only a few cases of anthrax were reported. Number of human anthrax cases increased significantly during this period because lack of food due to civil war in country forced people to handle and eat anthrax infected animals. Anthrax being a zoonotic disease, it first appeared in cattle and then spread in human population in all the affected areas of Zimbabwe.

Anthrax has been supposed to be developed for use as a bioweapon during world war-1 and world war-Ⅱ. Recently, in 2001, envelopes containing the *B. anthracis* organism were sent through the mail to different dignitaries in United States affecting 22 people. This was considered as an act of bioterrorism[3].

BIOLOGY OF *B. ANTHRACIS*

B. anthracis is a Gram positive, rod-shaped, aerobic, facultative anaerobic, sporulating, capsulated bacterium. It measures 1-1.2 μm in width and 3-5 μm in length. Under microscope, it appears as chain like structure. Though an aerobic organism, yet *B. anthracis* can survive in anaerobic environment because of its property of sporulation. In fact, it can survive for several years in soil, air and water in the form of spores. Unaffected to harsh environment, spores are resistant to high temperature, pressure, pH, chemicals, UV and deficiency of nutrients[22-24]. The capsule is composed of γ-linked poly-D-glutamic acid which gives mucoid appearance to the colony. Formation of capsule decides the virulence of bacteria. The capsule itself is non-toxic and doesn't provoke immune system of the host. However, it contributes significantly in establishing the infection, once the organism escapes phagocyte action, later phase of disease is controlled by anthrax toxin[25].

Pathogenic strains of *B. anthracis* harbour two virulent plasmids[26]. Plasmid *pXO1* carries toxins encoding genes and plasmid *pXO2* carries capsule encoding genes. Size of *pXO1* is 184.5 kb that harbours three structural genes, *pag* (coding for PA), *lef* (coding for lethal factor) *and cya,* coding edema factor[1]. Plasmid *pXO1* also encodes *atxA* gene which regulates the expression of gene encoded on *pXO1* and *pXO2*. Another plasmid pXO2 is 95.3 kb in size and carries the genes for capsule production, degradation and regulation. Genes *capB, capC and capA* code for capsule synthesis, and gene *dep* codes for its degradation[1]. A gerX operon is also present on plasmid *pXO1* and its deletion affects the germination of spores in macrophages. The operon codes for three proteins GerXA, GerXB and GerXC. These proteins are supposed to form a receptor, which specifically detects germinant within the host[27].

POTENCY OF *BACILLUS ANTHRACIS* AS BIOWARFARE AGENT

Anthrax was linked to soil contamination long before the identification of *B. anthracis* as its causative agent[14,16]. Spores can resist prolonged exposure to stress as desiccation, solvents and extreme temperature, pressure, pH, ultraviolet and ionizing radiation[28,29]. Spores of *Bacillus* genus are known to have a half life of about 100 years[30]. Spores are dormant form of the bacterium which returns into vegetative form on receiving the signals for germination. The surprisingly resistant spores have earned the status of potential bio-

terror weapon for anthrax. The possibility to create aerosol from spores makes *B. anthracis* a lethal biological weapon. All the attributes of spores: high resistance to temperature, pressure, pH, ionizing radiations and half life of 100 years make them a suitable bio-terror agent. After production and purification, anthrax spores can be stored in a dry form which remains viable for decades. Spores may survive in the water, soil and on surface for several years. Inhalation of spores causes inhalational anthrax which is the most dangerous form of disease. Inhalational anthrax is dangerous for obvious reasons as initial symptoms resemble to that of flu, making its early diagnosis difficult; by the time disease is correctly recognized it's too late.

The use of microorganisms as a means of waging war or as bioterror agents is becoming a real possibility now around the world. Any biological agent from a large gamut of human infection causing pathogens could be considered a potential biological weapon. However, only a small number of these agents fulfil the desirable criteria like ease of cultivation and dispersal or dissemination for recognition as possible biological weapons. Anthrax spores pose the biggest bioterrorism threat because it is easier to produce and preserve them. Anthrax spores have already been used in United States and in future also it is most likely preferable agent to be used for biothreat because of high case fatality rates, rapid transmission by aerosol and its stability in the environment. The release of any bio-warfare agent by a militant or miscreant would likely be silent and untraceable or nearly so. Therefore, of the recognized possible biological weapons, anthrax bacilli are rated the most lethal.

Naturally, anthrax is a zoonotic disease, which primarily occurs in animals and then spreads to human. Several animal species like cattle, goat and sheep are susceptible to this disease. A major public health preparedness challenge is increasing the importance of recognition of individual, potential sentinel cases of biothreat agent disease. According to CDC norms, *B. anthracis* is placed in high priority- Category A due to its ease of dissemination, high mortality rates, epidemic potential and special preparedness it requires. In 2001, mails deliberately contaminated with *B. anthracis* spores were used to terrorize people and subsequently research for the development of anthrax vaccine speeded up. Moreover, each category A biothreat agent has its unique clinical and diagnostic features and no single system can meet the challenges of all the agents. Besides, anthrax is still a concern of human as well as veterinary public heath in several states of country like India. Bioterrorism itself is an emerging problem for public health. Hence, it is not possible to look into bioterrorism and public health separately. Rather, it is the need of time to give more emphasis on such diseases which have both the potential.

DOSE-RESPONSE RELATIONSHIP

The information on dose-response relationship is prerequisite for assessment of risk of any biothreat agent. The LD_{50} of human inhalational anthrax is not known, but has been estimated from the animal studies and disease outbreaks. After conducting experiments on 1236 cynomolgus monkeys (*Macaca fascicularis*), Glassman estimated the median lethal dose to be 4130 spores with 95%CI range of 1980-8630[31]. Further, he suggested that LD_{25} was associated with a 10-fold decrease in dose *i.e.,* 413 spores. In 1957 in Manchester, 16 susceptible workers were exposed to *B. anthracis* in a goat hair processing mill and 4 persons were infected. Based on the 8-h inhaled dose, LD_{50} of *B. anthracis* was estimated to be 6200-22000 spores[32]. The infectious dose for inhalational anthrax in 50% of susceptible human population (ID_{50}) was estimated to be 8000-50000 spores by biodefense experts from the United States Army Institute of Infectious Diseases (USAMRIID, Fort Detrick, MD)[33]. In 1998, a panel of seven subject matter experts on anthrax calculated the ID_{10}, ID_{50} and ID_{90} as 1000-2000 spores, 8000 to 10000 spores and 50000 to 100000 spores, respectively[34]. Another group extrapolated the lethal dose (LD_{50}) values of 4100 spores[31] and 8000 spores[33] and suggested an LD_{10} of 50 or 98; an LD_5 of 14 or 28, an LD_2 of four or seven, and an LD_1 of one or three spores[35]. Although they did not establish the validity of extrapolation, yet they cautioned about the low number of spores.

Theoretically, even a single spore of *B. anthracis* can cause anthrax. However, in the low dose range, there is high uncertainty between the dose-response relationships of aerosolized *B. anthracis* for human. Recently, on the basis of experimental data on primates and epidemiological data of human anthrax, a new quantitative model known as Exposure-Infection-Symptomatic illness-Death (EISD) has been suggested for the dose-response as well as time course of pulmonary anthrax in human[36]. According to this model, the ID_{50}, ID_{10} and ID_1 of *B. anthracis* spores were 11000 (95%CI: 7200-17000), 1700 (1100-2600) and 160 (100-250), respectively. The ID_{50} (7200-17000) and ID_{10} (1100-2600) confidence ranges produced by this model were remarkably consistent with the corresponding ranges produced by an expert panel surveyed in 1998, *i.e.*, 8000-10000 and 1000-2000, respectively[34]. The confidence range of ID_1 from 100-250 spores as suggested by this model indicates that a threshold of 600 *B. anthracis* spore to human infection is underestimated and infection by even a single spore is overestimated in the literature. This model also suggested the median incubation time from exposure to onset of symptoms. For exposure with ID_{50} of *B. anthracis* spores, it was 9.9 d with 95%CI of 7.7 to 13.1 d, where as for ID_{10} and ID_1, it was 11.8 (95%CI: 9.5-15) d and 12.1 (95%CI: 9.9-15.3) d, respectively.

DIFFERENT STRAINS OF *BACILLUS ANTHRACIS*

Three well known strains of *B. anthracis* are Ames, Sterne and Vollum. Ames is a well studied, highly virulent strain

containing both plasmids, *i.e., pXO1* and *pXO2*. Originally it was isolated from a dead cow in Texas in 1981. Its geographic region is United States and United Kingdom. Another isolate of Ames strain is Florida which was first isolated from a victim of anthrax attack in 2001[37,38]. *B. anthracis* Sterne is a toxigenic but avirulent strain as it carries the anthrax toxin plasmid pXO1 but lacks the capsule forming plasmid pXO2[39]. This strain is generally used for vaccine development for animals. Its geographic region is in Canada[37,38]. In contrast to Sterne, Pasteur strain carries pXO2 plasmid but not pXO1. Vollum is low virulent strain used in research studies and is found in the United Kingdom, Spain and Zimbabwe[37]. Along with Vollum and Sterne, strain V770 is also used for toxin production and various research related studies.

B. anthracis belongs to *Bacillus cereus* sensu lato group, shared by six other species including *B. cereus*, *Bacillus mycoides*, *Bacillus pseudomycoides*, *Bacillus thuringiensis*, *Bacillus weihenstephanensis*, and *Bacillus cytotoxicus*[40]. *B. cereus* primarily causes foodborne illness. Besides, *B. cereus* is considered as an opportunistic pathogen that can cause wound infections, endocarditis and urinary tract infections in humans. Recent studies indicate that a *Bacillus* species other than *B. anthracis* can cause anthrax-like disease and a few *B. cereus* strains have been found to be associated with "anthrax like" infections in human[41,42]. In India, a *B. cereus* strain TF5 was isolated from the tissue fluid of cutaneous anthrax-like skin lesions of a human patient from an anthrax endemic area in India[43,44]. The strain harboured a PA gene, however, the pXO1 or pXO2-like plasmids were not present. Exoproteome analysis exhibiting qualitative and quantitative differences between the two strains indicated an altered regulatory mechanism and putative role of S-layer protein and sphingomyelinase in the pathogenesis of strain TF5[43].

EPIDEMIOLOGY OF ANTHRAX

B. anthracis bacteria are very fragile and susceptible to disinfectant or exposure to moderate temperature. However, *B. anthracis* vegetative cells convert into spores on exposure to air. These spores are highly resistant to heat and to most of the disinfectants. Therefore, post-mortem of anthrax infected animals is never recommended to avoid the exposure of bacteria to oxygen. A peculiar feature of anthrax infection in animals is that blood does not clot and drains from the natural orifices like nose, mouth and bowl. This results in contamination of soil and water with bacteria which ultimately transform into spores[45]. As much as 10^9 *B. anthracis* bacteria may be present in the oozing blood[46]. Even the processed parts and products like leather, hides, wool, *etc.*, of an anthrax infected animal can carry spores for year. The spores can remain viable for a prolonged period in the soil, especially when deposited 15 cm below the upper soil levels.

Environmental and climatic factors have a great influence on the ecology of anthrax[47]. Climatic factors like rainfall and temperature play a pivotal role in incidences of anthrax cases[48]. However, it is not easy to understand the anthrax occurrence and its epidemiology due to large variations in timing of different outbreaks and associated deaths of a particular species even within a single ecosystem[49]. It has been hypothesized that some soil factors like alkaline pH, high organic content, moisture, and ambient temperature (in excess of 15.5 ℃) favor the germination of *B. anthracis* spores into vegetative bacteria, which ultimately results into amplification of number of spores[22]. It has been observed that high pH and high contents of calcium in soil contribute to maintain the spores viable for a longer time. These soil spores cause new infections when come into contact of a suitable new host[22,50,51]. Therefore, alkaline pH of soil, high moisture and organic contents, precipitation and ambient temperature in excess of 15 ℃ are deciding factors for triggering a large anthrax outbreak and can be considered to predict exposure and infection risk of anthrax in a particular area[48]. During grazing, herbivores animals are most likely to be exposed to *B. anthracis* spores by inhalation or ingestion during grazing. It has been observed that *B. anthracis* bacteria need specific nutrients (animal blood, viscera) and physiological conditions and therefore it is very difficult to survive outside a viable host and convert into spores. Moreover, the vegetative cells of *B. anthracis* are poor competitor and are easily killed by other bacterial species outside the host in environment. Moreover, virulence of *B. anthracis* is reduced when grown outside the host and bacteria with reduced virulence will not lead to an outbreak[22].

According to an estimate, every year about 2000 to 20000 human anthrax cases occur globally. Apart from India and Pakistan, anthrax has also been reported from Bangladesh, Zimbabwe, United States, South Africa, Iran, Iraq and Turkey. In India, southern states are more prone to anthrax. Reports of anthrax appear almost every year from Andhra Pradesh, Tamil Nadu and Karnataka but exact figures are not available. In 1980s, there were only 2000 cases reported worldwide most of them were of cutaneous anthrax. Most of the anthrax cases recorded were from the persons involved in industrial occupations related to processing of animal parts and products like meat packing, bone meal processing, tanning of leather and sorting of hair wool[52]. Several outbreaks have been recorded in recent history. Anthrax outbreaks in animals are more prominent and common than humans. From 1991 to 1996, a total of 1612 anthrax outbreaks occurred in India. In Nepal, a total of 222 animals were affected during 19 different outbreaks in 1996[53]. In 1996, about 1570 cases of ruminant anthrax were reported in China. The death of 204 livestock in Australia was reported in 1997[54]. From 1984 to 1989, thousands of wild animals were killed in an anthrax epidemic in Namibia and South Africa[53]. In Iran, about one million sheep were killed during an anthrax outbreak in 1945. In Manchester, United States, a large anthrax epidemic occurred in 1957 in a goat hair processing plant resulting in four fatalities

and nine cases[55]. In Russia during 1979, an unusual, accidental anthrax outbreak in a Soviet military laboratory of Sverdlovsk killed 68 persons out of 79 infected[56]. In Zimbabwe, 10000 cases occurred between 1979 and 1980 leading to 182 deaths. In Tibet, 507 anthrax cases resulted in 162 deaths in 1989 and in China, 898 and 1210 anthrax cases were recorded in 1996 and 1997, respectively. Between 1991 and 1995, a relatively large number of anthrax incidences was observed in Spain[49,57], Central America[57] and Africa[53]. In most of the cases, exposure was through cutaneous route which accounts for a total of 95% cases. The inhalational route accounts for 5% anthrax cases reported, while gastrointestinal anthrax is quite rare[58,59]. In 2007, a few animal and human cases of anthrax were reported from Orissa and West Bengal, India[60]. The most recent anthrax cases were found in 2010 in Bangladesh. More than 600 peoples were killed in the outbreak due to consumption of infected cattle meat[61].

As India stands first in having the largest population of livestock in the world, therefore anthrax is endemic in several regions. Based on the epidemiological study from 1991 to 2010 by National Animal Disease Referral Expert System (NADRES) in India, anthrax was found one of the ten major diseases causing deaths in livestock[62]. During 1991-2010, anthrax was reported in eighteen states of India *viz.*, Andhra Pradesh, Assam, Bihar, Chhattisgarh, Gujrat, Himachal Pradesh, Jammu and Kashmir, Jharkhand, Karnataka, Kerala, Madhya Pradesh, Maharashtra, Manipur, Meghalaya, Odisha, Rajasthan, Tamil Nadu, and West Bengal. Although several regions are endemic for anthrax, yet seasonal fluctuation in the number of anthrax outbreaks has been observed. Most of the anthrax outbreaks are reported in post-monsoon season, *i.e.,* from July to September and November to January in different parts of India. Anthrax epidemics are generally reported between July to September and also in November and January, coinciding with the post monsoon months across the country. Several Southern states such as Andhra Pradesh, Tamil Nadu, Kerala, Karnataka and Orissa are common endemic regions with sporadic human anthrax cases reported time to time. From the Union Territory of Pondicherry, 28 cases of anthrax were detected in 1999 and 2000[45]. Both, animal as well as human anthrax cases are reported usually from certain anthrax endemic districts like Chittoor, Cuddapah, Guntur, Prakasam and Nellore of Andhra Pradesh[63]. In 2006, some cases were noticed near Narsinghpur, Madhya Pradesh also. In 2007, 20 people were affected in two cutaneous anthrax outbreaks in Murshidabad district, West Bengal. These anthrax outbreaks were caused due to slaughtering of sick cattle and subsequently handling of meat without taking proper preventive measures[64]. An increase in number of animal and human anthrax cases has been observed in this area in recent past[65]. During a tenure of 10 years, anthrax outbreak were reported at least 61 times from Orissa affecting 750 people[65]. The anthrax outbreak is a common phenomenon in this area because tribal population mainly depends on forest for livelihood. Most of the human anthrax cases occur in agricultural workers due to handling of meat or hides of diseased animal. An anthrax outbreak was reported in Orissa, India in 2013 where several people died due to consumption of infected goat meat[66]. Recently, nine cutaneous anthrax cases were reported from the tribal population of Midnapur, West Bengal in India[67].

VIRULENCE OF *B. ANTHRACIS*

Anthrax, being a disease of mainly herbivorous is generally prevalent in those areas where animals like cattle, horse, sheep, goat, *etc.*, graze. Several animal species like pigs, dogs, cats, rats and chicken are fairly resistant to anthrax. Many scavenging birds like vultures which feed on dead animals have a natural resistance to anthrax. However, such birds may disseminate the anthrax spores from infected animals through claws, beaks or feathers.

The spores of *B. anthracis* that can remain in the environment for a prolonged time become the infectious form of anthrax. For causing anthrax, spores first germinate, *i.e.,* lose their dormancy and resistance properties, regain metabolism and start vegetative growth[68,69]. After getting favourable environmental and nutritional growth condition, spores convert into vegetative bacteria and result in further multiplication. Human skin generally does not permit spores to invade; however, spores find access through small cuts or abrasion in skin to cause cutaneous anthrax. After entry into host, *B. anthracis* remains in the capillaries of invaded organs and produce lethal and edema toxins which cause the local and fatal effects of infection.

TOXINS OF *B. ANTHRACIS*

In soil, *B. anthracis* is found in its highly resistant endospore form and therefore, can remain live for a very long period in this state. Spores of *B. anthracis* can find entry in the body through lungs, skin lesion or gastrointestinal route and germinate to yield vegetative form. In case of cutaneous infections, *B. anthracis* comes into contact with a skin lesion, or cut. In inhalational cases, herbivorous and sometimes humans are infected after inhalation of spores. After inhalation, these spores reach alveoli of lungs through air passages. Generally, herbivores get gastrointestinal anthrax infection during grazing or browsing an anthrax spore infested agricultural field having spiky or rough vegetation. Gastrointestinal tract of animals probably gets wounds due to eating of spiky vegetation which facilitates the entry of spores into tissues and resulting in gastrointestinal anthrax.

The virulence of *B. anthracis* is attributed to a tripartite anthrax toxin and a poly-D-glutamic acid capsule. After entry into the host through ingestion or skin wounds, *B. anthracis* multiply inside the tissues of animal or human host, spread in the lymphatic system and undergo rapid multiplication. This results in production of anthrax

toxin inside the body and causes death of host within a few days or weeks.

Capsule formed by the virulent *B. anthracis* vegetative cells helps the bacterium to evade the host immune system by impeding the ability of macrophages to engulf and destroy the bacteria[7]. Three non-toxic proteins namely PA, LF and EF of anthrax tripartite toxin co-assemble to produce a series of free or cell-bound toxic complexes[8,9,70]. Two of the toxins, LF and EF, are enzymes that modify substrates within the cytosolic compartments of host cells[71]. PA binds on the receptors of host cells and makes a pore for transportation of LF and EF to the cytosol[72]. Thus, anthrax toxin is an A-B type toxin, where PA acts as B subunit and it combines with the LF and EF, which act as A subunits to form the edema toxin and lethal toxin, respectively[10,17].

Anthrax PA is an 83 kDa precursor polypeptide consisting of 735 amino acids which binds to anthrax toxin receptors. There are two distinct toxin cell receptors, ANTXR1 (TEM8, Tumor endothelial marker 8) and ANTXR2 (CMG2, Capillary morphogenesis protein 2) which are widely expressed in cells[73,74]. Cleavage of PA by cellular proteases of the furin family, or by serum proteases generates a nicked 20 kDa fragment (PA20) at N-terminal and a 63 kDa fragment (PA63) at C-terminal[75,76]. The 63 kDa fragment self-associates to form a prepore which is a heptameric ring and can bind up to three copies of EF and/or LF molecules[6]. A smaller population of PA octamers (20%-30% of oligomers) is also formed, which binds up to four molecules of EF and/or LF and this structure is more stable than heptamer[77]. These hetero-oligomeric complexes are endocytosed and brought to an acidic environment, where the PA prepore makes a translocase channel after inserting into the membrane[78]. This channel is used for translocation of LF and EF into the cytosol, where by enzymatic activities they disrupt the host cell[79]. Both, LF and EF toxins reach the late endosomal compartment, where EF remains associated with the late endosomal membranes that surrounds the nucleus forming a perinuclear necklace and LF is ejected into the cytoplasm[80,81].

LF is a zinc dependent metalloprotease which inactivates the members of mitogen-activated protein kinase kinase family (MAPKK)[82-84]. Inactivation of three major MEKs *i.e.,* extracellular signal regulated kinases, c-Jun N-terminal kinases and p38 MAPKs results in impairment of various cellular processes like cell division, cell differentiation, cellular response to different types of stress and ultimately apoptosis[17].

Another protein EF is has adenylate cyclase activity. It is produced in an inactive form by the bacterium and needs calcium modulated protein (calmodulin, CaM) for its activity[71]. CaM, which acts as Ca^{2++} sensor has two Ca^{2++} binding sites on each of the C- and N-terminal domain. CaM binds with helical domain of EF using its N-terminal domain. EF is a highly active and its adenylate cyclise activity is almost equal to that of most active known cyclase. Activity of EF is also regulated by intracellular level of Ca^{++} in a biphasic manner. Resting or little high levels of Ca^{++} activate the EF *via* CaM, whereas high levels of Ca^{2++} reduce its activity due to competition between Ca^{++} and Mg^{++} ion in the EF active site[85]. Because EF is associated with the perinuclear later endosomal membrane, therefore, a cAMP gradient decreasing from the nucleus to plasma membrane is generated[80,81,86]. Contrary, endogenous host adenylate cyclises generate a cAMP gradient in opposite orientation (decreasing from plasma membrane to nucleus) because these are localized on plasma membrane[86,87]. In anthrax infection, these two toxins are responsible for immune system failure and ultimate death of host[9].

PATHOGENESIS OF *B. ANTHRACIS*

Human anthrax is mainly of two types, agriculture related anthrax that occurs in a seasonal pattern, and occupation related that can occur at any time. On the basis of route of infection, there are three clinical forms of anthrax *viz.*, cutaneous (skin), gastrointestinal (ingestion) and pulmonary (through inhalation of spores)[88]. Recently, another type of anthrax has been identified among the heroin injecting drug users Europe[89,90]. The term injectional anthrax was then coined to describe this new mode of infection. A few anthrax cases have been reported due to insect bites also, which could probably be due to feeding of insect on an anthrax infected animal[91,92]. Once inside the mammalian host, the high nutrient content of the body triggers germination of spores, although there may be host-specific germination factors as well[93]. Sporulation does not appear to occur inside the host[94]; perhaps because once the available nutrients are depleted in the dead or dying host, the oxygen tension is too low for Sporulation[95] or possibly due to the repression of sporulation by the virulence gene regulator AtxA[96]. Spores infect macrophages at the site of entry, germinate into vegetative cells and proliferate into the tissues and start producing anthrax toxin within 3 h of spore germination[93].

Cutaneous anthrax infection starts with a small itching papule resembling an insect bite at the site of infection on skin. In a day or 2, this papule enlarges and transforms into a painless ulcer with a depressed necrotic centre and a raised and round edge. Generally, such lesions are formed with 2-5 d at the site of spore entry on skin. Finally, after 7-10 d, a black eschar, surrounded by edema is formed and this leaves permanent scar after anthrax cure[97]. Regional lymph nodes draining the infected area may be swollen and enlarged. Cutaneous anthrax infection mostly remains painless and limited to dermis. However, in certain cases it can become systemic when bacteria enter into blood stream causing bacterimia. Hemorrhagic lesions can be developed on any part of body and can be fatal in bacteremic anthrax.

Gastrointestinal (GI) anthrax occurs by eating the food contaminated with anthrax spores (most often contaminated meat). After ingestion, spores germinate

and can cause lesions anywhere in the body. Based on the lesions, GI anthrax is of two types, abdominal and oropharyngeal. In abdominal GI anthrax, lesions are formed mainly in the ileum and cecum. The incubation period is generally 3-7 d. The symptoms of abdominal GI anthrax include nausea, bloody vomiting, diarrhea, abdominal pain, headache, loss of appetite and massive ascites. Another variant of intestinal anthrax is oropharyngeal anthrax where lesions are formed mainly in the oral cavity and resemble the lesions of cutaneous anthrax. Symptoms include throat pain, problem in swallowing and swelling in neck due to edema and cervical lymphadenopathy[97].

Pulmonary or inhalational anthrax occurs by inhalation of spores into lungs. This is the most severe form of anthrax. Alveolar macrophages ingest the spores and transport to lymph nodes in mediastinum. Initially, symptoms of inhalation anthrax are like cold or flu-like with mild chest discomfort, shortness of breath, nausea and finally severe respiratory collapse. Pulmonary anthrax doesn't cause pneumonia, but causes hemorrhagic mediastinitis and pulmonary edema. Historical, mortality was 92%, but, it can be reduced significantly if treated early as only 45% mortality was observed during the 2001 anthrax attack in United States.

Symptoms of anthrax caused by injection remain the same as in cutaneous anthrax, but there may be infection deep under the skin or in the muscle where the drug is injected. Sometimes there is redness at the area of injection. Injectional anthrax is difficult to diagnose because several other common bacteria can cause skin and injection site infections. Therefore, it is hard to treat injectional anthrax as it spreads throughout the body very fast.

There are two basic stages in the systemic anthrax infection, a prodromal and fulminant. The prodromal stage is mainly asymptomatic and generally lasts 2-4 d[98]. In this stage, macrophages engulf the spores and release to lymph nodes near the port of entry. Behaviour of macrophages and phagocytic cells is changed due to action of anthrax toxins resulting in the apoptosis and release and germination of spores into vegetative bacteria. In the fulminant stage, bacteria multiply and are distributed to different organs through bloodstream[99,100]. In human inhalation anthrax, treatment is started after the onset of fulminant stage because prodromal stage is largely asymptomatic. The symptoms at fulminate stage are flu-like and include labored breathing, chest pain, hypotension, headache and disorientation[55,99-102]. Bacteria secrete anthrax toxins which affect functioning of different organs like spleen, lymph nodes, liver, kidney, heart and brain. It becomes very difficult to cure the disease by antibiotic therapy at this stage and action of anthrax toxins ultimately leads to septic shock and death of host in 1-2 d.

LIFE CYCLE OF *B. ANTHRACIS*

B. anthracis is found in two forms, vegetative cells and spores. Adverse environmental conditions induce the sporulation and endospores are released from the mother vegetative cells. The endospores are dormant, well organized and highly resistant to various stress conditions. Therefore, these endospores can remain viable for a prolonged time in the environment and can germinate into vegetative bacteria after getting the suitable environmental and nutritional requirements. During both the processes, *i.e.*, sporulation and germination, a lot of metabolical as well as morphological changes are observed. For spore formation, *B. anthracis* bacterium is divided asymmetrically by a septum into forespore (smaller portion) and mother cells (larger portion). Each portion gets a single copy of DNA. After the asymmetric division, forespore is engulfed by the mother cell with a double-membrane system. The mother cell DNA material is degraded and forespore DNA material is surrounded an inner membrane. Two peptidoglycan layers known as primordial germ cell wall (inner thin layer) and the cortex (outer thick layer) are synthesized between the inner and the outer membrane of forespore[103,104]. The outer membrane of forespore gets deposited by various proteins to form the coat. Thickness of spore coat varies among different species of *Bacillus*. In *B. anthracis* and *B. cereus*, the spore coat is compact whereas it can be distinguished in *B. subtilis*[105,106]. During spore maturation, spore acquires resistance for temperature and UV radiations and becomes dormant. Thus, spore coat imparts important functions to protect cortex and DNA of spore from various adverse conditions like environmental stress, chemicals and peptidoglycan lysing enzymes.

The life cycle of *B. anthracis* has been shown in Figure 1. Animals get infected by uptake of anthrax endospores present in the agriculture fields. Inside the mammalian host, endospores find the favourable conditions like aqueous environment with sufficient nutrients and therefore, start germination[107]. During anthrax pathogenesis, transformation of spore into vegetative cell is a crucial step, because it is the vegetative form of bacterium only which forms the virulent factors, *i.e.,* capsule and tripartite toxin[27]. The poly-γ-D glutamic acid capsule of *B. anthracis* makes a complex surface of the bacterium and is surrounded by peptidoglycan layer and S-layers[108]. The capsule evades the host immune system and thus is a crucial factor for the survival of the bacteria in the host. On death, the capsulated bacteria are released with blood into the environment through natural orifices. On coming into contact with oxygen, the vegetative bacteria convert into spores and thus again infest the agriculture fields for subsequent anthrax infection in grazing animals.

DIAGNOSIS OF ANTHRAX

As various outbreaks are reported time to time from different areas, there is a great need of an early diagnosis of the disease to save human and animal life. Besides, requirement of rapid and reliable detection, identification and diagnosis systems for anthrax has been emphasized

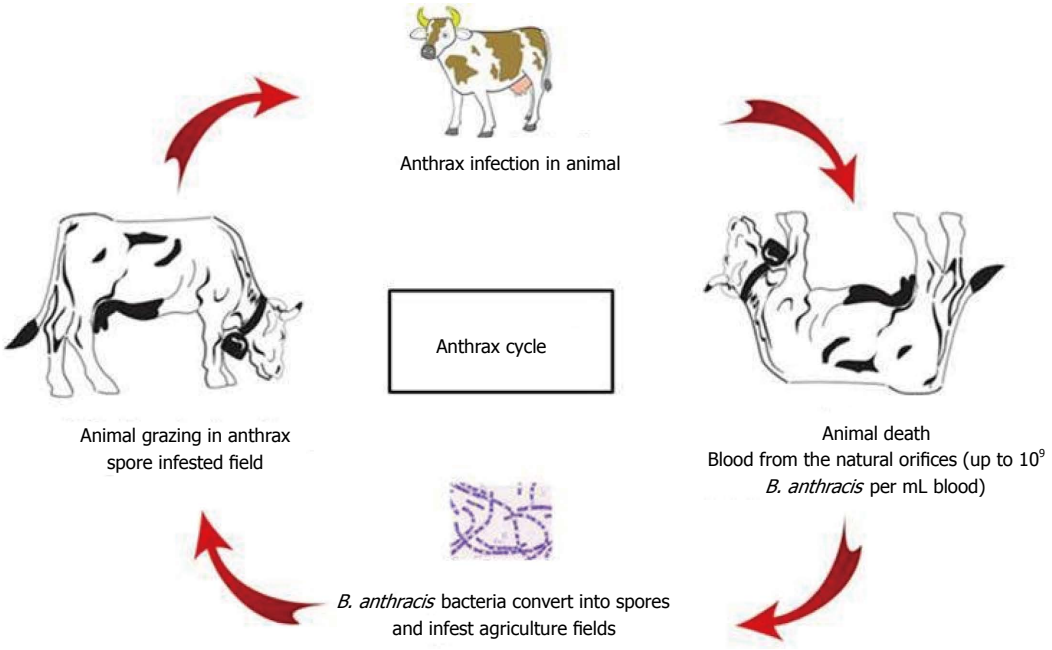

Figure 1 Life cycle of *B. anthracis*. *B. anthracis*: *Bacillus anthracis*.

by recent bioterrorism events. The early monitoring of the disease requires the detection of anthrax spores and infection both at environmental and clinical levels.

Cutaneous anthrax is diagnosed clinically employing traditional microbiological methods like gram-staining, capsule staining from the smear of the lesion or culturing of *B. anthracis*[109,110]. Several methods have been reported for isolation and identification of *B. anthracis*. However, on sheep Blood agar (5%) and other routine culture media, almost all *Bacillus* species grow well[111]. A selective media containing polymyxin-B, lysozyme, EDTA and thallous acetate was used for isolation of *B. anthracis* from contaminated and suspected samples[112]. Another media (bicarbonate agar) is used to induce capsule formation for subsequent identification of *B. anthracis*. However, there is very little utility of these selective growth media because several closely related bacteria of *B. anthracis* like *B. cereus* and *B. subtilis* also grow well on these media. Another undesirable feature is that it takes 18-24 h for *B. anthracis* to grow for characterization by various biochemical tests like catalase, oxidase, nitrate reduction, haemolysis, citrate utilization, urease[113]. Sometimes, microbiological methods like culture and Gram staining of *B. anthracis* do not hold good for patients who have already taken antibiotics before the sample[114]. Immunoflorescence has also been used for direct identification of *B. anthracis* spores[115].

Serodiagnosis is important for surveillance and confirmation of anthrax infection in animals and human. Anthrax toxin consists of PA, LF and EF. Antibodies response against these toxin components is used as a diagnostic tool for determination of past infection or vaccination.

It is well established that PA is the most important protein of anthrax tripartite toxin and it becomes the major component of anthrax vaccines including anthrax vaccine adsorbed. Therefore, antibody (IgG) levels against PA in human and animals are determined to study the host immune response to *B. anthracis* infection and anthrax vaccine[116,117]. In United States, a total of 22 individuals were identified with bioterrorism-related inhalation or cutaneous anthrax, 11 patients for each type from 4th October to 20th November 2001[118]. In 16 of 17 confirmed or suspected clinical anthrax patients, anti-PA IgG antibody could be detected after 11 d of onset of symptoms or probably 15 d after the exposure to *B. anthracis*. Antibodies against PA could be detected up to 8-16 mo in all the cases of inhalation anthrax and 7 out of 11 surviving cutaneous anthrax patients[118]. For serodiagnosis of cutaneous anthrax, an enzyme-linked immunosorbent assay was developed in India for determination of anti-PA IgGs with 99.4% specificity and 100% sensitivity[119]. A field based qualitative visual ELISA for anti-PA IgG was also developed for serodiagnosis of anthrax[120]. Results of sensitivity and specificity of visual ELISA were found compatible with the results obtained from standard ELISA measuring OD values. Likewise, a quantitative ELISA was developed for measurement of the anti-PA IgG level in human serum samples[121]. The minimum detection limits and lower limits of quantification of the assay for anti-PA IgG were 3.2 μg/mL and 4 μg/mL, respectively. The serum samples collected from the anthrax infected patients were found to have anti-PA IgG concentrations of 5.2 to 166 μg/mL[121]. CDC, United States has developed a lateral flow immunochromatographic device using colloidal gold nanoparticles for determination of anti-PA IgG in serum or whole blood[122].

However, animal studies with anthrax vaccine revealed that LF evokes higher IgG response in comparison to PA

in animals[123]. In patients of natural cutaneous anthrax, immune response to LF is higher and faster than the antibody response to EF and PA, which is lower and delayed[124]. Anti-LF IgG antibodies appeared in patients just after 4 d of onset of anthrax symptoms, whereas anti-LF and anti-PA IgG could be detected after 6 d and 13 d, respectively. In a study of human cutaneous anthrax, 11 of the 17 patients had measurable IgGs against one of the three toxin components. Anti-LF IgG was found in 65% patients, while anti-PA and anti-EF response could be found only in 18% and 24% patients. The anti-LF IgG titre in all the infected patients was higher than the titre of anti-PA or anti-EF IgG. After two weeks of infection, the mean anti-LF IgG titre in all infected patients was 69.3 μg/mL, which was twice the tire of anti-EF IgG (37.4 μg/mL) and thrice the titre of anti-PA IgG (22.6 μg/mL)[124]. It was also observed that in anthrax cases, class switching of antibody from IgM to IgG occurs faster. Anti-PA IgG could be detected just after 11 d of onset of symptoms in patients with inhalation anthrax, while no anti-PA IgG response was found till 21-34 d in patients with cutaneous anthrax[117]. Therefore, it is evident that LF evokes a faster and stronger host immune response in comparison to the other two anthrax toxins, *i.e.,* PA or EF. Therefore, detection of anti-LF IgG in human serum can be a good marker for serodiagnosis of anthrax. For detection of anti-LF antibodies, an indirect ELISA was developed for serodiagnosis of cutaneous anthrax in human[125]. The vaccinated and cases of natural anthrax infection can be differentiated by the anti-LF ELISA because PA is the principal component in anthrax vaccine.

Rapid diagnosis of anthrax at an early stage of infection *i.e.,* before the appearance of symptoms can be very useful for proper medical treatment to stop the further spread of infection and accumulation of toxins. For early diagnosis, detection of anthrax toxin in serum or plasma can be a reliable marker of infection[126]. An ultra sensitive immunoassay known as European Nanoparticle Immuno Assay (ENIA) has been developed using European nanoparticle for the detection of PA in sera, which has been found 100 times more sensitive than ELISA[85]. ENIA showed good linearity for detection of PA in the range of 10 pg/mL to 100 pg/mL, whereas range of PA detection in ELISA was 1-100 ng/mL. An engineered sandwich capture ELISA was also reported for the detection of both PA as well as LF[127]. In the sandwich ELISA for PA detection, anti-PA high affinity single chain fragment antibody or receptors for anthrax toxin (ANTXR2) were used for capturing the analyte (PA), and rabbit anti-PA polyclonal serum was used for revealing antibodies. The detection sensitivity of PA by was as low as 1 ng/mL in serum. The detection sensitivity of sandwich ELISA for LF, where PA_{63} was used for capturing of analyte was 20 ng/mL. Surface Plasmon Resonance (SPR) has also been found a very good technique for detection of PA from serum samples of human[128]. The SPR assay could detect 1 pg/mL of the purified PA and 10 pg/mL of PA in human serum[128].

Recently, a new method utilizing genetically modified phages has been developed for detection of pathogenic *B. anthracis* from clinical sources[129]. The reporter phage displays species specificity by its inability, or significantly reduced ability, to detect members of the closely related *B. cereus* group and other common bacterial pathogens.

Nucleic acid based detection methods have also been developed for detection of anthrax. These techniques make use of nucleic acid sequences unique to *B. anthracis*. The technique has gained enormous popularity for its specificity. Polymerase chain reaction (PCR) or real-time PCR amplify the specific chromosomal markers or virulence plasmids present in the *B. anthracis*. Such new rapid detection and diagnostic tests are important for clinicians for early identification of infection.

CONCLUSION

Anthrax, caused by *B. anthracis* is still an important endemic disease of public health importance in several countries of Asia, Africa and Europe. It is re-emerging in some western countries due to political unrest or changing life style (use of intravenous drugs) as evident from the recent outbreaks. In country like India, anthrax is a concern of public health as clandestinely encountering in several states like Andhra Pradesh, Kerala and Karnataka, Orissa and West Bengal. Although anthrax can be cured by prompt antibiotic therapy, yet it is fatal in several cases because of lack of proper diagnosis well in time. Among the three clinical forms of anthrax cutaneous anthrax is most frequent but can be easily cured. The other two forms, gastrointestinal and inhalational anthrax are less common but difficult to cure and have high mortality rate. Recently another form of anthrax, *i.e.,* injectional anthrax is also posing threats for early diagnosis and treatment. However, active surveillance, proper animal immunization and awareness can help to curb the disease. Rapid and accurate diagnosis of cutaneous anthrax is crucial for treatment well in time and making strategies for further spread and control of disease. Although a lot of molecular tests are available for anthrax, yet this is difficult to employ these systems keeping in mind the available resources at far off locations where anthrax is endemic. Therefore, rapid, user friendly, inexpensive serodiagnosis tests can be important tools for surveillance of anthrax and active surveillance can help to minimize the agriculture or occupation related anthrax.

ACKNOWLEDGMENTS

We are thankful to Director, Defence Research and Development Establishment (DRDE), Defence Research and Development Organization (DRDO), Ministry of Defence, Gwalior for providing necessary facilities and funds for this research work.

REFERENCES

1 **Dixon TC**, Meselson M, Guillemin J, Hanna PC. Anthrax. *N Engl J Med* 1999; **341**: 815-826 [PMID: 10477781 DOI: 10.1056/

NEJM199909093411107]
2 **Santelli E**, Bankston LA, Leppla SH, Liddington RC. Crystal structure of a complex between anthrax toxin and its host cell receptor. *Nature* 2004; **430**: 905-908 [PMID: 15243628 DOI: 10.1038/nature02763]
3 **Jernigan JA**, Stephens DS, Ashford DA, Omenaca C, Topiel MS, Galbraith M, Tapper M, Fisk TL, Zaki S, Popovic T, Meyer RF, Quinn CP, Harper SA, Fridkin SK, Sejvar JJ, Shepard CW, McConnell M, Guarner J, Shieh WJ, Malecki JM, Gerberding JL, Hughes JM, Perkins BA. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerg Infect Dis* 2001; **7**: 933-944 [PMID: 11747719 DOI: 10.3201/eid0706.010604]
4 **Kamboj DV**, Goel AK, Singh L. Biological Warfare Agents. *Defence Sci J* 2006; **56**: 495-506
5 **Atlas RM**. Bioterriorism: from threat to reality. *Annu Rev Microbiol* 2002; **56**: 167-185 [PMID: 12142472 DOI: 10.1146/annurev.micro.56.012302.160616]
6 **Collier RJ**, Young JA. Anthrax toxin. *Annu Rev Cell Dev Biol* 2003; **19**: 45-70 [PMID: 14570563 DOI: 10.1146/annurev.cellbio.19.111301.140655]
7 **Ezzell JW**, Welkos SL. The capsule of bacillus anthracis, a review *J Appl Microbiol* 1999; **87**: 250 [PMID: 10475959 DOI: 10.1046/j.1365-2672.1999.00881.x]
8 **Mock M**, Mignot T. Anthrax toxins and the host: a story of intimacy. *Cell Microbiol* 2003; **5**: 15-23 [PMID: 12542467 DOI: 10.1046/j.1462-5822.2003.00253.x]
9 **Turk BE**. Manipulation of host signalling pathways by anthrax toxins. *Biochem J* 2007; **402**: 405-417 [PMID: 17313374 DOI: 10.1042/BJ20061891]
10 **Singh Y**, Klimpel KR, Goel S, Swain PK, Leppla SH. Oligomerization of anthrax toxin protective antigen and binding of lethal factor during endocytic uptake into mammalian cells. *Infect Immun* 1999; **67**: 1853-1859 [PMID: 10085027]
11 **Rao TN**, Venkatachalam K, Ahmed K, Padmaja IJ, Bharthi M, Rao PA. A mini-outbreak of cutaneous anthrax in Vizianagaram District, Andhra Pradesh, India. *Indian J Dermatol Venereol Leprol* 2009; **75**: 416-418 [PMID: 19584478 DOI: 10.4103/0378-6323.53158]
12 **Kumar A**, Kanungo R, Badrinath S. Anthrax in Pondicherry, South India. *J Med Microbiol* 2000; **49**: 1129 [PMID: 11129726]
13 **Dirckx JH**. Virgil on anthrax. *Am J Dermatopathol* 1981; **3**: 191-195 [PMID: 7023266 DOI: 10.1097/00000372-198100320-00012]
14 **Davaine CT**. Recherches sun les infusoires du sang dans la maladie conmce scule nom de sang de rate. *C R Acad Sci* 1863; **47**: 351-386
15 **Topley WWC,** Wilson GS, Miles AA. Topley and Wilson's Principles of bacteriology and immunity. 5th ed. Baltimore: Williams & Wilkins, 1964
16 **Koch R.** Die Aetiologie der Milzbrand-Krankheit, begründet auf die Entwicklungsgeschichte des Bacillus anthracis. *Beiträge zur Biologie der Pflanzen* 1876; **2:** 277-310
17 **Pasteur L**, Chamberland CF, Roux E. Compte rendu sommaire des expériences faites à Pouilly-le-Fort, près Melun, sur la vaccination charbonneuse. *Comptes Rendus des séances De L' Académie des Sciences* 1881; **92:** 1378-1383
18 **Guichard A**, Nizet V, Bier E. New insights into the biological effects of anthrax toxins: linking cellular to organismal responses. *Microbes Infect* 2012; **14**: 97-118 [PMID: 21930233 DOI: 10.1016/j.micinf.2011.08.016]
19 **Bell JH**. On Anthrax and Anthracaemia in Wool-Sorters, Heifers, and Sheep. *Br Med J* 1880; **2**: 656-657 [PMID: 20749691 DOI: 10.1136/bmj.2.1034.656]
20 **Eurich FW**. Anthrax in the Woollen Industry, with Special Reference to Bradford. *Proc R Soc Med* 1913; **6**: 219-240 [PMID: 19977235]
21 **Laforce FM**. Woolsorters' disease in England. *Bull N Y Acad Med* 1978; **54**: 956-963 [PMID: 361121]
22 **Dragon DC**, Rennie RP. The ecology of anthrax spores: tough but not invincible. *Can Vet J* 1995; **36**: 295-301 [PMID: 7773917]
23 **Dutz W**, Kohout-Dutz E. Anthrax. *Int J Dermatol* 1981; **20**: 203-206 [PMID: 6792089 DOI: 10.1111/j.1365-4362.1981.tb00461.x]
24 **Ibrahim KH**, Brown G, Wright DH, Rotschafer JC. Bacillus anthracis: medical issues of biologic warfare. *Pharmacotherapy* 1999; **19**: 690-701 [PMID: 10391414 DOI: 10.1592/phco.19.9.690.31543]
25 **Turnbull PC**. Definitive identification of Bacillus anthracis-a review. *J Appl Microbiol* 1999; **87**: 237-240 [PMID: 10475956 DOI: 10.1046/j.1365-2672.1999.00876.x]
26 **Koehler TM**, Dai Z, Kaufman-Yarbray M. Regulation of the Bacillus anthracis protective antigen gene: CO2 and a trans-acting element activate transcription from one of two promoters. *J Bacteriol* 1994; **176**: 586-595 [PMID: 8300513]
27 **Mock M**, Fouet A. Anthrax. *Annu Rev Microbiol* 2001; **55**: 647-671 [PMID: 11544370 DOI: 10.1146/annurev.micro.55.1.647]
28 **Gould GW**. Recent advances in the understanding of resistance and dormancy in bacterial spores. *J Appl Bacteriol* 1977; **42**: 297-309 [PMID: 18433 DOI: 10.1111/j.1365-2672.1977.tb00697.x]
29 **Russell AD**. Bacterial spores and chemical sporicidal agents. *Clin Microbiol Rev* 1990; **3**: 99-119 [PMID: 2187595]
30 **Halvorson HO**. Two generations of spore research: from father to son. *Microbiologia* 1997; **13**: 131-148 [PMID: 9253754]
31 **Glassman HN**. Discussion. *Bacteriol Rev* 1966; **30**: 657-659 [PMID: 16350199]
32 **Dahlgren CM**, Buchanan LM, Decker HM, Freed SW, Phillips CR, Brachman PS. Bacillus anthracis aerosols in goat hair processing mills. *Am J Hyg* 1960; **72**: 24-31 [PMID: 13813720]
33 **United States Army Medical Research Institute of Infectious Diseases.** United States Army Medical Research Institute of Infectious Diseases's Medical Management of Biological Casualties Handbook. Washington, DC: US Government Printing Office, 2011
34 **Rickmeier GL**, McClellan GE, Anno GA. Biological warfare human response modeling. *Mil Oper Res* 2001; **6**: 35-57 [DOI: 10.5711/morj.6.3.35]
35 **Peters CJ**, Hartley DM. Anthrax inhalation and lethal human infection. *Lancet* 2002; **359**: 710-711 [PMID: 11879895 DOI: 10.1016/S0140-6736(02)07792-9]
36 **Toth DJ**, Gundlapalli AV, Schell WA, Bulmahn K, Walton TE, Woods CW, Coghill C, Gallegos F, Samore MH, Adler FR. Quantitative models of the dose-response and time course of inhalational anthrax in humans. *PLoS Pathog* 2013; **9**: e1003555 [PMID: 24058320 DOI: 10.1371/journal.ppat.1003555]
37 **Cummings RT**, Salowe SP, Cunningham BR, Wiltsie J, Park YW, Sonatore LM, Wisniewski D, Douglas CM, Hermes JD, Scolnick EM. A peptide-based fluorescence resonance energy transfer assay for Bacillus anthracis lethal factor protease. *Proc Natl Acad Sci USA* 2002; **99**: 6603-6606 [PMID: 11997440 DOI: 10.1073/pnas.062171599]
38 **Read TD**, Salzberg SL, Pop M, Shumway M, Umayam L, Jiang L, Holtzapple E, Busch JD, Smith KL, Schupp JM, Solomon D, Keim P, Fraser CM. Comparative genome sequencing for discovery of novel polymorphisms in Bacillus anthracis. *Science* 2002; **296**: 2028-2033 [PMID: 12004073 DOI: 10.1126/science.1071837]
39 **Demicheli V**, Rivetti D, Deeks JJ, Jefferson T, Pratt M. The effectiveness and safety of vaccines against human anthrax: a systematic review. *Vaccine* 1998; **16**: 880-884 [PMID: 9682332 DOI: 10.1016/S0264-410X(98)00023-1]
40 **Soufiane B**, Côté JC. Discrimination among Bacillus thuringiensis H serotypes, serovars and strains based on 16S rRNA, gyrB and aroE gene sequence analyses. *Antonie Van Leeuwenhoek* 2009; **95**: 33-45 [PMID: 18839329 DOI: 10.1007/s10482-008-9285-4]
41 **Hoffmaster AR**, Hill KK, Gee JE, Marston CK, De BK, Popovic T, Sue D, Wilkins PP, Avashia SB, Drumgoole R, Helma CH, Ticknor LO, Okinaka RT, Jackson PJ. Characterization

of Bacillus cereus isolates associated with fatal pneumonias: strains are closely related to Bacillus anthracis and harbor B. anthracis virulence genes. *J Clin Microbiol* 2006; **44**: 3352-3360 [PMID: 16954272 DOI: 10.1128/JCM.00561-06]

42 **Hoffmaster AR**, Ravel J, Rasko DA, Chapman GD, Chute MD, Marston CK, De BK, Sacchi CT, Fitzgerald C, Mayer LW, Maiden MC, Priest FG, Barker M, Jiang L, Cer RZ, Rilstone J, Peterson SN, Weyant RS, Galloway DR, Read TD, Popovic T, Fraser CM. Identification of anthrax toxin genes in a Bacillus cereus associated with an illness resembling inhalation anthrax. *Proc Natl Acad Sci USA* 2004; **101**: 8449-8454 [PMID: 15155910 DOI: 10.1073/pnas.0402414101]

43 **Ghosh N**, Goel AK, Alam SI. Exoproteome analysis of a novel strain of Bacillus cereus implicated in disease resembling cutaneous anthrax. *Infect Genet Evol* 2014; **22**: 1-11 [PMID: 24412723 DOI: 10.1016/j.meegid.2013.12.014]

44 **Ghosh N**, Alam S, Goel AK. Prevalence of Bacillus cereus strains associated with illness resembling cutaneous anthrax in South India. *Int J Infect Dis* 2012; **16** Suppl 1: e128 [DOI: 10.1016/j.ijid.2012.05.292]

45 **Thappa DM**, Karthikeyan K. Cutaneous anthrax: an Indian perspective. *Indian J Dermatol Venereol Leprol* 2002; **68**: 316-319 [PMID: 17656987]

46 **Turnbull PC**. Introduction: anthrax history, disease and ecology. *Curr Top Microbiol Immunol* 2002; **271**: 1-19 [PMID: 12224519 DOI: 10.1007/978-3-662-05767-4_1]

47 **Blackburn JK**, McNyset KM, Curtis A, Hugh-Jones ME. Modeling the geographic distribution of Bacillus anthracis, the causative agent of anthrax disease, for the contiguous United States using predictive ecological [corrected] niche modeling. *Am J Trop Med Hyg* 2007; **77**: 1103-1110 [PMID: 18165531]

48 **Hampson K,** Lembo T, Bessell P, Auty H, Packer C, Halliday J, Beesley CA, Fyumagwa R, Hoare R, Ernest E, Mentzel C, Metzger KL, Mlengeya T, Stamey K, Roberts K, Wilkins PP, Cleaveland S. Predictability of anthrax infection in the Serengeti, Tanzania. *J Appl Ecol* 2011; **48**: 1333-1344 [PMID: 22318563 DOI: 10.1111/j.1365-2664.2011.02030.x]

49 **Hugh-Jones ME**, de Vos V. Anthrax and wildlife. *Rev Sci Tech* 2002; **21**: 359-383 [PMID: 11974621]

50 **Van Ness GB**. Ecology of anthrax. *Science* 1971; **172**: 1303-1307 [PMID: 4996306 DOI: 10.1126/science.172.3990.1303]

51 **Hugh-Jones M**, Blackburn J. The ecology of Bacillus anthracis. *Mol Aspects Med* 2009; **30**: 356-367 [PMID: 19720074 DOI: 10.1016/j.mam.2009.08.003]

52 **Hinton MH**. Infections and intoxications associated with animal feed and forage which may present a hazard to human health. *Vet J* 2000; **159**: 124-138 [PMID: 10712800 DOI: 10.1053/tvjl.1999.0412]

53 **Bhatanagar R**, Batra S. The Anthrax Vaccine: Is it safe? Does it work? *Crit Rev Microbiology* 2001; **27**: 167-200

54 **Turner AJ**, Galvin JW, Rubira RJ, Condron RJ, Bradley T. Experiences with vaccination and epidemiological investigations on an anthrax outbreak in Australia in 1997. *J Appl Microbiol* 1999; **87**: 294-297 [PMID: 10475972]

55 **Plotkin SA**, Brachman PS, Utell M, Bumford FH, Atchison MM. An epidemic of inhalation anthrax, the first in the twentieth century: I. Clinical features. 1960. *Am J Med* 2002; **112**: 4-12; discussion 2-3 [PMID: 11812400 DOI: 10.1016/S0002-9343(01)01050-6]

56 **Abramova FA**, Grinberg LM, Yampolskaya OV, Walker DH. Pathology of inhalational anthrax in 42 cases from the Sverdlovsk outbreak of 1979. *Proc Natl Acad Sci USA* 1993; **90**: 2291-2294 [PMID: 8460135 DOI: 10.1073/pnas.90.6.2291]

57 **Schmid G**, Kaufmann A. Anthrax in Europe: its epidemiology, clinical characteristics, and role in bioterrorism. *Clin Microbiol Infect* 2002; **8**: 479-488 [PMID: 12197870 DOI: 10.1046/j.1469-0691.2002.00500.x]

58 **Cinquetti G**, Banal F, Dupuy AL, Girault PY, Couderc A, Guyot P, Alauzet C, Oddoux O, Ragot C, Puyhardy JM, Graffin B, Veran Y. Three related cases of cutaneous anthrax in France: clinical and laboratory aspects. *Medicine* (Baltimore) 2009; **88**: 371-375 [PMID: 19910752 DOI: 10.1097/MD.0b013e3181c202fa]

59 **Sirisanthana T**, Brown AE. Anthrax of the gastrointestinal tract. *Emerg Infect Dis* 2002; **8**: 649-651 [PMID: 12095428 DOI: 10.3201/eid0807.020062]

60 **PTI.** Four persons die of suspected anthrax in Orissa. The Times of India [updated 2008 Feb 3]. Available from: URL: http://timesofindia.indiatimes.com/india/Four-persons-die-of-suspected-anthrax-in-Orissa/articleshow/2753426.cms

61 **Siddiqui MA**, Khan MA, Ahmed SS, Anwar KS, Akhtaruzzaman SM, Salam MA. Recent outbreak of cutaneous anthrax in Bangladesh: clinico-demographic profile and treatment outcome of cases attended at Rajshahi Medical College Hospital. *BMC Res Notes* 2012; **5**: 464 [PMID: 22929128 DOI: 10.1186/1756-0500-5-464]

62 **Rahman H.** Epidemiology of anthrax in India. PD_ADMAS Technical Bulletin. India: Indian Council of Agricultural Research, New Delhi, 2012

63 **Sekhar PC**, Singh RS, Sridhar MS, Bhaskar CJ, Rao YS. Outbreak of human anthrax in Ramabhadrapuram village of Chittoor district in Andhra Pradesh. *Indian J Med Res* 1990; **91**: 448-452 [PMID: 2091991]

64 **Ray TK**, Hutin YJ, Murhekar MV. Cutaneous anthrax, West Bengal, India, 2007. *Emerg Infect Dis* 2009; **15**: 497-499 [PMID: 19239777 DOI: 10.3201/eid1503.080972]

65 **Patil RR**. Anthrax: public health risk in India and socio-environmental determinants. *Indian J Community Med* 2010; **35**: 189-190 [PMID: 20606952 DOI: 10.4103/0970-0218.62573]

66 **Herriman R**. India: at least 35 people sickened with suspected anthrax In Odisha. Indian Express [accessed 2013 June 12]. Available from: URL: http: //www.theglobaldispatch.com/india-at-least-35-people-sickened-with-suspected-anthrax-in-odisha-92049/

67 **Goswami B.** Anthrax scare in West Midnapore: Nine persons, including children, have been affected. The Statesman. 2014 June 28. Available from: URL: http://www.thestatesman.net/news/62264-anthrax-scare-in-west-midnapore.html

68 **Moir A**, Smith DA. The genetics of bacterial spore germination. *Annu Rev Microbiol* 1990; **44**: 531-553 [PMID: 2252393 DOI: 10.1146/annurev.mi.44.100190.002531]

69 **Nicholson WL,** Setlow P. Sporulation, germination and outgrowth. In: Hardwood CR, Cutting SM, eds. Molecular Biology Methods for Bacillus. Farmingtion: Wiley, 1990: 391-450

70 **Young JA**, Collier RJ. Anthrax toxin: receptor binding, internalization, pore formation, and translocation. *Annu Rev Biochem* 2007; **76**: 243-265 [PMID: 17335404 DOI: 10.1146/annurev.biochem.75.103004.142728]

71 **Leppla SH**. Anthrax toxin edema factor: a bacterial adenylate cyclase that increases cyclic AMP concentrations of eukaryotic cells. *Proc Natl Acad Sci USA* 1982; **79**: 3162-3166 [PMID: 6285339 DOI: 10.1073/pnas.79.10.3162]

72 **Collier RJ**. Membrane translocation by anthrax toxin. *Mol Aspects Med* 2009; **30**: 413-422 [PMID: 19563824 DOI: 10.1016/j.mam.2009.06.003]

73 **Bradley KA**, Mogridge J, Mourez M, Collier RJ, Young JA. Identification of the cellular receptor for anthrax toxin. *Nature* 2001; **414**: 225-229 [PMID: 11700562 DOI: 10.1038/n35101999]

74 **Scobie HM**, Rainey GJ, Bradley KA, Young JA. Human capillary morphogenesis protein 2 functions as an anthrax toxin receptor. *Proc Natl Acad Sci USA* 2003; **100**: 5170-5174 [PMID: 12700348 DOI: 10.1073/pnas.0431098100]

75 **Omotade TO**, Heffron JD, Klimko CP, Marchand CL, Miller LL, Halasahoris SA, Bozue JA, Welkos SL, Cote CK. D-cycloserine or similar physiochemical compounds may be uniquely suited for use in Bacillus anthracis spore decontamination strategies. *J Appl Microbiol* 2013; **115**: 1343-1356 [PMID: 23927578 DOI: 10.1111/jam.12322]

76 **Klimpel KR**, Molloy SS, Thomas G, Leppla SH. Anthrax toxin protective antigen is activated by a cell surface protease with the sequence specificity and catalytic properties of furin. *Proc Natl Acad Sci USA* 1992; **89**: 10277-10281 [PMID: 1438214]

77 **Kintzer AF**, Thoren KL, Sterling HJ, Dong KC, Feld GK, Tang II, Zhang TT, Williams ER, Berger JM, Krantz BA. The protective antigen component of anthrax toxin forms functional octameric complexes. *J Mol Biol* 2009; **392**: 614-629 [PMID: 19627991 DOI: 10.1016/j.jmb.2009.07.037]

78 **Friedlander AM**. Macrophages are sensitive to anthrax lethal toxin through an acid-dependent process. *J Biol Chem* 1986; **261**: 7123-7126 [PMID: 3711080]

79 **Abrami L**, Reig N, van der Goot FG. Anthrax toxin: the long and winding road that leads to the kill. *Trends Microbiol* 2005; **13**: 72-78 [PMID: 15680766 DOI: 10.1016/j.tim.2004.12.004]

80 **Guidi-Rontani C**, Weber-Levy M, Mock M, Cabiaux V. Translocation of Bacillus anthracis lethal and oedema factors across endosome membranes. *Cell Microbiol* 2000; **2**: 259-264 [PMID: 11207582 DOI: 10.1046/j.1462-5822.2000.00057.x]

81 **Zornetta I**, Brandi L, Janowiak B, Dal Molin F, Tonello F, Collier RJ, Montecucco C. Imaging the cell entry of the anthrax oedema and lethal toxins with fluorescent protein chimeras. *Cell Microbiol* 2010; **12**: 1435-1445 [PMID: 20438574 DOI: 10.1111/j.1462-5822.2010.01480.x]

82 **Duesbery NS**, Webb CP, Leppla SH, Gordon VM, Klimpel KR, Copeland TD, Ahn NG, Oskarsson MK, Fukasawa K, Paull KD, Vande Woude GF. Proteolytic inactivation of MAP-kinase-kinase by anthrax lethal factor. *Science* 1998; **280**: 734-737 [PMID: 9563949 DOI: 10.1126/science.280.5364.734]

83 **Park JM**, Greten FR, Li ZW, Karin M. Macrophage apoptosis by anthrax lethal factor through p38 MAP kinase inhibition. *Science* 2002; **297**: 2048-2051 [PMID: 12202685 DOI: 10.1126/science.1073163]

84 **Vitale G**, Pellizzari R, Recchi C, Napolitani G, Mock M, Montecucco C. Anthrax lethal factor cleaves the N-terminus of MAPKKS and induces tyrosine/threonine phosphorylation of MAPKS in cultured macrophages *J Appl Microbiol* 1999; **87**: 288 [PMID: 10475970 DOI: 10.1046/j.1365-2672.1999.00893.x]

85 **Tang WJ**, Guo Q. The adenylyl cyclase activity of anthrax edema factor. *Mol Aspects Med* 2009; **30**: 423-430 [PMID: 19560485 DOI: 10.1016/j.mam.2009.06.001]

86 **Dal Molin F**, Tonello F, Ladant D, Zornetta I, Zamparo I, Di Benedetto G, Zaccolo M, Montecucco C. Cell entry and cAMP imaging of anthrax edema toxin. *EMBO J* 2006; **25**: 5405-5413 [PMID: 17082768 DOI: 10.1038/sj.emboj.7601408]

87 **Dal Molin F**, Zornetta I, Puhar A, Tonello F, Zaccolo M, Montecucco C. cAMP imaging of cells treated with pertussis toxin, cholera toxin, and anthrax edema toxin. *Biochem Biophys Res Commun* 2008; **376**: 429-433 [PMID: 18793614 DOI: 10.1016/j.bbrc.2008.09.012]

88 **Goossens PL**. Animal models of human anthrax: the Quest for the Holy Grail. *Mol Aspects Med* 2009; **30**: 467-480 [PMID: 19665473 DOI: 10.1016/j.mam.2009.07.005]

89 **Price EP**, Seymour ML, Sarovich DS, Latham J, Wolken SR, Mason J, Vincent G, Drees KP, Beckstrom-Sternberg SM, Phillippy AM, Koren S, Okinaka RT, Chung WK, Schupp JM, Wagner DM, Vipond R, Foster JT, Bergman NH, Burans J, Pearson T, Brooks T, Keim P. Molecular epidemiologic investigation of an anthrax outbreak among heroin users, Europe. *Emerg Infect Dis* 2012; **18**: 1307-1313 [PMID: 22840345 DOI: 10.3201/eid1808.111343]

90 **Hicks CW**, Sweeney DA, Cui X, Li Y, Eichacker PQ. An overview of anthrax infection including the recently identified form of disease in injection drug users. *Intensive Care Med* 2012; **38**: 1092-1104 [PMID: 22527064 DOI: 10.1007/s00134-012-2541-0]

91 **Bradarić N**, Punda-Polić V. Cutaneous anthrax due to penicillin-resistant Bacillus anthracis transmitted by an insect bite. *Lancet* 1992; **340**: 306-307 [PMID: 1353216 DOI: 10.1016/0140-6736(92)92395-V]

92 **Turell MJ**, Knudson GB. Mechanical transmission of Bacillus anthracis by stable flies (Stomoxys calcitrans) and mosquitoes (Aedes aegypti and Aedes taeniorhynchus). *Infect Immun* 1987; **55**: 1859-1861 [PMID: 3112013]

93 **Guidi-Rontani C**, Weber-Levy M, Labruyère E, Mock M. Germination of Bacillus anthracis spores within alveolar macrophages. *Mol Microbiol* 1999; **31**: 9-17 [PMID: 9987105 DOI: 10.1046/j.1365-2958.1999.01137.x]

94 **Jones WI**, Klein F, Walker JS, Mahlandt BG, Dobbs JP, Lincoln RE. In vivo growth and distribution of anthrax bacilli in resistant, susceptible, and immunized hosts. *J Bacteriol* 1967; **94**: 600-608 [PMID: 6068144]

95 **ROTH NG**, LIVERY DH, HODGE HM. Influence of oxygen uptake and age of culture on sporulation of Bacillus anthracis and Bacillus globigii. *J Bacteriol* 1955; **69**: 455-459 [PMID: 14367301]

96 **Bongiorni C**, Stoessel R, Shoemaker D, Perego M. Rap phosphatase of virulence plasmid pXO1 inhibits Bacillus anthracis sporulation. *J Bacteriol* 2006; **188**: 487-498 [PMID: 16385039 DOI: 10.1128/JB.188.2.487-498.2006]

97 **Burke AC**. Anthrax. 2008 Available from: URL: http://emedicine.medscape.com/article/212127-overview

98 **Ross JM**. The pathogenesis of anthrax following the administration of spores by the respiratory route. *J Pathol Bacteriol* 1957; **73:** 485-494 [DOI: 10.1002/path.1700730219]

99 **Grinberg LM**, Abramova FA, Yampolskaya OV, Walker DH, Smith JH. Quantitative pathology of inhalational anthrax I: quantitative microscopic findings. *Mod Pathol* 2001; **14**: 482-495 [PMID: 11353060 DOI: 10.1038/modpathol.3880337]

100 **Albrink WS**, Brooks SM, Biron RE, Kopel M. Human inhalation anthrax. A report of three fatal cases. *Am J Pathol* 1960; **36**: 457-471 [PMID: 13792449]

101 **Holty JE**, Kim RY, Bravata DM. Anthrax: a systematic review of atypical presentations. *Ann Emerg Med* 2006; **48**: 200-211 [PMID: 16857469 DOI: 10.1016/j.annemergmed.2005.11.035]

102 **Holty JE**, Bravata DM, Liu H, Olshen RA, McDonald KM, Owens DK. Systematic review: a century of inhalational anthrax cases from 1900 to 2005. *Ann Intern Med* 2006; **144**: 270-280 [PMID: 16490913 DOI: 10.7326/0003-4819-144-4-200602210-00009]

103 **Betty JM**, Shafa F, Gerhardt P. Structural details of anthrax spores during stages of transformation into vegetative cells. *J Bacteriol* 1966; **92:** 220-228

104 **Tipper DJ**, Linnett PE. Distribution of peptidoglycan synthetase activities between sporangia and forespores in sporulating cells of Bacillus sphaericus. *J Bacteriol* 1976; **126**: 213-221 [PMID: 1262302]

105 **Santo LY**, Doi RH. Ultrastructural analysis during germination and outgrowth of Bacillus subtilis spores. *J Bacteriol* 1974; **120**: 475-481 [PMID: 4213660]

106 **Driks A**. Maximum shields: the assembly and function of the bacterial spore coat. *Trends Microbiol* 2002; **10**: 251-254 [PMID: 12088650 DOI: 10.1016/S0966-842X(02)02373-9]

107 **Setlow B**, Cowan AE, Setlow P. Germination of spores of Bacillus subtilis with dodecylamine. *J Appl Microbiol* 2003; **95**: 637-648 [PMID: 12911713 DOI: 10.1046/j.1365-2672.2003.02015.x]

108 **Mesnage S**, Tosi-Couture E, Gounon P, Mock M, Fouet A. The capsule and S-layer: two independent and yet compatible macromolecular structures in Bacillus anthracis. *J Bacteriol* 1998; **180**: 52-58 [PMID: 9422592]

109 **Ivins BE**, Welkos SL, Little SF, Crumrine MH, Nelson GO. Immunization against anthrax with Bacillus anthracis protective antigen combined with adjuvants. *Infect Immun* 1992; **60**: 662-668 [PMID: 1730501]

110 **Iacono-Connors LC**, Welkos SL, Ivins BE, Dalrymple JM. Protection against anthrax with recombinant virus-expressed protective antigen in experimental animals. *Infect Immun* 1991; **59**: 1961-1965 [PMID: 1903769]

111 **Berg T**, Suddes H, Morrice G, Hornitzky M. Comparison

of PCR, culture and microscopy of blood smears for the diagnosis of anthrax in sheep and cattle. *Lett Appl Microbiol* 2006; **43**: 181-186 [PMID: 16869902 DOI: 10.1111/j.1472-765X.2006.01931.x]

112 **Marston CK**, Beesley C, Helsel L, Hoffmaster AR. Evaluation of two selective media for the isolation of Bacillus anthracis. *Lett Appl Microbiol* 2008; **47**: 25-30 [PMID: 18554264 DOI: 10.1111/j.1472-765X.2008.02375.x]

113 **Turnbull PCB**, Quinn CP, Hewson R, Stockbridge MC, Melling J. Protection conferred by microbially supplemented UK and purified PA vaccines. *Salisbury Med Bull* 1990; **68**: 89-91

114 **Ivins BE**, Welkos SL, Knudson GB, Little SF. Immunization against anthrax with aromatic compound-dependent (Aro-) mutants of Bacillus anthracis and with recombinant strains of Bacillus subtilis that produce anthrax protective antigen. *Infect Immun* 1990; **58**: 303-308 [PMID: 2105269]

115 **Goel AK**, Kamboj DV, Singh L. Enrichment and rapid detection of Bacillus anthracis spores by direct immunofluorescence assay. *Indian J Microbiol* 2005; **45:** 269-272

116 **Quinn CP**, Semenova VA, Elie CM, Romero-Steiner S, Greene C, Li H, Stamey K, Steward-Clark E, Schmidt DS, Mothershed E, Pruckler J, Schwartz S, Benson RF, Helsel LO, Holder PF, Johnson SE, Kellum M, Messmer T, Thacker WL, Besser L, Plikaytis BD, Taylor TH, Freeman AE, Wallace KJ, Dull P, Sejvar J, Bruce E, Moreno R, Schuchat A, Lingappa JR, Martin SK, Walls J, Bronsdon M, Carlone GM, Bajani-Ari M, Ashford DA, Stephens DS, Perkins BA. Specific, sensitive, and quantitative enzyme-linked immunosorbent assay for human immunoglobulin G antibodies to anthrax toxin protective antigen. *Emerg Infect Dis* 2002; **8**: 1103-1110 [PMID: 12396924 DOI: 10.3201/eid0810.020380]

117 **Quinn CP**, Dull PM, Semenova V, Li H, Crotty S, Taylor TH, Steward-Clark E, Stamey KL, Schmidt DS, Stinson KW, Freeman AE, Elie CM, Martin SK, Greene C, Aubert RD, Glidewell J, Perkins BA, Ahmed R, Stephens DS. Immune responses to Bacillus anthracis protective antigen in patients with bioterrorism-related cutaneous or inhalation anthrax. *J Infect Dis* 2004; **190**: 1228-1236 [PMID: 15346332 DOI: 10.1086/423937]

118 **Jernigan DB**, Raghunathan PL, Bell BP, Brechner R, Bresnitz EA, Butler JC, Cetron M, Cohen M, Doyle T, Fischer M, Greene C, Griffith KS, Guarner J, Hadler JL, Hayslett JA, Meyer R, Petersen LR, Phillips M, Pinner R, Popovic T, Quinn CP, Reefhuis J, Reissman D, Rosenstein N, Schuchat A, Shieh WJ, Siegal L, Swerdlow DL, Tenover FC, Traeger M, Ward JW, Weisfuse I, Wiersma S, Yeskey K, Zaki S, Ashford DA, Perkins BA, Ostroff S, Hughes J, Fleming D, Koplan JP, Gerberding JL. Investigation of bioterrorism-related anthrax, United States, 2001: epidemiologic findings. *Emerg Infect Dis* 2002; **8**: 1019-1028 [PMID: 12396909 DOI: 10.3201/eid0810.020353]

119 **Ghosh N**, Goel AK. Anti-protective antigen IgG enzyme-linked immunosorbent assay for diagnosis of cutaneous anthrax in India. *Clin Vaccine Immunol* 2012; **19**: 1238-1242 [PMID: 22718130 DOI: 10.1128/CVI.00154-12]

120 **Ghosh N**, Tomar I, Goel AK. A field usable qualitative anti-protective antigen enzyme-linked immunosorbent assay for serodiagnosis of human anthrax. *Microbiol Immunol* 2013; **57**: 145-149 [PMID: 23252995 DOI: 10.1111/1348-0421.12014]

121 **Ghosh N**, Gunti D, Lukka H, Reddy BR, Padmaja J, Goel AK. Development and validation of a quantitative anti-protective antigen IgG enzyme linked immunosorbent assay for serodiagnosis of cutaneous anthrax. *Indian J Med Res* 2014; In Press

122 **Biagini RE**, Sammons DL, Smith JP, MacKenzie BA, Striley CA, Snawder JE, Robertson SA, Quinn CP. Rapid, sensitive, and specific lateral-flow immunochromatographic device to measure anti-anthrax protective antigen immunoglobulin g in serum and whole blood. *Clin Vaccine Immunol* 2006; **13**: 541-546 [PMID: 16682473 DOI: 10.1128/CVI.13.5.541-546.2006]

123 **Price BM**, Liner AL, Park S, Leppla SH, Mateczun A, Galloway DR. Protection against anthrax lethal toxin challenge by genetic immunization with a plasmid encoding the lethal factor protein. *Infect Immun* 2001; **69**: 4509-4515 [PMID: 11401993 DOI: 10.1128/IAI.69.7.4509-4515.2001]

124 **Brenneman KE**, Doganay M, Akmal A, Goldman S, Galloway DR, Mateczun AJ, Cross AS, Baillie LW. The early humoral immune response to Bacillus anthracis toxins in patients infected with cutaneous anthrax. *FEMS Immunol Med Microbiol* 2011; **62**: 164-172 [PMID: 21401726 DOI: 10.1111/j.1574-695X.2011.00800.x]

125 **Ghosh N**, Tomar I, Lukka H, Goel AK. Serodiagnosis of human cutaneous anthrax in India using an indirect anti-lethal factor IgG enzyme-linked immunosorbent assay. *Clin Vaccine Immunol* 2013; **20**: 282-286 [PMID: 23269414 DOI: 10.1128/CVI.00598-12]

126 **Kobiler D**, Weiss S, Levy H, Fisher M, Mechaly A, Pass A, Altboum Z. Protective antigen as a correlative marker for anthrax in animal models. *Infect Immun* 2006; **74**: 5871-5876 [PMID: 16988266 DOI: 10.1128/IAI.00792-06]

127 **Mabry R**, Brasky K, Geiger R, Carrion R, Hubbard GB, Leppla S, Patterson JL, Georgiou G, Iverson BL. Detection of anthrax toxin in the serum of animals infected with Bacillus anthracis by using engineered immunoassays. *Clin Vaccine Immunol* 2006; **13**: 671-677 [PMID: 16760326 DOI: 10.1128/CVI.00023-06]

128 **Ghosh N**, Gupta N, Gupta G, Boopathi M, Pal V, Goel AK. Detection of protective antigen, an anthrax specific toxin in human serum by using surface plasma.]n resonance. *Diagn Microbiol Infect Dis* 2013; **77**: 14-19 [PMID: 23773677 DOI: 10.1016/j.diagmicrobio.2013.05.006]

129 **Schofield DA**, Sharp NJ, Vandamm J, Molineux IJ, Spreng KA, Rajanna C, Westwater C, Stewart GC. Bacillus anthracis diagnostic detection and rapid antibiotic susceptibility determination using 'bioluminescent' reporter phage. *J Microbiol Methods* 2013; **95**: 156-161 [PMID: 23994352 DOI: 10.1016/j.mimet.2013.08.013]

P- Reviewer: Kayabas U, Vaughan G **S- Editor**: Ji FF
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DOI: 10.12998/wjcc.v3.i1.34

World J Clin Cases 2015 January 16; 3(1): 34-41
ISSN 2307-8960 (online)

MINIREVIEWS

Enamel microabrasion: An overview of clinical and scientific considerations

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Received: July 28, 2014
Peer-review started: July 28, 2014
First decision: September 16, 2014
Revised: October 6, 2014
Accepted: October 28, 2014
Article in press: December 23, 2014
Published online: January 16, 2015

Abstract

Superficial stains and irregularities of the enamel are generally what prompt patients to seek dental intervention to improve their smile. These stains or defects may be due to hypoplasia, amelogenesis imperfecta, mineralized white spots, or fluorosis, for which enamel microabrasion is primarily indicated. Enamel microabrasion involves the use of acidic and abrasive agents, such as with 37% phosphoric acid and pumice or 6% hydrochloric acid and silica, applied to the altered enamel surface with mechanical pressure from a rubber cup coupled to a rotatory mandrel of a low-rotation micromotor. If necessary, this treatment can be safely combined with bleaching for better esthetic results. Recent studies show that microabrasion is a conservative treatment when the enamel wear is minimal and clinically imperceptible. The most important factor contributing to the success of enamel microabrasion is the depth of the defect, as deeper, opaque stains, such as those resulting from hypoplasia, cannot be resolved with microabrasion, and require a restorative approach. Surface enamel alterations that result from microabrasion, such as roughness and microhardness, are easily restored by saliva. Clinical studies support the efficacy and longevity of this safe and minimally invasive treatment. The present article presents the clinical and scientific aspects concerning the microabrasion technique, and discusses the indications for and effects of the treatment, including recent works describing microscopic and clinical evaluations.

Key words: Dental bleaching; Enamel microabrasion; Enamel surface; Esthetic treatment; Fluorosis; Hypoplasia

Core tip: Enamel microabrasion is indicated for the removal of superficial stains and irregularities of the enamel, mainly located in esthetic areas. The technique involves the mechanical rubbing of acidic and abrasive agents on the altered surface. Recent studies show that the technique

is a conservative treatment when the enamel wear is minimal and clinically imperceptible, and is effective and long lasting. The present literature review aims to discuss indications and clinical and scientific aspects of the microabrasion technique, as well as its effects on the enamel surface.

Pini NIP, Sundfeld-Neto D, Aguiar FHB, Sundfeld RH, Martins LRM, Lovadino JR, Lima DANL. Enamel microabrasion: An overview of clinical and scientific considerations. *World J Clin Cases* 2015; 3(1): 34-41 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i1/34.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i1.34

INTRODUCTION

Several treatments have been introduced to the dental market for the restoration of dental appearance to a level that satisfies what patients seek regarding dental esthetics. These techniques are still being evaluated in order to ensure an efficient treatment with minimal chair time and low cost that is safe for professionals and patients. For superficial enamel stains or defects, enamel microabrasion is preferred, as it is considered an esthetic and conservative treatment[1-3]. Since its introduction by Croll *et al*[4] in 1986, there have been numerous reports describing various approaches[5-8], related products, and clinical successes[9-12].

The main indication for enamel microabrasion is intrinsic discoloration or texture alteration due to enamel hypoplasia, amelogenesis imperfecta, or fluorosis[13]. The technique removes the porous surface enamel layer, as well as the entrapped stains, by rubbing a gel that contains an acid and an abrasive compound in a similar way that a dental prophylaxis with pumice and water is performed. The enamel stain or defect is removed by a combination of the erosive and abrasive effects of the recommended mixture containing low acid concentrations and an abrasive agent, applied mechanically using a low-rotation micromotor[13-15]. It should be the first option for the management of teeth with intrinsic stains because it removes opaque, brown stains and smoothens surface irregularities by providing a more regular and lustrous surface[13,16]. As the technique is considered safe and minimally invasive, it can also be combined with tooth bleaching when necessary[1,9,10,13].

The success of enamel microabrasion is directly related to the correct indication of the clinical case and the proper execution of the technique. This review discusses aspects of microabrasion, such as its evolution, indications, advantages, clinical steps, and effects on the enamel structure, in order to address some concerns regarding newer trends presented in the latest research and clinical reports.

EVOLUTION OF THE TECHNIQUE

Enamel microabrasion was initially performed for the removal of fluorotic white spots using 36% hydrochloric acid, as recommended by Kane in 1926[14,17,18]. A heated metallic instrument was used to apply the acid to the altered enamel to increase its penetration[14,18] and hasten the chemical reaction between the acid and the enamel[3]. Concerned about the safety of the technique, Raper *et al*[19] suggested the use of 18% hydrochloric acid applied and rubbed with a wooden spatula wrapped with cotton for a maximum time of 10 min[19]. The authors drew attention to the thickness of the enamel, particularly at the cervical third of the tooth, which is thinner compared to the medium and incisal third. They also recommended the use of sodium bicarbonate to neutralize the effects of the hydrochloric acid.

Mechanical application with a low-rotation micromotor was first indicated in the 1970s, using a mixture of 18% hydrochloric acid, hydrogen peroxide and ether[20]. Combination with an abrasive agent was later indicated by Murrin *et al*[21] in 1982, who added pumice to 36% hydrochloric acid, resulting in a slurry that was applied using a rubber cup coupled to a micromotor[21]. Concerned about the acid concentration, Croll *et al*[4] recommended the use of the same mixture but with 18% hydrochloric acid. Croll later stated that an ideal microabrasive system should include a low acid concentration and abrasive particles in a water-soluble mixture that are applied with a low-rotation handpiece to avoid scattering the compounds, thus making the procedure safer[14]. The author again proposed the use of an extra-fine diamond bur prior to the use of the microabrasive agents to reduce the clinical time needed to perform the procedure[22].

The association of hydrochloric acid to abrasive particles resulted in the development of commercially available products. Prema Compound (Premier Dental Company, Philadelphia, PA, United States), which contains 10% hydrochloric acid, was the first to be introduced to the market. Currently, a lower concentration of hydrochloric acid is used, approximately 6.6%, under the commercial product name of Opalustre (Ultradent Products Inc., South Jordan, UT, United States). Both products use silicon carbide as an abrasive with different granulations (Table 1) dispersed in a water-soluble gel for easy removal[13]. The use of 35% phosphoric acid instead of hydrochloric acid was proposed by Kamp in 1989, and was considered advantageous as it is commonly used in clinical practice for other procedures[3,23].

INDICATIONS FOR ENAMEL MICROABRASION

The proper indications for enamel microabrasion are summarized in Table 2. Dental fluorosis is the most common indication[16], which results from demineralization of enamel caused by excessive fluoride intake. Fluorosis produces opaque white areas or yellow to dark brown discolorations with porosities on the enamel surface, depending on severity[24,25]. Fluoride-induced enamel changes range from thin, white, opaque

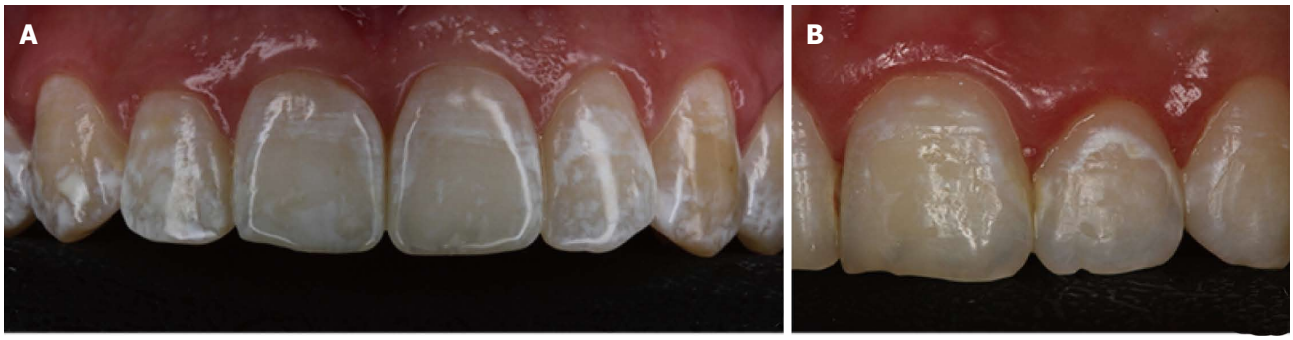

Figure 1 Indications for enamel microabrasion. Tooth staining from A: Fluorosis; B: Mineralized white spots.

Table 1 Commercial products used for microabrasion

Material	Manufacturer	Acid	Abrasive	Particle size (mm)
Prema compound	Premier Dental Company (Philadelphia, PA, United States)	10% hydrochloric acid	Silicon carbide/dioxide	30-60
Opalustre	Ultradent Products (South Jordan, UT, United States)	6.6% hydrochloric acid	Silicon carbide	20-160
Pumice	Pumex (Newcastle-under-lyme, Staffordshire, United Kingdom)	-	Pumice	30-50

Table 2 Summary of indications and advantages of the microabrasion technique

Indications	Requirements	Advantages
Stains or defects restricted only to enamel	Shallow alterations just in the enamel surface	Safe and conservative treatment
Dental fluorosis	Use of rubber dam	Minimal loss of enamel
Mineralized white stains	After completion of orthodontic treatment, if necessary	Leaves enamel surface lustrous, shiny and glass-like
Correction of surface irregularities	Supplemented with bleaching, if necessary	Roughness and microhardness alterations easily resolved by saliva
Localized enamel hypoplasia		Reduced bacterial colonization on enamel surface
Polishing of enamel and auxiliary removal of composite resin residues after orthodontic therapy		Lasting and stable esthetic results

lines corresponding to perikymata running across the tooth surface, to an entirely chalky white surface[24]. They are characterized by the presence of bilateral, diffuse, and horizontal striations[25] observed on all teeth that mineralize at the same time (Figure 1A). Enamel microabrasion usually improves esthetic appearance in cases of mild and moderate fluorosis (Thylstrup-Fejerskov Index 1-7)[16,26,27], and should always be considered the first option in the management of these cases[13,16]. Even in situations with yellow or brown discolorations, enamel microabrasion can improve the esthetic appearance of the teeth[28]. As these stains are formed by the discoloration of demineralized surfaces and from external sources, the depth of the stain is likely associated with the penetration of the staining agents[16].

Microabrasion treatment may be indicated for correction of surface irregularities on dental enamel, which may be caused by imperfect enamel formation or acquired after the removal of orthodontic appliances[13], such as the removal of residual resin composite from brackets with diamond burs, and resulting in a smooth and polished enamel surface[29]. Microabrasion is also indicated for opaque, white areas or discolorations, even with porosities, from the demineralization/remineralization process common in the enamel region adjacent to orthodontic bands or brackets (Figure 1B), or from disturbances in the mineralization process, such as hypocalcification[7,13,30]. The white spots caused by orthodontics should first be treated with mineralizing agents, such as sodium fluoride[12,31], or with an infiltration technique[29]. Infiltration of the enamel by resin was recently developed as a way to obstruct the diffusion pathways for acids and dissolved minerals[32]. The resins used have low viscosity, high surface tension, and low contact angle with the enamel, as well as a refraction index similar to enamel[33]. The infiltration technique may also be used in cases of mineralized lesions[29,34]. The technique requires pre-conditioning of the surface with 15% hydrochloric acid, which removes approximately 40 μm of enamel surface, to ensure resin penetration[32]. In

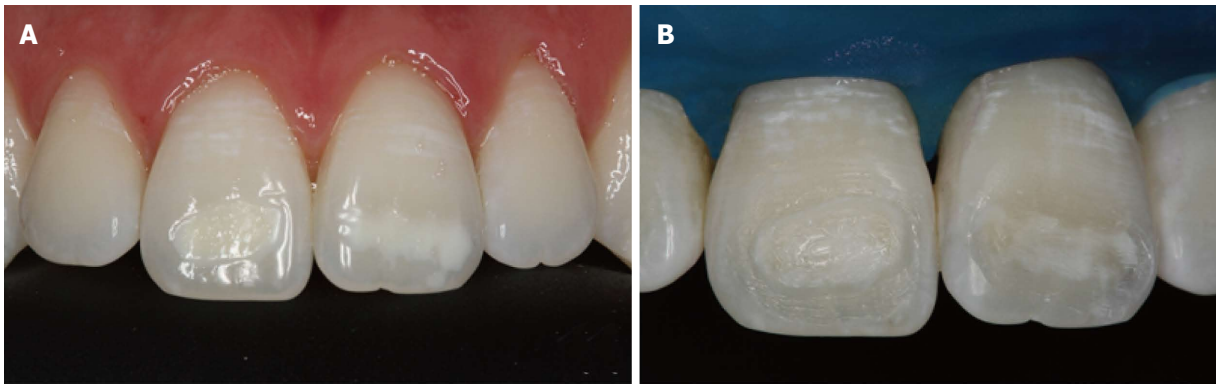

Figure 2 Deep enamel staining due to hypoplasia. A: Hypoplasia; B: Ineffective microabrasion treatment of the right central incisor.

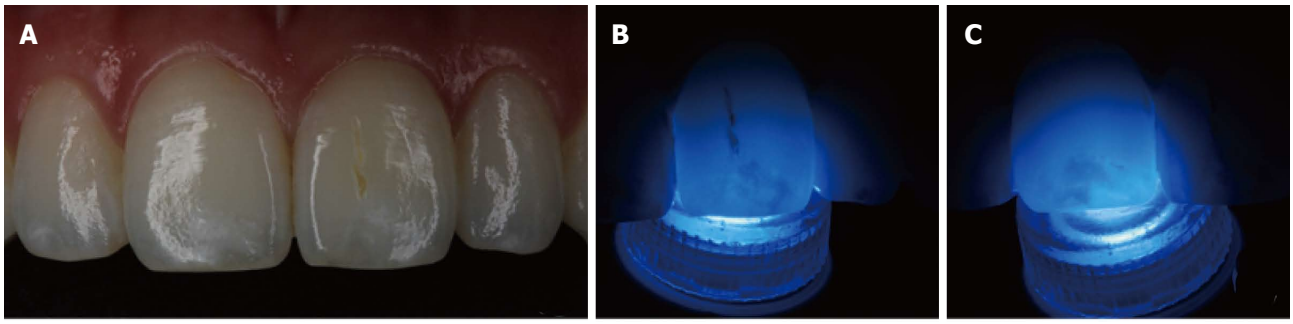

Figure 3 Transillumination to determine staining depth. A: Enamel hypoplasia in both central incisors; B, C:: Transillumination to evaluate the staining.

this way, the thickness of the enamel removed for resin infiltration is similar to microabrasion. However, there are no clinical trials evaluating the staining, abrasion wear or bacterial colonization of resin-infiltrated surfaces.

Microabrasion may be utilized in cases of localized or idiopathic enamel hypoplasia that is limited to the outer enamel layer[15,35]. Although this condition can sometimes require a restorative approach with composite resin or laminate veneer[36] (Figure 2), microabrasion should be considered as the first treatment option[16,36]. In addition to improving esthetics, it may reduce the need for enamel wear for a restorative approach, which is mainly important in young patients[36]. Otherwise, the infiltration technique may be used in cases with deeper stains not resolved by microabrasion, and may be an alternative for the invasive restorative approach[37,38]. Even if all whitish parts of a lesion do not completely disappear, the infiltration technique usually leads to considerable improvement in appearance[37] and masks the enamel stain[34,38].

Enamel microabrasion is not indicated if the patient presents deficient lip sealing, as the teeth are always exposed to air and dehydrate more easily, thus a moistened film is not formed under the enamel. With this condition, the stained appearance of the tooth is more evident, and it may characterize the failure of the microabrasion. Therefore, these patients are encouraged to first seek orthodontic treatment and/or speech therapy[1,13].

The most important factors contributing the success of enamel microabrasion are the location and depth of the enamel stain or defect[8,13,16]. The alteration must be restricted to enamel tissue, without involvement of the dentin[13]. Deeper, opaque stains, such as those resulting from hypoplasia, cannot be resolved with microabrasion, and require a restorative approach[36]. An LED/light curing unit positioned in the palatine or lingual face of the tooth can help the clinician to examine the enamel stain (Figure 3). This can be used to estimate the lesion depth, as a darker color indicates deeper staining[9]. It is also important to perform the diagnosis in wet conditions, as the difference in the refractive index between air and enamel is greater than between water and enamel[12]. Commonly, white spots are more obvious on dry teeth, thus a lesion visible on a wet tooth can be considered deeper than a lesion visible only on dry enamel.

TECHNIQUE

An ideal microabrasion technique should produce insignificant enamel loss, no damage to pulp or periodontal tissues, and satisfactory and permanent results in a short clinical time without discomfort to the patient[4]. The use of a rubber cup coupled to the rotatory mandrel enables precise application of the compound on the enamel surface, which eliminates splattering of the compound and makes the procedure safer, easier, and quicker[13]. For the safety of the patient, a rubber dam should be in place[39], though

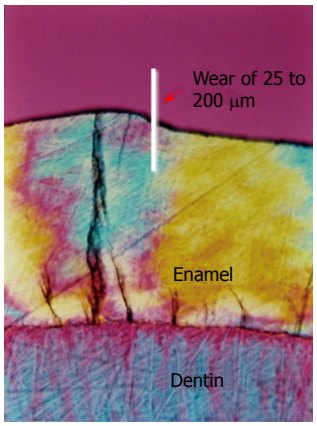

Figure 4 Depth of enamel removal. Polarized light microscopy showing the ground tooth section after enamel microabrasion with Opalustre (reprinted with permission from Sundfeld *et al*[44]).

this may be difficult when the teeth are not completely erupted[13]. It is also important that the patient, clinician, and assistants all wear eye protection during the procedure[1].

The number of applications can vary according to the severity of the enamel staining[1,9,10,12]. To reduce the clinical time, the enamel can first be "regularized" with a tapered fine-diamond bur to lightly abrade the affected area, referred to as enamel macroreduction[1,9,13,30]. With this procedure, the application of microabrasive slurry can be reduced to two or three applications to remove the remaining stains and to smooth the enamel surface ground with the diamond bur[1]. Afterwards, polishing of the microabraded surface with felt discs and polishing[26] or fluoridated[1,9,10,40] pastes is recommended. Application of sodium fluoride gel[1,9,26] is also recommended to promote the remineralization process.

Because enamel microabrasion is a noninvasive technique, it can be supplemented with bleaching procedures[1,9,13,15,41]. Often, this is necessary as microabraded teeth can acquire a darker or yellowish coloration after treatment, and the remaining enamel is thinner and more clearly reveals the dentin. Bleaching is also indicated to reduce the contrast between the remaining white-spotted lesions and the tooth surface[26,42,43]. In either situation, a low concentration of carbamide peroxide is recommended using the home-bleaching technique[1,9,10,13].

CLINICAL AND SCIENTIFIC CONSIDERATIONS

Effects of the technique

Enamel microabrasion has been shown as an effective and conservative treatment[1,9,13,15,43]. According to reports by Sundfeld *et al*[13,43,44], 5 to 10 applications of microabrasive systems (35% phosphoric acid with pumice, Opalustre) can result in the loss of 25 to 200 μm of enamel, which is acceptable for clinical conditions (Figure 4). A recent study showed that 120 s of microabrasive treatment reduces approximately 10% of the enamel thickness[5], suggesting it is a safe and conservative procedure. According to Dalzell *et al*[45], the pressure used during the microabrasion procedure is crucial for total enamel removal, such that the higher the pressure, the greater the quantity of enamel removed. In addition, enamel wear from the microabrasion technique is time-dependent[46].

In addition to the removal of discolored enamel, the microabrasion technique changes the optical characteristics of the enamel surface, called the "abrasion effect"[47,48]. The simultaneous abrasion and acid erosion of enamel prisms may compact mineralized tissue within the organic area, replacing the outer layer of prism-rich enamel with a densely compacted, prism-free region[48]. Microabrasion presents a lustrous, shiny, and glass-like surface of the enamel, which may reflect and refract light differently[13,41]. These optical properties may be able to camouflage any remaining subsurface enamel stains[48]. Tooth hydration by saliva augments these favorable optical properties[47,48]. Schimdlin *et al*[2] found that the luminescence and fluorescence of enamel after microabrasion of demineralized lesions was decreased in comparison with the untreated demineralized enamel.

Several studies have examined the effects of microabrasion on the remaining enamel surface[2,5-8,46,49-51]. The potential erosive and abrasive effects depend on several parameters, including the type, concentration and pH of the acid used, the abrasive medium, time of instrumentation, application mode, force applied, and revolutions per minute[8,50]. The microabrasion technique increases the roughness of the enamel surface, regardless of whether 18% or 35% phosphoric acid or 6.6% hydrochloric acid with abrasive was used[5,7,44,51]. Similarly, enamel microabrasion is also related to reduced enamel microhardness[6,49]. However, both effects can be reversed by the polishing procedure or saliva exposure[5,6,49,51]. Rodrigues *et al*[5] found that unlike that seen with microabrasion, the enamel surface maintained the same roughness through all the evaluated stages when mechanically treated with a silicon polisher; the authors suggested that the chemical features of enamel microabrasion are responsible for the roughness effects. Despite their concentration differences, phosphoric acid and hydrochloric acid have similar erosive effects[5,6,49], such as alterations in the enamel micromorphology with exposition of the interprismatic spaces, similar to the enamel conditioning patterns[7,46]. Although the microabrasive system causes change in the enamel surface, which can be observed by scanning electron microscopy, confocal imaging demonstrates that the subsurface is not altered (Figure 5). The smoother, dense, mineralized enamel layer created by microabrasive systems is also less favorable for bacterial colonization, particularly by *Streptococcus mutans*[52]. Additionally, Hoeppner *et al*[53] reported that the enamel surface was more resistant to demineralization four months after microabrasion with 35% phosphoric acid.

Bertoldo *et al*[49] recently reported that microabrasion with 6.6% hydrochloric acid and silica results in the incorporation of chloride ions and silica into the enamel.

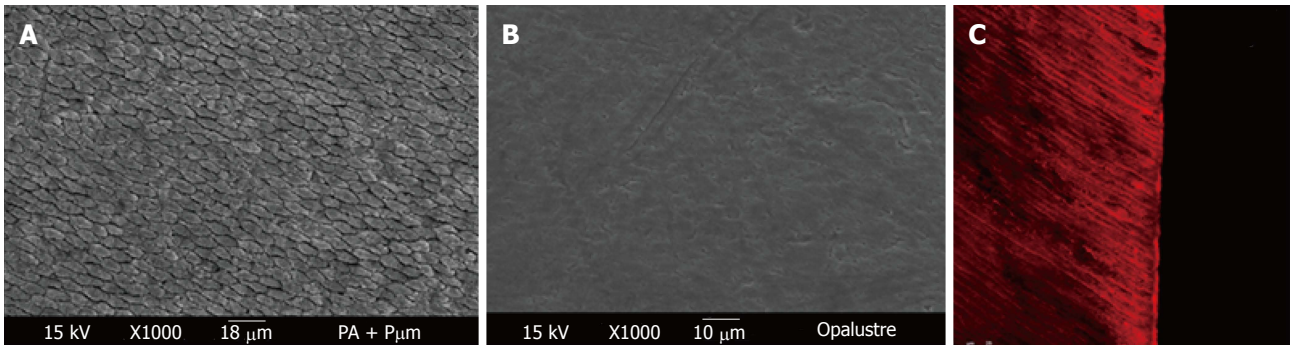

Figure 5 Enamel alterations after microabrasion. Scanning electron microscopy showing the acid conditioning pattern on the enamel surface caused by microabrasion with A: Phosphoric acid and pumice; B: Opalustre; C: Confocal laser scanning microscopy showing the minimal alteration of the enamel surface, but intact subsurface, after microabrasion with Opalustre.

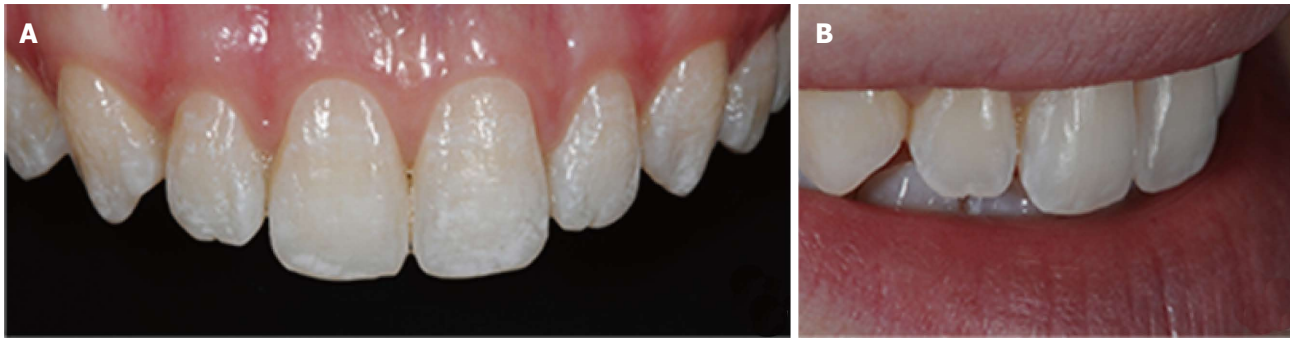

Figure 6 Resolution of fluorosis staining by microabrasion. A: Clinical case of fluorosis before treatment; B: Results after enamel microabrasion (reprinted with permission Machado *et al*[58]).

These, along with results from additional studies concerning the effects of artificial[6,49] and human[51] saliva on microabraded enamel, should encourage clinicians to consider this method. Chloride ions are strongly associated with enamel rehardening, as they account for more than 60% of the ionic strength of saliva[54,55], and the silica compound is used in a bioactive material (Ca_3SiO_5) that efficiently induces a new apatite layer on acid-etched enamel[56]. Some authors believe that these properties should be maximized and, rather than polishing the microabraded enamel, a light polishing with a feltrum disc and fluoridates or diamond toothpaste with low granulation should be applied[1,5,9].

Clinical success

Several case reports demonstrate the lasting and stable esthetic results of the microabrasion technique[1,9,10,12,35,41]. According to clinical results, enamel microabrasion produced permanent color modification of superficial enamel coloration defects because the discolored enamel was removed, rather than altered or masked[57]. Microabraded enamel surfaces achieved a brilliant luster over time[13,57]. An example clinical result of enamel microabrasion is presented in Figure 6[58].

Loguercio *et al*[59] compared two commercially available products for microabrasion for removal of fluorosis stains, and found that treatment with Opalustre was more effective than Prema Compound. This effect was possibly due to the larger size of the silica granules in the Opalustre. However, both products were efficient, and the patients were highly satisfied with the results. Similarly, Sheoran *et al*[57] compared 35% phosphoric and 18% hydrochloric acid with pumice, and found no clinical difference between them, with microabrasive compounds successful in treating enamel opacities.

Enamel microabrasion is considered effective in cases of white, yellow or brown stains located in the outer enamel layer[60]. However, it is important to recognize the severity of enamel stains when facing fluorosis. Celik *et al*[16] performed enamel microabrasion with Opalustre in mild-to-severe fluorosed teeth and found that more applications were needed when lesions were more severe. Mild staining was treated with five applications, whereas moderate to severe staining needed ten applications. Train *et al*[27] also showed that the appearance of mildly fluorosed teeth was moderately improved, but microabrasion only slightly improved the appearance of severely fluorosed teeth. However, enamel microabrasion should still be the first option for patients that seek minimally invasive treatment, even in cases with severe fluorosis. In such cases, removal of opaque white areas or brown stains may increase the success of further treatment, such as bleaching, to achieve a uniform tooth shade[16]. Castro *et al*[26] showed that enamel microabrasion combined with at-home tooth bleaching effectively reduced staining in cases of mild to severe fluorosis, improving the esthetic

appearance of the teeth and the self-perception of the patient, without incidence of side effects such as tooth sensitivity.

CONCLUSION

Accumulating evidence suggests that enamel microabrasion is efficient and effective for producing esthetic improvements. This technique involves minimal enamel loss, leaving a smooth and shiny enamel surface with permanent results. The procedure is considered a safe, conservative, atraumatic method for removing superficial enamel stains and defects. The laboratory and clinical results presented in these articles support the use of enamel microabrasion as a first treatment option for patients who prefer a less-invasive approach.

REFERENCES

1 **Sundfeld RH**, Franco LM, Gonçalves RS, de Alexandre RS, Machado LS, Neto DS. Accomplishing esthetics using enamel microabrasion and bleaching-a case report. *Oper Dent* 2014; **39**: 223-227 [PMID: 23919624 DOI: 10.2341/13-002-S]

2 **Schmidlin PR**, Göhring TN, Schug J, Lutz F. Histological, morphological, profilometric and optical changes of human tooth enamel after microabrasion. *Am J Dent* 2003; **16** Spec No: 4A-8A [PMID: 14674490]

3 **Mondelli JM**, Mondelli RL, Alves MTA, Franco EB. Microabrasão com ácido fosfórico. *Revista Brasileira Odontógica* 1995; **52**: 20-22

4 **Croll TP**, Cavanaugh RR. Enamel color modification by controlled hydrochloric acid-pumice abrasion. II. Further examples. *Quintessence Int* 1986; **17**: 157-164 [PMID: 3458266]

5 **Rodrigues MC**, Mondelli RF, Oliveira GU, Franco EB, Baseggio W, Wang L. Minimal alterations on the enamel surface by micro-abrasion: in vitro roughness and wear assessments. *J Appl Oral Sci* 2013; **21**: 112-117 [PMID: 23739863 DOI: 10.1590/1678-7757201302117]

6 **Fragoso LS**, Lima DA, de Alexandre RS, Bertoldo CE, Aguiar FH, Lovadino JR. Evaluation of physical properties of enamel after microabrasion, polishing, and storage in artificial saliva. *Biomed Mater* 2011; **6**: 035001 [PMID: 21487176 DOI: 10.1088/1748-6041/6/3/035001]

7 **Meireles SS**, Andre Dde A, Leida FL, Bocangel JS, Demarco FF. Surface roughness and enamel loss with two microabrasion techniques. *J Contemp Dent Pract* 2009; **10**: 58-65 [PMID: 19142257]

8 **Paic M**, Sener B, Schug J, Schmidlin PR. Effects of microabrasion on substance loss, surface roughness, and colorimetric changes on enamel in vitro. *Quintessence Int* 2008; **39**: 517-522 [PMID: 19057750]

9 **Sundfeld RH**, Sundfeld-Neto D, Machado LS, Franco LM, Fagundes TC, Briso AL. Microabrasion in tooth enamel discoloration defects: three cases with long-term follow-ups. *J Appl Oral Sci* 2014; **22**: 347-354 [PMID: 25141208]

10 **Sundfeld RH**, Rahal V, de Alexandre RS, Briso AL, Sundfeld Neto D. Smile restoration through use of enamel microabrasion associated with tooth bleaching. *Compend Contin Educ Dent* 2011; **32**: e53-e57 [PMID: 23738859]

11 **Wang Y**, Sa Y, Liang S, Jiang T. Minimally invasive treatment for esthetic management of severe dental fluorosis: a case report. *Oper Dent* 2013; **38**: 358-362 [PMID: 23210860 DOI: 10.2341/12-238-S]

12 **Nahsan FP**, da Silva LM, Baseggio W, Franco EB, Francisconi PA, Mondelli RF, Wang L. Conservative approach for a clinical resolution of enamel white spot lesions. *Quintessence Int* 2011; **42**: 423-426 [PMID: 21519563]

13 **Sundfeld RH**, Croll TP, Briso AL, de Alexandre RS, Sundfeld Neto D. Considerations about enamel microabrasion after 18 years. *Am J Dent* 2007; **20**: 67-72 [PMID: 17542197]

14 **Croll TP**. Enamel microabrasion: the technique. *Quintessence Int* 1989; **20**: 395-400 [PMID: 2756095]

15 **Benbachir N**, Ardu S, Krejci I. Indications and limits of the microabrasion technique. *Quintessence Int* 2007; **38**: 811-815 [PMID: 18197319]

16 **Celik EU**, Yildiz G, Yazkan B. clinical evaluation of enamel microabrasion for the aesthetic management of mild-to-severe dental fluorosis. *J Esthet Restor Dent* 2013; **25**: 422-430 [PMID: 24320061 DOI: 10.1111/jerd.12052]

17 **McCloskey RJ**. A technique for removal of fluorosis stains. *J Am Dent Assoc* 1984; **109**: 63-64 [PMID: 6589292]

18 **Croll TP**. Enamel microabrasion: observations after 10 years. *J Am Dent Assoc* 1997; **128** Suppl: 45S-50S [PMID: 9120146]

19 **Raper HR**, Manser JG. Removal of brow stain from fluorine mottled teeth. *Dentistry Digital* 1941; **9**: 390-396

20 **Chandra S**, Chawla TN. Clinical evaluation of the sandpaper disk method for removing fluorosis stains from teeth. *J Am Dent Assoc* 1975; **90**: 1273-1276 [PMID: 1056394]

21 **Murrin JR**, Barkmeier WW. Chemical treatment of endemic dental fluorosis. *Quintessence Int Dent Dig* 1982; **13**: 363-369 [PMID: 6955830]

22 **Croll TP**. Hastening the enamel microabrasion procedure eliminating defects, cutting treatment time. *J Am Dent Assoc* 1993; **124**: 87-90 [PMID: 8340552]

23 **Kamp AA**. Removal of white spot lesions by controlled acid-pumice abrasion. *J Clin Orthod* 1989; **23**: 690-693 [PMID: 2639881]

24 **Fejerskov O**, Kidd E. Dental Caries - The disease and its clinical management. 2nd ed. USA: Wiley-Blackwell, 2008

25 **Denbesten P**, Li W. Chronic fluoride toxicity: dental fluorosis. *Monogr Oral Sci* 2011; **22**: 81-96 [PMID: 21701193 DOI: 10.1159/000327028]

26 **Castro KS**, Ferreira AC, Duarte RM, Sampaio FC, Meireles SS. Acceptability, efficacy and safety of two treatment protocols for dental fluorosis: a randomized clinical trial. *J Dent* 2014; **42**: 938-944 [PMID: 24486675 DOI: 10.1016/j.jdent.2014.01.011]

27 **Train TE**, McWhorter AG, Seale NS, Wilson CF, Guo IY. Examination of esthetic improvement and surface alteration following microabrasion in fluorotic human incisors in vivo. *Pediatr Dent* 1996; **18**: 353-362 [PMID: 8897526]

28 **Ng F**, Manton DJ. Aesthetic management of severely fluorosed incisors in an adolescent female. *Aust Dent J* 2007; **52**: 243-248 [PMID: 17969294]

29 **Knösel M**, Eckstein A, Helms HJ. Durability of esthetic improvement following Icon resin infiltration of multibracket-induced white spot lesions compared with no therapy over 6 months: a single-center, split-mouth, randomized clinical trial. *Am J Orthod Dentofacial Orthop* 2013; **144**: 86-96 [PMID: 23810050 DOI: 10.1016/j.ajodo.2013.02.029]

30 **Croll TP**, Bullock GA. Enamel microabrasion for removal of smooth surface decalcification lesions. *J Clin Orthod* 1994; **28:** 365-370 [PMID: 8613515]

31 **Ardu S**, Castioni NV, Benbachir N, Krejci I. Minimally invasive treatment of white spot enamel lesions. *Quintessence Int* 2007; **38**: 633-636 [PMID: 17823680]

32 **Paris S**, Schwendicke F, Seddig S, Müller WD, Dörfer C, Meyer-Lueckel H. Micro-hardness and mineral loss of enamel lesions after infiltration with various resins: influence of infiltrant composition and application frequency in vitro. *J Dent* 2013; **41**: 543-548 [PMID: 23571098 DOI: 10.1016/j.jdent.2013.03.006]

33 **Paris S**, Meyer-Lueckel H, Cölfen H, Kielbassa AM. Penetration coefficients of commercially available and experimental composites intended to infiltrate enamel carious lesions. *Dent Mater* 2007; **23**: 742-748 [PMID: 16911822]

34 **Kim S**, Kim EY, Jeong TS, Kim JW. The evaluation of resin

infiltration for masking labial enamel white spot lesions. *Int J Paediatr Dent* 2011; **21**: 241-248 [PMID: 21401750 DOI: 10.1111/j.1365-263X.2011.01126.x]
35 **Wray A**, Welbury R. UK National Clinical Guidelines in Paediatric Dentistry: Treatment of intrinsic discoloration in permanent anterior teeth in children and adolescents. *Int J Paediatr Dent* 2001; **11**: 309-315 [PMID: 11570449]
36 **Reston EG**, Corba DV, Ruschel K, Tovo MF, Barbosa AN. Conservative approach for esthetic treatment of enamel hypoplasia. *Oper Dent* 2011; **36**: 340-343 [PMID: 21740246 DOI: 10.2341/10-189-T]
37 **Attal JP**, Atlan A, Denis M, Vennat E, Tirlet G. White spots on enamel: treatment protocol by superficial or deep infiltration (part 2). *Int Orthod* 2014; **12**: 1-31 [PMID: 24503373 DOI: 10.1016/j.ortho.2013.12.011]
38 **Muñoz MA**, Arana-Gordillo LA, Gomes GM, Gomes OM, Bombarda NH, Reis A, Loguercio AD. Alternative esthetic management of fluorosis and hypoplasia stains: blending effect obtained with resin infiltration techniques. *J Esthet Restor Dent* 2013; **25**: 32-39 [PMID: 23374407 DOI: 10.1111/j.1708-8240.2012.00527.x]
39 **Croll TP**, Killian CM, Miller AS. Effect of enamel microabrasion compound on human gingiva: report of a case. *Quintessence Int* 1990; **21**: 959-963 [PMID: 2082423]
40 **Sundfeld RH**, Rahal V, Croll TP, De Aalexandre RS, Briso AL. Enamel microabrasion followed by dental bleaching for patients after orthodontic treatment--case reports. *J Esthet Restor Dent* 2007; **19**: 71-77; discussion 78 [PMID: 17374110]
41 **Croll TP**, Helpin ML. Enamel microabrasion: a new approach. *J Esthet Dent* 2000; **12**: 64-71 [PMID: 11326505]
42 **Pontes DG**, Correa KM, Cohen-Carneiro F. Re-establishing esthetics of fluorosis-stained teeth using enamel microabrasion and dental bleaching techniques. *Eur J Esthet Dent* 2012; **7**: 130-137 [PMID: 22645728]
43 **Sundfeld RH**, Komatsu J, Russo M, Holland Jr. C, Castro MAM, Quintella LPAS, Mauro SJ. Remoção de manchas no esmalte dental: estudo clínico e microscópico. *Revista Brasileira Odontológica* 1990; **47**:29-34
44 **Sundfeld RH**, Croll TP, Killian CM. Smile recovery: VII. Proving the efficiency and versatility of the enamel microabrasion technique. *Jornal Brasileiro de Dentística Estéticat* 2002; **1**: 77-86
45 **Dalzell DP**, Howes RI, Hubler PM. Microabrasion: effect of time, number of applications, and pressure on enamel loss. *Pediatr Dent* 1995; **17**: 207-211 [PMID: 7617497]
46 **Tong LS**, Pang MK, Mok NY, King NM, Wei SH. The effects of etching, micro-abrasion, and bleaching on surface enamel. *J Dent Res* 1993; **72**: 67-71 [PMID: 8418110]
47 **Croll TP**. Enamel microabrasion. Chicago: Quintessence. *J Dent* 1991: 13-21 [DOI: 10.1016/0300-5712(93)90032-L]
48 **Donly KJ**, O'Neill M, Croll TP. Enamel microabrasion: a microscopic evaluation of the "abrosion effect". *Quintessence Int* 1992; **23**: 175-179 [PMID: 1641458]
49 **Bertoldo CES,** Pini NIP, Miranda DA, Catelan A, Ambrosano GMB, Lima DANL, Aguiar FHB, Lovadino JR. Physicochemical properties of enamel after microabrasion technique. *JDR* 2014; **2:** 176-188
50 **Zuanon AC**, Santos-Pinto L, Azevedo ER, Lima LM. Primary tooth enamel loss after manual and mechanical microabrasion. *Pediatr Dent* 2005; **30**: 420-423 [PMID: 18942602]
51 **Pini NIP**, Lima DANL, Sundfeld RH, Ambrosano GMB, Aguiar FHB, Lovadino JR. In Situ assessment of the saliva effect on enamel morphology after microabrasion technique. *Brazilian J Oral Science* 2014; In press
52 **Segura A**, Donly KJ, Wefel JS. The effects of microabrasion on demineralization inhibition of enamel surfaces. *Quintessence Int* 1997; **28**: 463-466 [PMID: 9477896]
53 **Hoeppner MG**, Mauro SJ, Alexandre RS, Sundefeld ML, Sundfeld RH. Evaluation "in situ" of tag formation in dental enamel submitted to microabrasion technique. Effect of two etching times. *Acta Odontol Latinoam* 2010; **23**: 153-157 [PMID: 21053690]
54 **Jager DH,** Vieira AM, Ligtenberg AJ, Bronkhorst E, Huysmans MC, Vissink A Effect of salivary factors on the susceptibility of hydroxyapatite to early erosion. *Caries Res* 2011; **45**: 532-537 [PMID: 21997255 DOI: 10.1159/000331938]
55 **Humphrey SP**, Williamson RT. A review of saliva: normal composition, flow, and function. *J Prosthet Dent* 2001; **85**: 162-169 [PMID: 11208206]
56 **Wang Y**, Li X, Chang J, Wu C, Deng Y. Effect of tricalcium silicate (Ca(3)SiO(5)) bioactive material on reducing enamel demineralization: an in vitro pH-cycling study. *J Dent* 2012; **40**: 1119-1126 [PMID: 23000524 DOI: 10.1016/j.jdent.2012.09.006]
57 **Sheoran N**, Garg S, Damle SG, Dhindsa A, Opal S, Gupta S. Esthetic management of developmental enamel opacities in young permanent maxillary incisors with two microabrasion techniques-a split mouth study. *J Esthet Restor Dent* 2014; **26**: 345-352 [PMID: 24588784 DOI: 10.1111/jerd.12096]
58 **Machado LS**, Sundfeld-Neto D, Oliveira FG, Franco LM, Anchieta RB, Sundfeld RH. Association between enamel microabrasion and bleaching for esthetic recovering of natural teeth. Case report. *Revista Dental Press de Estética* 2013; **10**: 83-90
59 **Loguercio AD**, Correia LD, Zago C, Tagliari D, Neumann E, Gomes OM, Barbieri DB, Reis A. Clinical effectiveness of two microabrasion materials for the removal of enamel fluorosis stains. *Oper Dent* 2007; **32**: 531-538 [PMID: 18051001]
60 **Price RB**, Loney RW, Doyle MG, Moulding MB. An evaluation of a technique to remove stains from teeth using microabrasion. *J Am Dent Assoc* 2003; **134**: 1066-1071 [PMID: 12956346]

P- Reviewer: Carrilho EP, Lalli E **S- Editor**: Ji FF **L- Editor**: A
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DOI: 10.12998/wjcc.v3.i1.42

World J Clin Cases 2015 January 16; 3(1): 42-51
ISSN 2307-8960 (online)

MINIREVIEWS

Recent advances in the HER2 targeted therapy of gastric cancer

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Supported by KAKENHI (Grant-in-Aid for Scientific Research), No. 23390329; and the National Cancer Center Research and Development Fund (23-A-9).

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Received: August 4, 2014
Peer-review started: August 6, 2014
First decision: September 16, 2014
Revised: October 9, 2014
Accepted: November 17, 2014
Article in press: December 23, 2014
Published online: January 16, 2015

Abstract

Recent advances in molecular targeted therapies, including targeting human epidermal growth factor receptor 2 (HER2), had a major forward step in the therapy for gastric cancer patients. Application of HER2-targeted therapies, in particular trastuzumab in combination with chemotherapy in metastatic HER2-positive gastric cancers, resulted in improvements in response rates, time to progression and overall survival. Nevertheless, as with breast cancer, many patients with gastric cancer develop resistance to trastuzumab. Several promising therapies are currently being developed in combination with chemotherapy to increase the efficacy and overcome the cancer-resistance. Here we review the current overview of clinical application of agents targeting HER2 in gastric cancer. We also discuss the ongoing trials supporting the use of HER2-targeted agents combined with cytotoxic agents or other monoclonal antibodies.

Key words: Human epidermal growth factor receptor 2; Gastric cancer; Targeting therapy; Trastuzumab

Core tip: This review summarizes the development of diagnostic and therapeutic approach for the patients with human epidermal growth factor receptor 2 (HER2)-overexpressed/amplified gastric cancer. The biology of HER2-dependent signalling is also described. The ToGA trial highlighted the importance of accurate HER2 testing to guide treatment choice of gastric cancer. Future strategies beyond the ToGA trial to address EFGR family, including HER2 pathway are discussed according to current ongoing clinical trials, as well as experimental studies.

Matsuoka T, Yashiro M. Recent advances in the HER2 targeted therapy of gastric cancer. *World J Clin Cases* 2015; 3(1): 42-51 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i1/42.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i1.42

INTRODUCTION

Gastric cancer is the fourth most common malignant

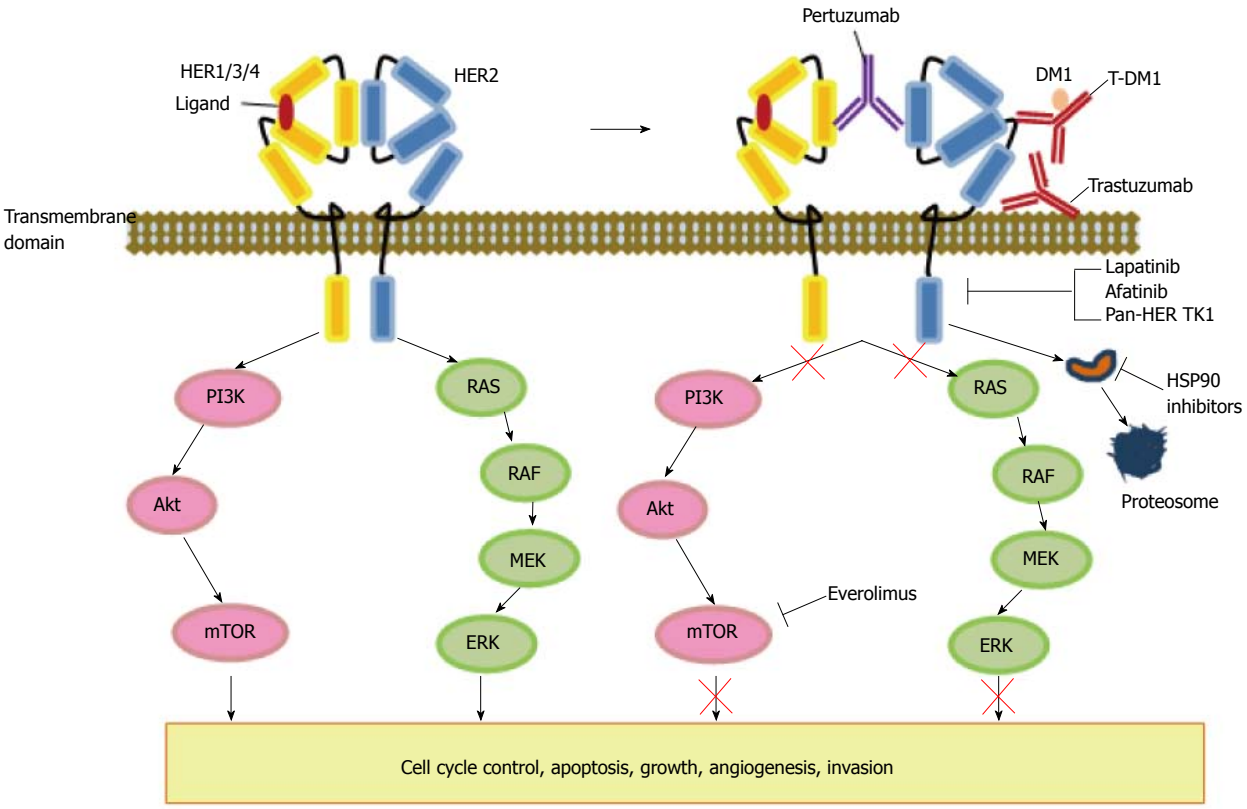

Figure 1 Human epidermal growth factor receptor 2 signaling pathway and interaction with other pathways. This demonstrates schematic representation of the HER-2 family of receptor and their interaction with downstream signalling, along the pathway which are responsible for a variety of biological processes involving cell cycle control, apoptosis, cellular growth, invasion, and angiogenesis. Examples of classes of drugs and corresponding compounds targeting the HER-2 network are also presented. HER1-4 are transmembrane proteins with associated tyrosine kinases. Heterodimerization result in tyrosine kinase activation with the subsequent signaling cascade, and subsequently activates downstream signals, including members of MAPK and PI3K/Akt/mTOR pathways. Trastuzumab and t-DM1 targtets to the extracellular domain IV of HER2. Anti-cancer activity of pertuzumab is interference with HER-receptor dimerization. Lapatinib, afatinib, and tyrosine kinase inhibitors (TKIs) compete for the binding of ATP in the intracellular domain of the receptors. HSP90 suppresses the NH2-terminal ATP binding site which leads to the degradation of client proteins by the ubiquitin proteasome pathway. HER: Human epidermal growth factor receptor; MAPK: Mitogen-activated protein kinase; MEK: Mitogen-activated protein kinase kinase; ERK: Extracellular signal-regulated kinase; PI3K: Phosphatidylinositol 3-kinase; mTOR: Mammalian target of rapamycin.

disease and the second leading cause of cancer-related death worldwide[1]. Despite the current improvements in survival of patients with gastric cancer, it is often diagnosed at an advanced stage and its prognosis is still unsatisfactory due to the high frequency of metastasis[2,3].

Recent studies have shown that several combination chemotherapies have been shown to significantly increase survival for patients with gastric cancer[4]. SPIRITS trial (S1 plus cisplatin *vs* S1 in RCT in the treatment of stomach cancer) showed that combined therapy of S1 with cisplatin significantly prolonged survival as a first-line treatment for advanced gastric cancer. Overall survival (OS) of patients treated with S1 plus cisplatin was 13.0 mo compared 11.0 mo with S1 alone[5]. Additionally, other cytotoxic agents, including docetaxel and irinotecan also prolonged survival[6,7]. Notably, capecitabine and oxaliplatin showed to be non-inferior to fluorouracil and cisplatin[8,9]. However, even with these treatments, most patients with advanced disease have a median overall survival in the range of 6-11 mo[2].

To date, with greater knowledge of the molecular basis of tumor initiation, several kinds of targeted agents have led to a better prognosis for solid tumors. One of the most important targets in human malignancy is the epidermal growth factor receptor (EGFR) family[10]. The human epidermal growth factor receptor-2 (HER2) is a receptor of tyrosine kinase and a member of the EGFR family[11]. HER2 is expressed in a significant proportion of gastric cancer[12]. Trastuzumab, a recombinant humanized monoclonal antibody that targets the extracellular domain Ⅳ of HER2, has recently been noticeably altered the treatment of gastric cancer. Trastuzumab has demonstrated a survival advantage in patients with HER2-overexpressed gastric cancer[13].

In this article, we will outline the issues concerning novel biologic agents for advanced gastric cancer, focusing on anti-HER2 therapies, such as trastuzumab, and other novel agents. We will also discuss the current clinical evidence and ongoing trials supporting the use of HER2-targeted agents combined with cytotoxic agents or other monoclonal antibodies.

MOLECULAR FEATURES OF HER2

HER2, a proto-oncogene encoded by *ERBB2* on chromosome 17, is a cell membrane surface-bound receptor

tyrosine kinase and belongs to EGFR family, including EGFR/HER1, HER2/neu, HER3, and HER4[11]. Each receptor has an extracellular domain, lipophilic transmembrane domain, and intracellular kinase domain (Figure 1). Although HER1, 3, 4 are activated by ligand binding, the specific ligand to HER2 have not been identified yet[14]. Nevertheless, aberrant HER2 activity and activation of the HER2 receptor leads to receptor dimerization (*e.g.*, HER2/HER3), and subsequently activate downstream signals, including members of the Ras/Raf/mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3 kinase/protein kinase-B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathways (Figure 1)[15,16]. Overexpression of HER2 has been found to aggressively promote these signals which are responsible for regulating a variety of tumor biology, such as cancer cell growth, differentiation, invasion and survival[17,18]. Dimerization of HER2 and HER3 is known to be the most active HER signaling dimer. With regard to gastric cancer, HER2 and HER3 are significant predictors of poor survival in multivariate study. HER3 may become another candidate for molecular-targeted therapy in gastric cancer, especially for the diffuse histological type[19,20].

HER2 EXPRESSION AND GASTRIC CANCER

The reported HER2 amplification in patients with gastric cancer ranges from 6% to 23%[13,21,22]. The rates of HER2 amplification or overexpression in gastric cancers are different depending on the primary location of the tumor, which is more frequent in cancers located in the gastroesophageal junction compared with those from elsewhere in the stomach[13,23]. Histological evaluation revealed HER2 overexpression was predominantly seen in the intestinal-type than in diffuse-type cancers (32% *vs* 6%)[22].

HER2 amplification is associated with clinicopathological features, such as age, male gender, tumor size, serosal invasion and lymph node metastasis[24,25]. HER2 expression is a biomarker for the prediction of trastuzumab response[26]. However, the prognostic significance of HER2 overexpression in gastric cancer remains controversial. A number of retrospective studies have demonstrated that HER2 positivity is a prognostic factor associated with increased risk of invasion, metastasis, and worse survival[19,27-29]. HER2 status has been reported as the second poorest prognostic variable following nodal status[30,31]. On the other hand, other studies found no association between HER2 and prognosis in both early and advanced stage cancers[13,32-38].

Several studies have investigated how differences in expression of HER2 between of primary gastric tumor and metastatic lesions. The majority of these reports has described that HER2 expression of primary and secondary sites revealed a high concordance rate, except two studies[35,39]. These data suggest that the evaluation of HER2 expression in the primary cancer is a reliable basis for determing treatment with anti-HER2 agents in patients with metastatic gastric cancer.

HER2 expression is usually determined by immunohistochemistry (IHC) or by the detection of HER2 gene amplification by fluorescence *in situ* hybridization (FISH). The evaluation of HER2 immunostained samples in gastric cancer is carried out as outlined by Hofmann *et al*[40] and optimized by Rüschoff *et al*[41]. HER2 testing is distinct from breast cancer immunohistochemistry testing. The major difference in scoring HER2 IHC staining between gastric cancer and breast cancer is that an incomplete basolateral or lateral staining alone is considered as a positive result, which lead to the frequent incidence of tumor heterogeneity[40]. This heterogeneity may represent the HER2 testing inaccuracy, resulting in the controversy of significance of HER2-expression in gastric cancer. Thus, further studies have been proposed to improve the quality of HER2 testing to make certain that patients receive the best possible therapy for their HER2-positive disease.

A recent study presented the Collaborative Enzyme Enhanced Reactive (CEER) immunoassay may be a useful technique to investigate the HER2 expression[42]. CEER-based assays showed higher sensitivity and specificity as compared to IHC-based assays. Evaluation with this high sensitivity of HER3 resulted in -20% of the IHC/FISH HER2 negative gastric cancers still expressed total HER2 although. Another study presented that the use of a quantitative variable that could be objectively measured, such as the *HER2* gene copy number or the *HER2* amplification ratio, which seems preferable to a subjective classification in accordance with IHC scores that are not regularly consistent[43]. These current development of technology may be useful for elucidating the expression of HER2 more precisely and improving prediction of clinical outcome in gastric cancer patients treated with trastuzumab.

TREATMENT FOR HER2 POSITIVE GASTRIC CANCER

Trastuzumab

Trastuzumab is the first molecular targeted agent approved as standard treatment in gastric cancer[13,44]. This agent induces antibody-dependent cellular cytotoxicity, inhibits HER2-mediated signaling and prevents cleavage of the extracellular domain of HER2 (Figure 1). Trastuzumab for Gastric Cancer (ToGA) study was an open-label phase Ⅲ, randomized controlled trial undertaken in 122 centers among 24 countries[13]. ToGA trial showed that an addition of trastuzumab to conventional cytotoxic chemotherapy demonstrated a clinical benefit compared to chemotherapy alone in terms of tumor response, which suggested that combined chemotherapy with trastuzumab can be cited as a novel accepted option for patients with HER2-positive advanced gastric cancer. Recently, a role of trastuzumab as a second-line chemotherapy got attention because of the usefulness of trastuzumab as a first-line chemotherapy. In

Table 1 Clinical trials of HER2-targeted therapy in gastric cancer (after ToGA study)

Trial	Study design	No. of patients	HER2 status	Regimen duration of treatment	Response rate	Prognosis
LOGiC	Phase Ⅲ/1st Randomized Double Blind	545	HER2 amplification	Lapatinib + XELOX XELOX No description of duration		non-significant prolongation
TyTAN	Phase Ⅲ/2nd Parallel group Randomized	1923	HER2 amplification	Lapatinib +Paclitaxel Paclitaxel 24 mo	27% *vs* 9%	OS: 11.0 mo *vs* 8.9 mo PFS: 5.4 mo *vs* 4.4 mo
HERBIS-1	Phase Ⅱ/1st Non-Randomized	56	IHC 3+ IHC 2+ FISH +	S-1/cisplatin + trastuzumab No description of duration	68%	OS: 16.0 mo PFS: 7.8 mo
PF299804	Phase Ⅱ/2nd Non-Randomized	28 (estimated)	IHC 3+ IHC 2+ FISH +	PF299804 Cycles of 28 d	7.40%	Ongoing
HIROISE (NCT01450646)	Phase Ⅲ/1st Randomized	400 (estimated)		Trastuzumab + cisplatin + capecitabine 33 wk		Ongoing
NCT01472029	Phase Ⅱ/1st Non-Randomized	53		5-FU, leucovorin, docetaxel, oxaliplatin (FLOT), trastuzumab No description of duration		Ongoing
NCT01130337	Phase Ⅱ/ preoperative Non-Randomized	36		Trastuzumab + XELOX 12 mo		Ongoing
NCT01522768	Phase Ⅱ/advanced Non-Randomized	40	IHC 3+ IHC 2+ FISH +	Afatinib + trastuzumab 24 mo		Ongoing
NCT01402401	Phase Ⅱ/2nd Non-Randomized	21	IHC 3+ IHC 2+ FISH +	AUY922 + trastuzumab Every 6 wk		Ongoing
NCT01641939	Phase Ⅱ/Ⅲ/1st Randomized	412 (estimated)	IHC 3+ IHC 2+ FISH +	Trastuzumab emtansine Taxane 12 wk		Ongoing

HER2: Human epidermal growth factor receptor; OS: Overall survival; PFS: Progression-free survival; IHC: Immunohistochemistry; FISH: Fluorescence *in situ* hybridization.

a recent retrospective analysis, gastric cancer patients with HER2 overexpression applied trastuzumab in addition to their first-line chemotherapy with or without trastuzumab maintenance therapy. The median PFS was 14.6 mo and OS was 16.4 mo with an acceptable benefit[45] (Table 1).

On the other hand, the efficacy of HER2-targeted agents have shown to be limited and unsatisfactory than that would be expected[13,46]. These insufficiencies may be overcome by the development of combined therapy with other cytotoxic agents, and strategies against primary or acquired resistance in the patients with gastric cancer. The HERBIS-1 study is the muticenter phase Ⅱ trial undertaken at 22 hospitals in Japan[47]. Patients with HER2-positive advanced gastric cancer received S1 on day 1-14, cisplatin, on 1 d, and trastuzumab on day 1 of a 21-d cycle. The RR based on RECIST was 68% (95%CI: 54%-80%; 80%CI: 58%-76%) and the disease control rate was 94% (95%CI: 84%-99%). Median OS, PFS, and TTF were estimated as 16.0, 7.8, and 5.7 mo, respectively. Trastuzumab combined with SP would be a potential new strategy for patients with HER-2 positive advanced gastric cancer. Another study presented that the level of synergistic effect on combination therapy with trastuzumab and anti-cancer drug was different depending on the expression level of HER-2. The HER-2 expression may be applied to standard for drug selection in combination of trastuzumab with known cytotoxic agents in gastric cancer[48].

Pertuzumab

Pertuzumab, one of the HER2-targeted monoclonal antibody, is distinct and complementary to trastuzumab. Pertuzumab binds the extracellular domain Ⅱ of the HER2 receptor and disrupts HER2 dimerization (Figure 1)[49]. Similar to trastuzumab, pertuzumab activates antibody-dependent cellular cytotoxicity, with equivalent efficacy, leading to cancer cell death[50]. The combination of trastuzumab plus pertuzumab was reported to be synergistic in breast cancer. This combination reduced HER2/EGFR and HER2/HER3 heterodimer formation, leading to in induction of apoptosis *in vitro*[49]. Thus the therapeutic achievement of pertuzumab in metastatic HER2 positive breast cancer provides hope for HER2 positive gastric cancer by using a similar approach. With regard to gastric cancer, a phase Ⅱa study of first-line pertuzumab in combination with trastuzumab, capecitabine and cisplatin in patients with HER2 positive advanced gastric cancer was carried out[51]. Patients were divided into two arms: pertuzumab 840 mg for cycle 1 and trastuzumab 420 mg q3w for cycle 2-6 *vs* pertuzumab 840 mg q3w for six cycles. Partial responses were achieved by 86% and 55% of patients, respectively.

Lapatinib

Lapatinib is a small tyrosine kinase inhibitor of EGFR and HER2 that interferes activation by binding to the intracellular ATP binding site of these kinases (Figure 1).

This agent inhibits HER2 and EGFR dependent activation of PI3K and Ras pathways, leading to downregulation of receptor tyrosine kinase phosphorylation in tumor cells (Figure 1). The synergistic activity was shown by lapatinib in combination with trastuzumab for HER2 positive breast cancer that presented through two lines of trastuzumab related treatments[52]. Regarding to gastric cancer, modest activity was demonstrated with single-agent lapatinib in the Southwest Oncology Group (SWOG) 0413 trial[53]. Subsequently, Tykerb with Taxol in Asian ErbB2 gastric cancer (TyTAN), an open-label randomized phase Ⅲ study comparing paclitaxel with paclitaxel plus lapatinib in patients with HER2 FISH-positive IHC3 + gastric cancer as a second-line therapy was performed. Although the median OS was prolonged by two months with lapatinib, this trial failed to achieve any OS and PFS benefit because statistically significance was not obtained[46]. Moreover, the Lapatinib Optimization study in HER2 positive Gastric Cancer (LOGiC) trial is a phase Ⅲ trial of capecitabine and oxaliplatin with or without lapatinib in first-line advanced HER2 FISH amplified gastric and GEJ cancers suggested not any signs of activity for lapatinib[54]. These negative results of TyTAN and LOGiC trials indicate that there is a presence of drug resistance or an alternative pathways from HER2-targeted therapy. On the other hand, lapatinib may be useful for treating the trastuzumab-resistant HER2-positive gastric cancer. A previous study described that lapatinib showed the antitumor efficacy for trastuzumab-resistant cell lines which was due to both G_1 cell-cycle arrest and apoptosis induction[55].

Trastuzumab-emtansine

Antibody-drug conjugates have been said to transfer cytotoxic drugs directly to tumor cells. Trastuzumab emtansine (TDM-1) is an antibody-drug conjugate of trastuzumab and, a potent microtubule inhibitor, DM1(derivative of maytansine). In preclinical gastric cancer models, TDM-1 has shown more aggressive tumor activity than trastuzumab[56]. A multicenter adaptive phase Ⅱ/Ⅲ of TDM-1 is currently underway with HER2 positive advanced gastric cancer after progression following first line treatment (NIH study trial registration number NCT01641939; ClinicalTrials. gov).

STRATEGIES TO OVERCOME TRASTUZUMAB RESISTANCE IN GASTRIC CANCER

Although HER2 targeting therapy has been advanced, most patients with gastric cancer still develop acquired resistance to trastuzumab[54]. To achieve better benefits for HER2-targeted therapy in patients with HER2-positive gastric cancer, there is an urgent need to clarify the mechanisms underlying the cancer-resistance. Some papers described that intra-tumoral heterogeneity of gastric cancer may play a role in the resistance[57,58]. In this section, we will discuss selected novel agents including those based on proposed mechanisms of resistance to HER2-targeted therapy (Figure 1).

Afatinib

Afatinib (Gilotrif, Boehringer Ingelheim), an irreversible inhibitor of EGFR, HER2, and HER4, has been shown to be effective in the elimination of cancer cells with *HER2* gene mutations[59]. This orally-bioavailable compound binds to its targets and has potential against receptors with acquired mutations that are resistant to first-generation inhibitors. The usefulness of this agent is currently examined in phase Ⅲ study in EGFR-positive non small cell lung cancer, breast cancer, and head and neck squamous cell carcinoma[59]. Phase Ⅱ study in metastatic HER2 positive trastuzumab refractory esophagogastric cancer is underway (NIH study trial registration number NCT01522768; ClinicalTrials.gov).

mTOR inhibitors

One of the most important mechanisms underlying trastuzumab resistance is dysregulation of HER2 downstream signal substrate, including the PI3K/Akt/mTOR pathway. It is well known that *PIK3CA* mutations and phosphate and tensin homolog (PTEN) inactivation result in constitutive activation of the downstream signals. HER2 overexpression is said to be significantly associated with p-Akt expression, suggesting that *PIK3CA* mutation and PTEN inactivation may affect the effectiveness of HER2-targeted therapy[60]. Inhibition of the mTOR/S6K signal by mTOR inhibitor, everolimus, enhanced fluorouracil-induced apoptosis in gastric cancer cells with HER2 amplification. Thus, it is plausible that concomitant therapy between HER2-targeted agents and mTOR inhibitor may provide substantial benefit in patients with HER2-positive gastric cancer.

HSP90 inhibitors

HSP90 is an ATP-dependent, conserved molecular chaperone that is involved in the structural folding and stability of proteins. Suppression at the NH2-terminal ATP binding site results in the degradation of client proteins by the ubiquitin proteasome pathway, which lead to the degradation of HER2 (Figure 1)[61]. Furthermore, p95-HER2, which is amino-terminal truncated form of HER2 and also a major factor of trastuzumab resistance due to the lacks of the trastuzumab binding site, shown to be degraded by HSP90 inhibitors. Several HSP90 inhibitors are undergoing early clinical evaluation. AUY922 is part of the isoxazole HSP90-inhibitor family. HSP90 inhibition by AUY922 leads to decrease the ErbB2 protein level and downstream signaling via PI3K in HER2-positive gastric cancer[62]. A recent study described that a significant synergy exists between AUY922 and trastuzumab in HER2-amplified gastric cancer. The combination of AUY922 and trastuzumab is also synergistic in HER2-amplified trastuzumb-progressed gastric cancer, which may be due to reinforce the rationale behind dual mechanisms of blockade in

HER2-amplified diseases[63]. Clinical trials on the basis of this study are currently underway in gastric cancers (NIH study trial registration number NCT01402401; ClinicalTrials.gov). Thus, the dual inhibition of HSP90 and HER2 may enhance the attenuate effects on downstream signaling, especially in trastuzumab-resistant patients.

Pan-HER TK1

Recent studies have suggested that HER3 plays a pivotal role in tumor resistance to molecular agents targeting HER2[64], and is causing the maintenance of HER2-amplified cell growth. Therefore, it is plausible that a pan-HER TK1, which targets all HER family members, may have more potent activity in HER expressed malignancies. PF00299804 (Decomitib) is an orally bioavailable, second-generation, irreversible pan-HER TKI currently under clinical development[65]. The combination of PF00299804 with chemotherapeutic agents or molecular-targeted agents including trastuzumab produced synergistic effects. These data suggested that PF00299804 may augment the antitumor efficacy of chemotherapy and/or molecular-targeted agents.

Met inhibitors

c-Met is a cell surface receptor for hepatocyte growth factor (HGF), which regulates a variety of cellular processes involved in cell growth, invasion and angiogenesis[66]. A functional crosstalk between Met and HER family members has been shown to acquire an invasive and progressive phenotype, suggesting that Met can be the dimerization partner or crosstalk with HER2[67]. Furthermore, the Met signaling has been implicated as a mediator of resistance to therapies targeting members of the HER family in several solid tumors[68]. These data indicate that HER2 targeted agents combined with Met inhibitor may be useful to facilitate the efficacy and overcome the resistance of HER2 therapy in patients with HER2-positive gastric cancer. Similarly, HGF activation of MET receptors has been described to rescue cells from lapatinib-induced growth inhibition by restimulating the downstream pathways[69]. This effect was abrogated by inhibiting MET with PHA-665752 (a highly specific MET inhibitor), suggesting that lapatinib-induced growth inhibition may be abrogated through the activation of MET. Thus, the dual application of lapatinib and MET inhibitor may be a favorite model to overcome the lapatinib-resistant gastric cancer.

FUTURE PERSPECTIVES

This review has discussed some of a large number of data showing the clinical benefits of trastuzumab for treating HER2-positive gastric cancer. Combination therapy between trastuzumab and conventional chemotherapy is now cited as a standard first-line treatment for HER2 overexpressing gastric cancer in patient with advanced stage. This treatment remains to be under investigation for more potent utilization. Abundant clinical trials are planned or currently underway to evaluate the role of anti-HER2 agents in metastatic disease in combination with cytotoxic chemotherapy as well as with targeted therapy. As previously described, some studies with anti-HER2 combination treatments indicate that the use of more than one HER2-targeted therapy was superior to one of these agents alone in HER2 positive gastric cancer[63,69-71]. With the expansion of utilizing anti-HER2 agents, identifying the right combination of these various novel agents will be urgent to benefit the clinical outcomes in patients with advanced gastric cancer.

There still are several subjects to be discussed and settled for the advancement of HER2-targeted therapy in gastric cancer.

Dose increases of trastuzumab

To date, the clinical relevance of trastuzumab's kinetic variable is not defined. It has been considered that higher dosing may be required in patients with gastric cancer (Roche, Inc. Herceptin package insert. Available at: http://www.medsafe.govt.nz/profs/datasheet/h). Pharmacokinetics data showed in the ToGA study described that the trastuzumab clearance is 0.378 L/d based on the current standard dosing, 70% higher than the rates in trastuzumab-treated patients with breast cancer. The HELOISE study: a study of trastuzumab in combination with chemotherapy in patients with HER2-positive metastatic gastric or gastro-esophageal cancer is currently under investigation (NIH study trial registration number NCT01450696; ClinicalTrials.gov.). In this phase Ⅲ study, patients are randomized to either standard dosing or higher dosing arm (trastuzumab given at 8 mg/kg loading dose followed by 10 mg/kg every 3 wk) in combination with cisplatin based chemotherapy.

Possible candidates as a new biomarker

To date, there are no predictive biomarkers of response to trastuzumab. Thus, identifying a biomarker is one of the most importance in the development of an effective targeted agent. The NeoSphere trial, examining 16 different biomarkers, including HER2 expression, *PI3KCA* mutation, p95HER2, and insulin-like growth factor receptor expression in patients with breast cancer, resulted in failure of predicting response to pertuzumab[72]. In contrast, the presence of HER2 phosphorylation and low HER3 mRNA expression were associated with improved efficacy in patients with ovarian cancer treated with pertuzumab[73]. In some clinical trials, *PIK3CA* mutation or PTEN loss has been evaluated as a possible predictive biomarker. Therefor, to clarify the association between HER2 expression and PI3K/Akt pathway alterations is necessary to develop a new therapeutic strategy.

With regard to gastric cancer, several experimental studies showed the possibility of several factors which may be useful for predicting the efficacy of trastuzumab alone or combined chemotherapy. Trastuzumab resistant cells were noted to express the decreased amount of

p27KIP1 levels and increased CDK2 activity[74]. As a result, p27Kip1 level may be utilized as a marker of trastuzumab response and potential therapeutic target in trastuzumab-resistant gastric cancer. The serum level of HER2-extracellular domain (ECD) has been said to evaluate the HER2 status of patients with gastric cancer. Moreover, the serum HER2-ECD test could enable monitoring of the dynamic changes in HER2 status over the clinical course of the disease. It can be used as an easily accessible real-time biomarker for longitudinal assessments of disease status[75].

Mechanism of resistance

Resistance to trastuzumab is currently emerging in HER2 positive gastric cancers. PI3K pathway may confer resistance to tratuzumab in preclinical studies. Enhanced signaling from HER family receptors, including overexpression of HER3 and formation of high levels of HER2-HER3 heterodimers, and insulin-like growth factor-1 receptor (IGF-1R) are also correlated with PI3K signaling activity and resistance of anti-HER2 agents[76]. Recently, several studies have presented the mechanisms of resistance in patients with gastric cancer. Cancer stem cells may be postulated mediators of the chemoresistance. The c-Met inhibitor may be a promising target molecule for irinotecan-based chemotherapy of gastric cancer[77]. Heregulin 1 can cause resistance to lapatinib in gastric cancers *in vitro* through HER3 and Akt activation[78]. Interestingly, epithelial-mesenchymal transition plays an important role in acquiring resistance to HER2-directed treatment in HER2 positive gastric cancer[79].

CONCLUSION

HER2 signaling lead to receptor dimerization such as HER2/HER3 and positively mediates its downstream signals which lead to a variety of tumor biology. Dimerization of HER2 and HER3 is known to be the most active HER signaling dimer and HER3 may be a subsequent target of therapy in gastric cancer as well as HER2, especially for the diffuse histological type. Current development of technology for identifying HER2 expression is convincing and may result in the improved clinical outcome in trastuzumab applied patients with gastric cancer. There are several molecular HER2-targeted agents applied practically and showing clinical benefits compared to chemotherapy alone in gastric cancer. However, the efficacy of these agents has shown to be modest and unsatisfactory than that would be expected which may be due to the acquisition of resistance or an unmatched combination to known cytotoxic agents. To overcome the trastuzumab resistance, several examinations have elucidated the mechanisms of resistance in gastric cancer. Clinical and experimental studies using several other molecules, which shows synergistic activity by concomitant use with trastuzumab or has potential against receptors with acquired resistance, are under investigation. There still are several subjects to be discussed for the advancement of HER2-targeted therapy in gastric cancer, such as determining the suitable dose of trastuzumab, identifying a predictive biomarker. In conclusion, HER2-targeted therapy is now acceptable for management of patients with gastric cancer and recent studies including resistance-control will provide superior strategies for treating HER2-positive gastric cancer patients. In the meanwhile, considering the low expression (6%-23%) of HER2 and modest effect of ToGA trial (only 2.7 mo prolonged survival) in gastric cancer, the development of a novel molecular targeted therapy which has a more potent activity for gastric cancer might be desirable.

REFERENCES

1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

2 **Wagner AD**, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, Fleig WE. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2010; **(3)**: CD004064 [PMID: 20238327]

3 **Nashimoto A**, Akazawa K, Isobe Y, Miyashiro I, Katai H, Kodera Y, Tsujitani S, Seto Y, Furukawa H, Oda I, Ono H, Tanabe S, Kaminishi M. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. *Gastric Cancer* 2013; **16**: 1-27 [PMID: 22729699 DOI: 10.1007/s10120-012-0163-4]

4 **Murad AM**, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993; **72**: 37-41 [PMID: 8508427 DOI: 10.1002/1097-0142(19930701)72: 1<37: : AID-CNCR2820720109>3.0.CO; 2-P]

5 **Koizumi W**, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; **9**: 215-221 [PMID: 18282805 DOI: 10.1016/S1470-2045(08)70035-4]

6 **Van Cutsem E**, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML, Ajani JA. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24**: 4991-4997 [PMID: 17075117 DOI: 10.1200/JCO.2006.06.8429]

7 **Dank M**, Zaluski J, Barone C, Valvere V, Yalcin S, Peschel C, Wenczl M, Goker E, Cisar L, Wang K, Bugat R. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. *Ann Oncol* 2008; **19**: 1450-1457 [PMID: 18558665 DOI: 10.1093/annonc/mdn166]

8 **Cunningham D**, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358**: 36-46 [PMID: 18172173 DOI: 10.1056/NEJMoa073149]

9 **Okines AF**, Norman AR, McCloud P, Kang YK, Cunningham D. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. *Ann*

Oncol 2009; **20**: 1529-1534 [PMID: 19474114 DOI: 10.1093/annonc/mdp047]
10 **Fornaro L**, Lucchesi M, Caparello C, Vasile E, Caponi S, Ginocchi L, Masi G, Falcone A. Anti-HER agents in gastric cancer: from bench to bedside. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 369-383 [PMID: 21647199 DOI: 10.1038/nrgastro.2011.81]
11 **Akiyama T**, Sudo C, Ogawara H, Toyoshima K, Yamamoto T. The product of the human c-erbB-2 gene: a 185-kilodalton glycoprotein with tyrosine kinase activity. *Science* 1986; **232**: 1644-1646 [PMID: 3012781 DOI: 10.1126/science.3012781]
12 **Tai W**, Mahato R, Cheng K. The role of HER2 in cancer therapy and targeted drug delivery. *J Control Release* 2010; **146**: 264-275 [PMID: 20385184 DOI: 10.1016/j.jconrel.2010.04.009]
13 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Ruschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210]
14 **Olayioye MA**, Neve RM, Lane HA, Hynes NE. The ErbB signaling network: receptor heterodimerization in development and cancer. *EMBO J* 2000; **19**: 3159-3167 [PMID: 10880430 DOI: 10.1093/emboj/19.13.3159]
15 **Hsieh AC**, Moasser MM. Targeting HER proteins in cancer therapy and the role of the non-target HER3. *Br J Cancer* 2007; **97**: 453-457 [PMID: 17667926 DOI: 10.1038/sj.bjc.6603910]
16 **Okines A**, Cunningham D, Chau I. Targeting the human EGFR family in esophagogastric cancer. *Nat Rev Clin Oncol* 2011; **8**: 492-503 [PMID: 21468131 DOI: 10.1038/nrclinonc.2011.45]
17 **Li SG**, Li L. Targeted therapy in HER2-positive breast cancer. *Biomed Rep* 2013; **1**: 499-505 [PMID: 24648975]
18 **Komoto M**, Nakata B, Amano R, Yamada N, Yashiro M, Ohira M, Wakasa K, Hirakawa K. HER2 overexpression correlates with survival after curative resection of pancreatic cancer. *Cancer Sci* 2009; **100**: 1243-1247 [PMID: 19432892 DOI: 10.1111/j.1349-7006.2009.01176.x]
19 **Begnami MD**, Fukuda E, Fregnani JH, Nonogaki S, Montagnini AL, da Costa WL, Soares FA. Prognostic implications of altered human epidermal growth factor receptors (HERs) in gastric carcinomas: HER2 and HER3 are predictors of poor outcome. *J Clin Oncol* 2011; **29**: 3030-3036 [PMID: 21709195 DOI: 10.1200/JCO.2010.33.6313]
20 **Zhang XL**, Yang YS, Xu DP, Qu JH, Guo MZ, Gong Y, Huang J. Comparative study on overexpression of HER2/neu and HER3 in gastric cancer. *World J Surg* 2009; **33**: 2112-2118 [PMID: 19636613 DOI: 10.1007/s00268-009-0142-z]
21 **Sheng WQ**, Huang D, Ying JM, Lu N, Wu HM, Liu YH, Liu JP, Bu H, Zhou XY, Du X. HER2 status in gastric cancers: a retrospective analysis from four Chinese representative clinical centers and assessment of its prognostic significance. *Ann Oncol* 2013; **24**: 2360-2364 [PMID: 23788757 DOI: 10.1093/annonc/mdt232]
22 **Gravalos C**, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. *Ann Oncol* 2008; **19**: 1523-1529 [PMID: 18441328 DOI: 10.1093/annonc/mdn169]
23 **Yarden Y**. The EGFR family and its ligands in human cancer. signalling mechanisms and therapeutic opportunities. *Eur J Cancer* 2001; **37** Suppl 4: S3-S8 [PMID: 11597398 DOI: 10.1016/S0959-8049(01)00230-1]
24 **Tanner M**, Hollmén M, Junttila TT, Kapanen AI, Tommola S, Soini Y, Helin H, Salo J, Joensuu H, Sihvo E, Elenius K, Isola J. Amplification of HER-2 in gastric carcinoma: association with Topoisomerase IIalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. *Ann Oncol* 2005; **16**: 273-278 [PMID: 15668283 DOI: 10.1093/annonc/mdi064]
25 **Cho J**, Jeong J, Sung J, Sung CO, Kim KM, Park CK, Choi MG, Sohn TS, Bae JM, Kim S. A large cohort of consecutive patients confirmed frequent HER2 positivity in gastric carcinomas with advanced stages. *Ann Surg Oncol* 2013; **20** Suppl 3: S477-S484 [PMID: 23274580 DOI: 10.1245/s10434-012-2818-0]
26 **Moelans CB**, van Diest PJ, Milne AN, Offerhaus GJ. Her-2/neu testing and therapy in gastroesophageal adenocarcinoma. *Patholog Res Int* 2011; **2011**: 674182 [PMID: 21188213]
27 **Qiu MZ**, Li Q, Wang ZQ, Liu TS, Liu Q, Wei XL, Jin Y, Wang DS, Ren C, Bai L, Zhang DS, Wang FH, Li YH, Xu RH. HER2-positive patients receiving trastuzumab treatment have a comparable prognosis with HER2-negative advanced gastric cancer patients: a prospective cohort observation. *Int J Cancer* 2014; **134**: 2468-2477 [PMID: 24155030 DOI: 10.1002/ijc.28559]
28 **Kim KC**, Koh YW, Chang HM, Kim TH, Yook JH, Kim BS, Jang SJ, Park YS. Evaluation of HER2 protein expression in gastric carcinomas: comparative analysis of 1,414 cases of whole-tissue sections and 595 cases of tissue microarrays. *Ann Surg Oncol* 2011; **18**: 2833-2840 [PMID: 21468783 DOI: 10.1245/s10434-011-1695-2]
29 **Jørgensen JT**. Role of human epidermal growth factor receptor 2 in gastric cancer: biological and pharmacological aspects. *World J Gastroenterol* 2014; **20**: 4526-4535 [PMID: 24782605 DOI: 10.3748/wjg.v20.i16.4526]
30 **Nakajima M**, Sawada H, Yamada Y, Watanabe A, Tatsumi M, Yamashita J, Matsuda M, Sakaguchi T, Hirao T, Nakano H. The prognostic significance of amplification and overexpression of c-met and c-erb B-2 in human gastric carcinomas. *Cancer* 1999; **85**: 1894-1902 [PMID: 10223227 DOI: 10.1002/(SICI)1097-0142(19990501)85: 9<1894: : AID-CNCR3>3.0.CO; 2-J]
31 **Park DI**, Yun JW, Park JH, Oh SJ, Kim HJ, Cho YK, Sohn CI, Jeon WK, Kim BI, Yoo CH, Son BH, Cho EY, Chae SW, Kim EJ, Sohn JH, Ryu SH, Sepulveda AR. HER-2/neu amplification is an independent prognostic factor in gastric cancer. *Dig Dis Sci* 2006; **51**: 1371-1379 [PMID: 16868827 DOI: 10.1007/s10620-005-9057-1]
32 **Van Cutsem E**, Bang YJ, Feng-Yi F, Xu JM, Lee KW, Jiao SC, Chong JL, Lopez-Sanchez RI, Price T, Gladkov O, Stoss O, Hill J, Ng V, Lehle M, Thomas M, Kiermaier A, Ruschoff J. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. *Gastric Cancer* 2014 Jul 20; Epub ahead of print [PMID: 25038874 DOI: 10.1007/s10120-014-0402-y]
33 **Terashima M**, Kitada K, Ochiai A, Ichikawa W, Kurahashi I, Sakuramoto S, Katai H, Sano T, Imamura H, Sasako M. Impact of expression of human epidermal growth factor receptors EGFR and ERBB2 on survival in stage II/III gastric cancer. *Clin Cancer Res* 2012; **18**: 5992-6000 [PMID: 22977193 DOI: 10.1158/1078-0432.CCR-12-1318]
34 **Grabsch H**, Sivakumar S, Gray S, Gabbert HE, Müller W. HER2 expression in gastric cancer: Rare, heterogeneous and of no prognostic value - conclusions from 924 cases of two independent series. *Cell Oncol* 2010; **32**: 57-65 [PMID: 20208134]
35 **Janjigian YY**, Werner D, Pauligk C, Steinmetz K, Kelsen DP, Jäger E, Altmannsberger HM, Robinson E, Tafe LJ, Tang LH, Shah MA, Al-Batran SE. Prognosis of metastatic gastric and gastroesophageal junction cancer by HER2 status: a European and USA International collaborative analysis. *Ann Oncol* 2012; **23**: 2656-2662 [PMID: 22689179 DOI: 10.1093/annonc/mds104]
36 **Ajani JA**, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, Vynnychenko I, Garin A, Lang I, Falcon S. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. *J Clin Oncol* 2010; **28**: 1547-1553 [PMID: 20159816 DOI: 10.1200/JCO.2009.25.4706]
37 **Vanhoefer U**, Rougier P, Wilke H, Ducreux MP, Lacave AJ, Van Cutsem E, Planker M, Santos JG, Piedbois P, Paillot B, Bodenstein H, Schmoll HJ, Bleiberg H, Nordlinger B, Couvreur

ML, Baron B, Wils JA. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: A trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. *J Clin Oncol* 2000; **18**: 2648-2657 [PMID: 10894863]

38 **Lordick F**, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, Kurteva G, Volovat C, Moiseyenko VM, Gorbunova V, Park JO, Sawaki A, Celik I, Götte H, Melezínková H, Moehler M. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; **14**: 490-499 [PMID: 23594786 DOI: 10.1016/S1470-2045(13)70102-5]

39 **Bozzetti C**, Negri FV, Lagrasta CA, Crafa P, Bassano C, Tamagnini I, Gardini G, Nizzoli R, Leonardi F, Gasparro D, Camisa R, Cavalli S, Silini EM, Ardizzoni A. Comparison of HER2 status in primary and paired metastatic sites of gastric carcinoma. *Br J Cancer* 2011; **104**: 1372-1376 [PMID: 21487407 DOI: 10.1038/bjc.2011.121]

40 **Hofmann M**, Stoss O, Shi D, Büttner R, van de Vijver M, Kim W, Ochiai A, Rüschoff J, Henkel T. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. *Histopathology* 2008; **52**: 797-805 [PMID: 18422971 DOI: 10.1111/j.1365-2559.2008.03028.x]

41 **Rüschoff J**, Dietel M, Baretton G, Arbogast S, Walch A, Monges G, Chenard MP, Penault-Llorca F, Nagelmeier I, Schlake W, Höfler H, Kreipe HH. HER2 diagnostics in gastric cancer-guideline validation and development of standardized immunohistochemical testing. *Virchows Arch* 2010; **457**: 299-307 [PMID: 20665045 DOI: 10.1007/s00428-010-0952-2]

42 **Lee J**, Kim S, Kim P, Liu X, Lee T, Kim KM, Do IG, Park JO, Park SH, Jang J, Hoe N, Harvie G, Kuller A, Jain A, Meyer G, Leesman G, Park YS, Choi MG, Sohn TS, Bae JM, Lim HY, Singh S, Kang WK. A novel proteomics-based clinical diagnostics technology identifies heterogeneity in activated signaling pathways in gastric cancers. *PLoS One* 2013; **8**: e54644 [PMID: 23372746 DOI: 10.1371/journal.pone.0054644]

43 **Gomez-Martin C**, Plaza JC, Pazo-Cid R, Salud A, Pons F, Fonseca P, Leon A, Alsina M, Visa L, Rivera F, Galan MC, Del Valle E, Vilardell F, Iglesias M, Fernandez S, Landolfi S, Cuatrecasas M, Mayorga M, Jose Paulés M, Sanz-Moncasi P, Montagut C, Garralda E, Rojo F, Hidalgo M, Lopez-Rios F. Level of HER2 gene amplification predicts response and overall survival in HER2-positive advanced gastric cancer treated with trastuzumab. *J Clin Oncol* 2013; **31**: 4445-4452 [PMID: 24127447 DOI: 10.1200/JCO.2013.48.9070]

44 **Roukos DH**. Targeting gastric cancer with trastuzumab: new clinical practice and innovative developments to overcome resistance. *Ann Surg Oncol* 2010; **17**: 14-17 [PMID: 19841980 DOI: 10.1245/s10434-009-0766-0]

45 **Palacio S**, Loaiza-Bonilla A, Kittaneh M, Kyriakopoulos C, Ochoa RE, Escobar M, Arango B, Restrepo MH, Merchan JR, Rocha Lima CM, Hosein PJ. Successful use of Trastuzumab with anthracycline-based chemotherapy followed by trastuzumab maintenance in patients with advanced HER2-positive gastric cancer. *Anticancer Res* 2014; **34**: 301-306 [PMID: 24403478]

46 **Satoh T**, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, Tsuji A, Omuro Y, Li J, Wang JW, Miwa H, Qin SK, Chung IJ, Yeh KH, Feng JF, Mukaiyama A, Kobayashi M, Ohtsu A, Bang YJ. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. *J Clin Oncol* 2014; **32**: 2039-2049 [PMID: 24868024 DOI: 10.1200/JCO.2013.53.6136]

47 **Kurokawa Y**, Sugimoto N, Miwa H, Tsuda M, Nishina S, Okuda H, Imamura H, Gamoh M, Sakai D, Shimokawa T, Komatsu Y, Doki Y, Tsujinaka T, Furukawa H. Phase II study of trastuzumab in combination with S-1 plus cisplatin in HER2-positive gastric cancer (HERBIS-1). *Br J Cancer* 2014; **110**: 1163-1168 [PMID: 24473399 DOI: 10.1038/bjc.2014.18]

48 **Cui H**, Cheng Y, Piao SZ, Xu YJ, Sun HH, Cui X, Li XZ, Zhang SN, Piao LZ, Jin YM, Lin ZH, Shen XH. Correlation between HER-2/neu(erbB-2) expression level and therapeutic effect of combination treatment with HERCEPTIN and chemotherapeutic agents in gastric cancer cell lines. *Cancer Cell Int* 2014; **14**: 10 [PMID: 24472145 DOI: 10.1186/1475-2867-14-10]

49 **Nahta R**, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. *Cancer Res* 2004; **64**: 2343-2346 [PMID: 15059883 DOI: 10.1158/0008-5472.CAN-03-3856]

50 **Scheuer W**, Friess T, Burtscher H, Bossenmaier B, Endl J, Hasmann M. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. *Cancer Res* 2009; **69**: 9330-9336 [PMID: 19934333 DOI: 10.1158/0008-5472.CAN-08-4597]

51 **Kang YK**, Rha SY, Tassone P, Barriuso J, Yu R, Szado T, Garg A, Bang YJ. A phase IIa dose-finding and safety study of first-line pertuzumab in combination with trastuzumab, capecitabine and cisplatin in patients with HER2-positive advanced gastric cancer. *Br J Cancer* 2014; **111**: 660-666 [PMID: 24960402 DOI: 10.1038/bjc.2014.356]

52 **Wood ER**, Truesdale AT, McDonald OB, Yuan D, Hassell A, Dickerson SH, Ellis B, Pennisi C, Horne E, Lackey K, Alligood KJ, Rusnak DW, Gilmer TM, Shewchuk L. A unique structure for epidermal growth factor receptor bound to GW572016 (Lapatinib): relationships among protein conformation, inhibitor off-rate, and receptor activity in tumor cells. *Cancer Res* 2004; **64**: 6652-6659 [PMID: 15374980 DOI: 10.1158/0008-5472.CAN-04-1168]

53 **Iqbal S**, Goldman B, Fenoglio-Preiser CM, Lenz HJ, Zhang W, Danenberg KD, Shibata SI, Blanke CD. Southwest Oncology Group study S0413: a phase II trial of lapatinib (GW572016) as first-line therapy in patients with advanced or metastatic gastric cancer. *Ann Oncol* 2011; **22**: 2610-2615 [PMID: 21415234 DOI: 10.1093/annonc/mdr021]

54 **Shimoyama S**. Unraveling trastuzumab and lapatinib inefficiency in gastric cancer: Future steps (Review). *Mol Clin Oncol* 2014; **2**: 175-181 [PMID: 24649329]

55 **Oshima Y**, Tanaka H, Murakami H, Ito Y, Furuya T, Kondo E, Kodera Y, Nakanishi H. Lapatinib sensitivities of two novel trastuzumab-resistant HER2 gene-amplified gastric cancer cell lines. *Gastric Cancer* 2014; **17**: 450-462 [PMID: 23948998 DOI: 10.1007/s10120-013-0290-6]

56 **Barok M**, Tanner M, Köninki K, Isola J. Trastuzumab-DM1 is highly effective in preclinical models of HER2-positive gastric cancer. *Cancer Lett* 2011; **306**: 171-179 [PMID: 21458915 DOI: 10.1016/j.canlet.2011.03.002]

57 **Barros-Silva JD**, Leitão D, Afonso L, Vieira J, Dinis-Ribeiro M, Fragoso M, Bento MJ, Santos L, Ferreira P, Rêgo S, Brandão C, Carneiro F, Lopes C, Schmitt F, Teixeira MR. Association of ERBB2 gene status with histopathological parameters and disease-specific survival in gastric carcinoma patients. *Br J Cancer* 2009; **100**: 487-493 [PMID: 19156142 DOI: 10.1038/sj.bjc.6604885]

58 **Gong SJ**, Jin CJ, Rha SY, Chung HC. Growth inhibitory effects of trastuzumab and chemotherapeutic drugs in gastric cancer cell lines. *Cancer Lett* 2004; **214**: 215-224 [PMID: 15363548 DOI: 10.1016/j.canlet.2004.04.029]

59 **Dungo RT**, Keating GM. Afatinib: first global approval. *Drugs* 2013; **73**: 1503-1515 [PMID: 23982599 DOI: 10.1007/s40265-013-0111-6]

60 **Matsuoka T**, Yashiro M. The Role of PI3K/Akt/mTOR Signaling in Gastric Carcinoma. *Cancers* (Basel) 2014; **6**: 1441-1463 [PMID: 25003395 DOI: 10.3390/cancers6031441]

61 **Banerji U**. Heat shock protein 90 as a drug target: some like

it hot. *Clin Cancer Res* 2009; **15**: 9-14 [PMID: 19118027 DOI: 10.1158/1078-0432.CCR-08-0132]
62 **Eccles SA**, Massey A, Raynaud FI, Sharp SY, Box G, Valenti M, Patterson L, de Haven Brandon A, Gowan S, Boxall F, Aherne W, Rowlands M, Hayes A, Martins V, Urban F, Boxall K, Prodromou C, Pearl L, James K, Matthews TP, Cheung KM, Kalusa A, Jones K, McDonald E, Barril X, Brough PA, Cansfield JE, Dymock B, Drysdale MJ, Finch H, Howes R, Hubbard RE, Surgenor A, Webb P, Wood M, Wright L, Workman P. NVP-AUY922: a novel heat shock protein 90 inhibitor active against xenograft tumor growth, angiogenesis, and metastasis. *Cancer Res* 2008; **68**: 2850-2860 [PMID: 18413753 DOI: 10.1158/0008-5472.CAN-07-5256]
63 **Wainberg ZA**, Anghel A, Rogers AM, Desai AJ, Kalous O, Conklin D, Ayala R, O'Brien NA, Quadt C, Akimov M, Slamon DJ, Finn RS. Inhibition of HSP90 with AUY922 induces synergy in HER2-amplified trastuzumab-resistant breast and gastric cancer. *Mol Cancer Ther* 2013; **12**: 509-519 [PMID: 23395886 DOI: 10.1158/1535-7163.MCT-12-0507]
64 **Kunii K**, Davis L, Gorenstein J, Hatch H, Yashiro M, Di Bacco A, Elbi C, Lutterbach B. FGFR2-amplified gastric cancer cell lines require FGFR2 and Erbb3 signaling for growth and survival. *Cancer Res* 2008; **68**: 2340-2348 [PMID: 18381441 DOI: 10.1158/0008-5472.CAN-07-5229]
65 **Nam HJ**, Ching KA, Kan J, Kim HP, Han SW, Im SA, Kim TY, Christensen JG, Oh DY, Bang YJ. Evaluation of the antitumor effects and mechanisms of PF00299804, a pan-HER inhibitor, alone or in combination with chemotherapy or targeted agents in gastric cancer. *Mol Cancer Ther* 2012; **11**: 439-451 [PMID: 22135232 DOI: 10.1158/1535-7163.MCT-11-0494]
66 **Sierra JR**, Tsao MS. c-MET as a potential therapeutic target and biomarker in cancer. *Ther Adv Med Oncol* 2011; **3**: S21-S35 [PMID: 22128285 DOI: 10.1177/1758834011422557]
67 **Lai AZ**, Abella JV, Park M. Crosstalk in Met receptor oncogenesis. *Trends Cell Biol* 2009; **19**: 542-551 [PMID: 19758803 DOI: 10.1016/j.tcb.2009.07.002]
68 **Engelman JA**, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, Lindeman N, Gale CM, Zhao X, Christensen J, Kosaka T, Holmes AJ, Rogers AM, Cappuzzo F, Mok T, Lee C, Johnson BE, Cantley LC, Jänne PA. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007; **316**: 1039-1043 [PMID: 17463250 DOI: 10.1126/science.1141478]
69 **Chen CT**, Kim H, Liska D, Gao S, Christensen JG, Weiser MR. MET activation mediates resistance to lapatinib inhibition of HER2-amplified gastric cancer cells. *Mol Cancer Ther* 2012; **11**: 660-669 [PMID: 22238368 DOI: 10.1158/1535-7163.MCT-11-0754]
70 **Singh R**, Kim WJ, Kim PH, Hong HJ. Combined blockade of HER2 and VEGF exerts greater growth inhibition of HER2-overexpressing gastric cancer xenografts than individual blockade. *Exp Mol Med* 2013; **45**: e52 [PMID: 24176949 DOI: 10.1038/emm.2013.111]
71 **Yamashita-Kashima Y**, Iijima S, Yorozu K, Furugaki K, Kurasawa M, Ohta M, Fujimoto-Ouchi K. Pertuzumab in combination with trastuzumab shows significantly enhanced antitumor activity in HER2-positive human gastric cancer xenograft models. *Clin Cancer Res* 2011; **17**: 5060-5070 [PMID: 21700765 DOI: 10.1158/1078-0432.CCR-10-2927]
72 **Sendur MA**, Aksoy S, Altundag K. Pertuzumab in HER2-positive breast cancer. *Curr Med Res Opin* 2012; **28**: 1709-1716 [PMID: 22953713 DOI: 10.1185/03007995.2012.728132]
73 **Nagumo Y**, Faratian D, Mullen P, Harrison DJ, Hasmann M, Langdon SP. Modulation of HER3 is a marker of dynamic cell signaling in ovarian cancer: implications for pertuzumab sensitivity. *Mol Cancer Res* 2009; **7**: 1563-1571 [PMID: 19737968 DOI: 10.1158/1541-7786.MCR-09-0101]
74 **Nahta R**, Takahashi T, Ueno NT, Hung MC, Esteva FJ. P27(kip1) down-regulation is associated with trastuzumab resistance in breast cancer cells. *Cancer Res* 2004; **64**: 3981-3986 [PMID: 15173011 DOI: 10.1158/0008-5472.CAN-03-3900]
75 **Oyama K**, Fushida S, Tsukada T, Kinoshita J, Watanabe T, Shoji M, Nakanuma S, Okamoto K, Sakai S, Makino I, Nakamura K, Hayashi H, Inokuchi M, Nakagawara H, Miyashita T, Tajima H, Takamura H, Ninomiya I, Kitagawa H, Fujimura T, Tajiri R, Ooi A, Ohta T. Evaluation of serum HER2-ECD levels in patients with gastric cancer. *J Gastroenterol* 2014 Feb 21; Epub ahead of print [PMID: 24557054]
76 **Martin HL**, Smith L, Tomlinson DC. Multidrug-resistant breast cancer: current perspectives. *Breast Cancer* (Dove Med Press) 2014; **6**: 1-13 [PMID: 24648765]
77 **Yashiro M**, Nishii T, Hasegawa T, Matsuzaki T, Morisaki T, Fukuoka T, Hirakawa K. A c-Met inhibitor increases the chemosensitivity of cancer stem cells to the irinotecan in gastric carcinoma. *Br J Cancer* 2013; **109**: 2619-2628 [PMID: 24129235 DOI: 10.1038/bjc.2013.638]
78 **Sato Y**, Yashiro M, Takakura N. Heregulin induces resistance to lapatinib-mediated growth inhibition of HER2-amplified cancer cells. *Cancer Sci* 2013; **104**: 1618-1625 [PMID: 24112719 DOI: 10.1111/cas.12290]
79 **Kim HP**, Han SW, Song SH, Jeong EG, Lee MY, Hwang D, Im SA, Bang YJ, Kim TY. Testican-1-mediated epithelial-mesenchymal transition signaling confers acquired resistance to lapatinib in HER2-positive gastric cancer. *Oncogene* 2014; **33**: 3334-3341 [PMID: 23873022 DOI: 10.1038/onc.2013.285]

P- Reviewer: Kapischke M, Lee JI, Omboni S, Pavlidis TE, Tang Y
S- Editor: Tian YL **L- Editor**: A **E- Editor**: Lu YJ

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DOI: 10.12998/wjcc.v3.i1.52

World J Clin Cases 2015 January 16; 3(1): 52-57
ISSN 2307-8960 (online)

Implant biomaterials: A comprehensive review

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Received: July 23, 2014
Peer-review started: July 25, 2014
First decision: September 16, 2014
Revised: September 29, 2014
Accepted: November 17, 2014
Article in press: December 23, 2014
Published online: January 16, 2015

Abstract

Appropriate selection of the implant biomaterial is a key factor for long term success of implants. The biologic environment does not accept completely any material so to optimize biologic performance, implants should be selected to reduce the negative biologic response while maintaining adequate function. Every clinician should always gain a thorough knowledge about the different biomaterials used for the dental implants. This article makes an effort to summarize various dental biomaterials which were used in the past and as well as the latest material used now.

Key words: Biomaterials; Zirconium; Surface roughness; Ceramic; Corrosion

Core tip: This article makes an effort to review and summarize all the biomaterials used for dental implants. Materials in this article are discussed according to the era in which they were used. This review also covers the pros and cons related to these materials. Recent trends in the field of dental implants biomaterials and why these materials are superior over the previous ones. The content of the article are clinically significant and will prove to be helpful for readers to make decision while choosing implant system.

Saini M, Singh Y, Arora P, Arora V, Jain K. Implant biomaterials: A comprehensive review. *World J Clin Cases* 2015; 3(1): 52-57 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i1/52.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i1.52

INTRODUCTION

In attempt to replace a missing tooth many materials have been tried as an implant . With all the advancements and developments in the science and technology, the materials available for dental implants also improved[1].

Implants are traceable to early Egyptians and South Central American cultures and with all the developments in material and biological science we have come a long way. Improvements in both the quality and quantity of the implant material have made this treatment modality very promising, budding and highly practiced in today's era. The Earliest dental implants of stone and ivory were

Table 1 Implant materials can be classified based on the type of material used and the biologic response they elicit when implanted[3]

Biodynamic activity	Chemical composition		
	Metals	Ceramics	Polymers
Biotolerant	Gold		Polyethylene
	Co-Cr alloys		Polyamide
	Stainless steel		Polymethylmethacrylate
	Niobium		Polytetrafluroethylene
	Tantalum		Polyurethane
Bio inert	Commercially pure titanium	Al oxide	
	Titanium alloy (Ti-6AL-4U)	Zirconium oxide	
Bioactive		Hydroxyapatite	
		Tricalcium phosphate	
		Bio glass	
		Carbon-silicon	

reported in China and Egypt. Also Gold and Ivory dental implants were reported in the 16th and 17th centuries[2]. Metal Implants of Gold, Lead, Iridium, Tantalum, stainless steel and cobalt alloy were also mentioned in the early 20th century. Between these two periods a variety of polymers, including ultrahigh molecular weight polyurethane, polyamide, polymethylmethacrylate resin, polytetrafluoroethylene, and polyurethane, have been used as dental implant. In the present era, due to the extensive research work and advancements in the field of biomaterials available for dental implants, newer materials came into being such as zirconia, roxolid, surface modified titanium implants. These materials not only fulfill the functional requirements but are also esthetically pleasing. This article makes an effort to review various implant materials, their properties and the various pros and cons associated to those materials. To identify relevant literature an electronic search was performed of Pubmed database using the following keywords, implant biomaterials, implant material biocompatibility, recent trends in implant dentistry. The searches were limited to full text articles in English and those with associated abstracts. All the articles published from 1955 to 2012 are included in this review. All the articles in the language other than English and the articles related to surface coated implants and case reports are excluded.

Materials in this article are divided according to the era they were evolved as an implant material[3-6] (Table 1).

PROPERTIES OF AN IMPLANT BIOMATERIAL

Bulk properties[2,7]

Modulus of elasticity: Implant material with modulus of elasticity comparable to bone (18 GPa) must be selected to ensure more uniform distribution of stress at implant and to minimize the relative movement at implant bone interface.

Tensile, compressive and shear strength: An implant material should have high tensile and compressive strength to prevent fractures and improve functional stability. Improved stress transfer from the implant to bone is reported interfacial shear strength is increased, and lower stresses in the implant.

Yield strength, fatigue strength: An implant material should have high yield strength and fatigue strength to prevent brittle fracture under cyclic loading.

Ductility: According to ADA a minimum ductility of 8% is required for dental implant. Ductility in implant is necessary for contouring and shaping of an implant.

Hardness and Toughness: Increase in hardness decreases the incidence of wear of implant material and increase in toughness prevents fracture of the implants.

Surface properties

Surface tension and surface energy: It determines the wettability of implant by wetting fluid (blood) and cleanliness of implant surface. Osteoblasts show improved adhesion on implant surface. Surface energy also affects adsorption of proteins[2].

Surface roughness: Alterations in the surface roughness of implants influence the response of cells and tissue by increasing the surface area of the implant adjacent to bone and thereby improving cell attachment to the bone.

Implant surfaces have been classified on different criteria, such as roughness, texture and orientation of irregularities[8,9]: (1) Wennerberg and coworkers have divided implant surfaces according to the surface roughness as: Minimally rough (0.5-1 m), Intermediately rough (1-2 m), Rough (2-3 m); (2) The implant surface can also be classified according to their texture as: concave texture (mainly by additive treatments like hydroxyapatite (HA) coating and titanium plasma spraying),convex texture (mainly by subtractive treatment like etching and blasting); and (3) The implant surface can also be classified according to orientation of surface irregularities: Isotropic surfaces: have similar topography independent of measuring direction; Anisotropic surfaces: have clear directionality and vary considerably in roughness.

Biocompatibility

This is property of implant material to show favorable response in given biological environment in a particular function. It depends on the corrosion resistance and cytotoxicity of corrosion products.

Corrosion and corrosion resistance[9-11]: It is the loss of metallic ions from metal surface to the surrounding environment. Following types of corrosion are seen.

Crevice corrosion: It occurs in narrow region like implant screw-bone interface. When metallic ions dissolve, they can create a positively charged local environment in the crevice, which may provide opportunities for crevice corrosion.

Pitting corrosion: Pitting corrosion occurs in an implant with a small surface pit. In this the metal ions dissolve and combine with chloride ions. Pitting corrosion leads to roughening of the surface by formation of pits.

Galvanic corrosion: This occurs because of difference in the electrical gradients. Nickel and chrome ions from artificial prosthesis may pass to peri-implant tissues due to leakage of saliva between implant and superstructure .This may result in bone reabsorption and also affect the stability of the implant and eventually cause failure.

Electrochemical corrosion: In this anodic oxidation and cathodic reduction takes place resulting in metal deterioration as well as charge transfer *via* electrons. This type of corrosion can be prevented by presence of passive oxide layer on metal surface.

Clinical significance of corrosion: Implant bio-material should be corrosion resistant. Corrosion can result in roughening of the surface, weakening of the restoration, release of elements from the metal or alloy, toxic reactions. Adjacent tissues may be discolored and allergic reactions in patients may result due to release of elements.

ANCIENT ERA (through AD 1000)

Implants are traceable to ancient egyptian and south American civilization. There is a skull form pre Columbian era in which artificial tooth is carved with dark stone. Albucasis de condue Arabian surgeon, credited with a written paper of transplants as a means of replacing missing teeth[12].

Foundational period (1800-1910)

This era is the beginning of Endosseous oral implantology. Maggiolo in 1809 used gold in the shape of the tooth root. In 1887 Harris reported the use of teeth made of porcelain into which lead coated platinum posts were fitted. In 1890, Zamenski reported the implantation of teeth made of porcelain, gutta-percha, and rubber and in 1898 R.E payne places silver capsule in the tooth socket. In the early 1900's lambotte fabricated implants of aluminum, silver, brass, red copper, magnesium, gold and soft steel plated with gold and nickel[11,12].

Premodern era (1901-1930)

In 1901 a technique of capsule implantation was reported in dental cosmos which was presented by R.E payne at the clinics of third international dental congress. In 1903, Sholl in Pennsylvania, implanted porcelain tooth which was having a corrugated porcelain root. In 1913, Dr. Edward J. Greenfield introduced into the alveoli the basket of iridium and 24 carat gold. E. J Greenfield also introduced the concept of submerged implant, the healing tissue and dental implant immobility[12].

Dawn of the modern era (1935-1978)

In this era, synthetic polymers, ceramics and metal alloys started replacing the naturally derived materials because they have better performance and more predictable results than the natural ones.

Strock anchored a vitallium screw within bone and immediately mounted it with a porcelain crown. He was the first one to achieve an implant survival for 15 years[12,13].

POLYMERS

The early work with the methyl methacrylate resin implants met mostly with failures[14-18]. However, in 1969, Hodosh reported that polymers were biologically tolerable substances[16,17]. Research on polymethacrylate tooth-replica implants led to the development of the polymer dental implant concept by Milton Hodosh. In replacing a natural tooth, the polymer replica proved to be ideal for the restoration of function and appearance[18].

Polymers were selected for the following reasons[17]: (1) The physical characteristics of the polymers can be altered based on their use as their composition may be changed easily. Polymers can be changed in to more porous or softer form; (2) Polymers can be manipulated easily and allow better reproduction; (3) Polymers do not generate microwaves or electrolytic current as do metals; (4) They show fibrous connective tissue attachment; (5) They can be easily microscopically evaluated than with metals; and (6) They are more esthetically pleasing. There are some disadvantages: (1) inferior mechanical properties; (2) lack of adhesion to living tissues; and (3) adverse immunologic reactions.

Metals and metal alloys

Metals have biomechanical properties which made them suitable as an implant material. Besides these properties metals are also easy to process and have good finish. Metallic implants can be sterilized by the common sterilization procedure which makes them easy to use. But due to advancements with time and low success rates with metals (gold, stainless steel, cobalt-chromium), these materials have now become obsolete and are now replaced by newer ones. Titanium (Ti) and its alloys

(mainly Ti-6Al-4V) have become the metals of choice for dental implants. However, prosthetic components of the implants are still made from gold alloys, stainless steel, and cobalt-chromium and nickel-chromium alloys[3].

Cobalt chromium alloys

They are used in cast or cast and annealed metallurgic conditions. It allows the manufacture of customized implants, such as subperiosteal frames. The elemental composition of this alloy includes cobalt, chromium and molybdenum as the major elements. Cobalt provides continuous phase for basic properties. Chromium provides corrosion resistance through the oxide surface. Molybdenum provides strength and bulk corrosion resistance. Nickels biocorrosive product and carbon must be accurately controlled to enhance mechanical properties, such as ductility[19,20].

Iron-Chromium-Nickel Based Alloys

Stainless steel alloys are used for orthopedic and implant devices. Iron based alloys are used for ramus blade, ramus frame, stabilizer pins and some mucosal insert. The alloy is most prone to pitting corrosion and care must be taken to use and retain the passiviated (oxide) surface condition, as this alloy contains nickel as a major element. Its use in allergic patients must be avoided. They have high galvanic potentials and corrosion resistance.This can result in galvanic coupling and biocorrosion, if titanium, cobalt, zirconium or carbon implant biomaterials are used with it[8].

IMPLANTS IN 21ST CENTURY

Titanium

Titanium has a good record of being used successfully as an implant material and this success with titanium implants is credited to its excellent biocompatibility due to the formation of stable oxide layer on its surface[21,22].

The commercially pure titanium (cpTi) is classified into 4 grades which differ in their oxygen content. Grade 4 is having the most (0.4%) and grade 1 the least (0.18%) oxygen content. The mechanical differences that exist between the different grades of cpTi is primarily because of the contaminants that are present in minute quantities. Iron is added for corrosion resistance and aluminum is added for increased strength and decreased density, while vanadium acts as an aluminum scavenger to prevent corrosion. Hexagonal close-packed crystal lattice of Ti is called the α-Ti (α-phase). On heating it at 883 ℃ phase transformation occurs from hexagonal close packed to body-centered cubic lattice or β- phase. Ti is a reactive as it forms spontaneously a dense oxide film at its surface. Ti is a dimorphic metal i.e. below 882.5 ℃ it exists as α-phase and above this temperature it changes form α- phase to β phase. Because of the high passivity, controlled thickness, rapid formation, ability to repair itself instantaneously if damaged, resistance to chemical attack, catalytic activity for a number of chemical reactions, and modulus of elasticity compatible with that of bone o, Ti is the material of choice for intraosseous applications[3,22-25].

Disadvantage: There is esthetic issue due to gray color of titanium and this is more pronounced when soft tissue situation is not optimal and the dark color shines through the thin mucosa.

Titanium alloys Ti6Al4V

Titanium reacts with several other elements for eg: silver, Al, Ar, Cu, Fe, Ur, Va and Zn to form alloys. Titanium alloys exists in three forms alpha, beta and α-β. These types originate when pure titanium is heated with elements Al, Va in certain concentrations and cooled, these type originate. These added elements play like Phase- condition stabilizers. Aluminum is alpha-phase condition stabilizer and it also increases the strength and decrease the weight of the alloy. Vanadium acts as beta-phase stabilizer. The temperature at which α-to β transformation occurs changes to a range of temperatures as Al or Va is added to Ti. Both α and β forms exist in this range. Temperatures to which the desired form is present can be obtained by quenching alloy at room temperature.To increase the strength, these alloys may be heat treated. The alloys most commonly used for dental implants are of the alpha-beta variety. The most common contains 6% Al and 4% Va. (Ti 6 Al 4V)[3,26].

Ceramics

Ceramics were used for surgical implant devices because of their inert behavior and good strength and physical properties such as minimum thermal and electrical conductivity. Certain properties of ceramics like low ductility and brittleness has limited the use of ceramics[3].

Aluminum, titanium and zirconium oxides

Root form or endosteal plate form, and pin-type dental implants are generally made from High ceramics from aluminum, titanium and zirconium oxides. The compressive, tensile and bending strengths exceed the strength of compact bone by 3 to 5 times. These properties combined with high moduli of elasticity and especially with fatigue and fracture strength have resulted in specialized design requirements for this class of biomaterials[8].

MODERN ERA

Modern Implant dentistry is delineated from the period of mid 1930's to the present. Today's popularity of implants in dentistry is attributed to the developments and the research work which laid the foundation of this field. It is because of all this work in the past that we are seeing the emergence of implant concepts developing into the most refined and popularly utilized systems.

In recent years the treatment options and modalities for achieving optimal functional and aesthetic outcomes with implant restorations have clearly changed. Pure titanium is generally preferred for dental implant because

of its excellent biocompatibilty and mechanical properties. There might be aesthetic problems due to the gray color of titanium. In some situations, there may be a soft tissue recession; in such situations there is an unaesthetic display of the metal components. Therefore, implant research has focused on discovering tooth-colored implant material that improves the aesthetic appearance of dental implants and, at the same time, is highly biocompatible and able to withstand the forces present in the oral cavity and therefore zirconia came into being[27-29].

Zirconia

Zirconia was used for dental prosthetic surgery with endosseous implants in early nineties. Cranin and coworkers published first research work on Zirconia in 1975. Ceramic implants were introduced for osseointegration, less plaque accumulation resulting in improvement of the soft tissue management, and aesthetic consideration as an alternative to titanium implants[30,31].

Monoclinic (M), cubic (C), and tetragonal (T) are the three crystal forms in which polymorphic Zirconia structure is present. Zirconia,on room temperature, acquires a monoclinic structure and changes into tetragonal phase at 1170 ℃, followed by a cubic phase at 2370 ℃. At room temperature these phases are unstable and break into pieces,on cooloing. The C-phase of pure Zirconia can be stabilized by adding CaO, MgO, and Y_2O_3 (Yttrium) resulting in multiphase material called partially stabilized zirconia (PSZ) combining cubic, monoclinic, and tetragonal phases in the order of importance. Tetragonal zirconia polycrystals (TZP), containing tetragonal phase only can be obtained by adding Yttrium at room temperature. Yttria stabilized TZP possesses low porosity, high density, high bending, and compression strength and is suitable for biomedical application[32].

Titanium-zirconium alloy (Straumann Roxolid)

Titanium zirconium alloys with 13%-17% zirconium (TiZr1317) have better mechanical attributes, such as increased elongation and the fatigue strength, than pure titanium. Growth of osteoblasts, that are essential for osseointegration is not prevented by Titanium and Zirconium. Straumann developed Roxolid that fulfills requirements of dental implantologists and is 50% stronger than pure titanium.

Sandblasting and acid-etching on, TiZr1317 with a monophasic a structure results in a topographically identical surface as on pure titanium implants. Because of its superior mechanical properties.Thin implants and implant components that can be subjected to high strains can be produced using TiZr1317 due to its better mechanical properties, provided that the material shows a similar good biocompatibility as pure titanium[33].

CONCLUSION

In evaluating the present and predicting the future, one must also reconsider the past. The implant materials, their composition and properties are not talked about in most of the implant related literature. The literature also lacks the effect of the material properties on success and failure of implants and its effects on the tissues surrounding the implants.

Modern dentistry is beginning to understand, realize, and utilize the benefits of biotechnology in health care. Study of material sciences along with the biomechanical sciences provides optimization of design and material concepts for surgical implants[34].

Implants have been gaining popularity amongst the patients and frequently are being considered as a first treatment option. In the last decade implants have dominated the other treatment modalities and moved into the mainstream of dental practice. "We have come a long way but there is still more to achieve".

REFERENCES

1 **Hulbert SF**, Bennett JT. State of the art in dental implants. *J Dent Res* 1975; **54** Spec No B: B153-B157 [PMID: 1055740 DOI: 10.1177/00220345750540021001]
2 **Misch CE.** Contemporary implant dentistry. *Implant Dentistry* 1999; **8**: 90 [DOI: 10.1097/00008505-199901000-00013]
3 **Sykaras N**, Iacopino AM, Marker VA, Triplett RG, Woody RD. Implant materials, designs, and surface topographies: their effect on osseointegration. A literature review. *Int J Oral Maxillofac Implants* 2000; **15**: 675-690 [PMID: 11055135]
4 **Lemons JE**. Dental implant biomaterials. *J Am Dent Assoc* 1990; **121**: 716-719 [PMID: 2277157]
5 **Carvalho TL**, Araújo CA, Teófilo JM, Brentegani LG. Histologic and histometric evaluation of rat alveolar wound healing around polyurethane resin implants. *Int J Oral Maxillofac Surg* 1997; **26**: 149-152 [PMID: 9151174 DOI: 10.1016/S0901-5027(05)80838-0]
6 **Kawahara H**. Cellular responses to implant materials: biological, physical and chemical factors. *Int Dent J* 1983; **33**: 350-375 [PMID: 6581129]
7 **Muddugangadhar BC,** Amarnath GS, Tripathi S, Divya SD. Biomaterials for Dental Implants: An Overview. *International Journal of Oral Implantology and Clinical Research* 2011; **2:** 13-24 [DOI: 10.5005/jp-journals-10012-1030]
8 **Wennerberg A**, Albrektsson T. On implant surfaces: a review of current knowledge and opinions. *Int J Oral Maxillofac Implants* 2010; **25**: 63-74 [PMID: 20209188]
9 **Chaturvedi TP**. An overview of the corrosion aspect of dental implants (titanium and its alloys). *Indian J Dent Res* 2009; **20**: 91-98 [PMID: 19336868 DOI: 10.4103/0970-9290.49068]
10 **Manivasagam G,** Dhinasekaran D, Rajamanickam A. Biomedical Implants: Corrosion and its Prevention - A Review. *Recent Patents on Corrosion Science* 2010; **2:** 40-54 [DOI: 10.2174/1877610801002010040]
11 **Adya N,** Alam M, Ravindranath T,Mubeen A, Saluja B. Corrosion in titanium dental implants: literature review. *Journal of Indian Prosthodontic Society* 2005; **5**: 126-131 [DOI: 10.4103/0972-4052.17104]
12 **Block MS,** Kent JN, Guerra LR. Implants in dentistry. Philadelphia: W.B. Saunders company, 1997: 4
13 **Huebsch N**, Mooney DJ. Inspiration and application in the evolution of biomaterials. *Nature* 2009; **462**: 426-432 [PMID: 19940912 DOI: 10.1038/nature08601]
14 **Waerhaug J**, Zander HA. Implantation of acrylic roots in tooth sockets. *Oral Surg Oral Med Oral Pathol* 1956; **9**: 46-54 [PMID: 13297364 DOI: 10.1016/0030-4220(56)90173-6]
15 **Gettleman L**, Nathanson D, Myerson RL. Effect of rapid curing procedures on polymer implant materials. *J Prosthet*

Dent 1977; **37**: 74-82 [PMID: 264323 DOI: 10.1016/0022-3913(77)90195-0]
16 **Ashman A**. Acrylic resin tooth impant: a progress report. *J Prosthet Dent* 1971; **25**: 342-347 [PMID: 5276857 DOI: 10.1016/0022-3913(71)90197-1]
17 **Hodosh M**, Povar M, Shklar G. The dental polymer implant concept. *J Prosthet Dent* 1969; **22**: 371-380 [PMID: 4979523 DOI: 10.1016/0022-3913(69)90200-5]
18 **Shklar G,** Hodosh M, Povar M. Tissue reactions to polymer-coated Vitallium pin Implants. *J Prosth Dent* 1970; **24**: 636-645 [PMID: 4991130 DOI: 10.1016/0022-3913(70)90100-9]
19 **Arvidson K**, Cottler-Fox M, Hammarlund E, Friberg U. Cytotoxic effects of cobalt-chromium alloys on fibroblasts derived from human gingiva. *Scand J Dent Res* 1987; **95**: 356-363 [PMID: 3476989]
20 **Phillips RW.** Skinner's science of dental materials. 8th ed. Philadelphia: WB Saunders, 1982
21 **Cranin AN,** Silverbrand H, Sher J, Satler N. The requirements and clinical performance of dental implants. *Biocompatibility of dental materials* 1982; **4**: 92-102
22 **Tschernitschek H**, Borchers L, Geurtsen W. Nonalloyed titanium as a bioinert metal--a review. *Quintessence Int* 2005; **36**: 523-530 [PMID: 15997933]
23 **Wennerberg A**, Albrektsson T, Andersson B. Bone tissue response to commercially pure titanium implants blasted with fine and coarse particles of aluminum oxide. *Int J Oral Maxillofac Implants* 1996; **11**: 38-45 [PMID: 8820121]
24 **Meffert RM**, Langer B, Fritz ME. Dental implants: a review. *J Periodontol* 1992; **63**: 859-870 [PMID: 1453301 DOI: 10.1902/jop.1992.63.11.859]
25 **Williams DF**. Implants in dental and maxillofacial surgery. *Biomaterials* 1981; **2**: 133-146 [PMID: 7023554 DOI: 10.1016/0142-9612(81)90039-9]
26 **Ravnholt G**. Corrosion current and pH rise around titanium coupled to dental alloys. *Scand J Dent Res* 1988; **96**: 466-472 [PMID: 3201121]
27 **Prithviraj DR**, Deeksha S, Regish KM, Anoop N. A systematic review of zirconia as an implant material. *Indian J Dent Res* 2012; **23**: 643-649 [PMID: 23422612 DOI: 10.4103/0970-9290.107383]
28 **Depprich R**, Zipprich H, Ommerborn M, Naujoks C, Wiesmann HP, Kiattavorncharoen S, Lauer HC, Meyer U, Kübler NR, Handschel J. Osseointegration of zirconia implants compared with titanium: an in vivo study. *Head Face Med* 2008; **4**: 30 [PMID: 19077228 DOI: 10.1186/1746-160X-4-30]
29 **Kohal RJ**, Weng D, Bächle M, Strub JR. Loaded custom-made zirconia and titanium implants show similar osseointegration: an animal experiment. *J Periodontol* 2004; **75**: 1262-1268 [PMID: 15515343 DOI: 10.1902/jop.2004.75.9.1262]
30 **Hoffmann O**, Angelov N, Gallez F, Jung RE, Weber FE. The zirconia implant-bone interface: a preliminary histologic evaluation in rabbits. *Int J Oral Maxillofac Implants* 2008; **23**: 691-695 [PMID: 18807566]
31 **Özkurt Z**, Kazazoğlu E. Zirconia dental implants: a literature review. *J Oral Implantol* 2011; **37**: 367-376 [PMID: 20545529 DOI: 10.1563/AAID-JOI-D-09-00079]
32 **Adatia ND**, Bayne SC, Cooper LF, Thompson JY. Fracture resistance of yttria-stabilized zirconia dental implant abutments. *J Prosthodont* 2009; **18**: 17-22 [PMID: 19166544 DOI: 10.1111/j.1532-849X.2008.00378.x]
33 **Chiapasco M**, Casentini P, Zaniboni M, Corsi E, Anello T. Titanium-zirconium alloy narrow-diameter implants (Straumann Roxolid(®)) for the rehabilitation of horizontally deficient edentulous ridges: prospective study on 18 consecutive patients. *Clin Oral Implants Res* 2012; **23**: 1136-1141 [PMID: 22092806 DOI: 10.1111/j.1600-0501.2011.02296.x]
34 **Smith DC**. Dental implants: materials and design considerations. *Int J Prosthodont* 1993; **6**: 106-117 [PMID: 8329086]

P- Reviewer: Cho SY, Haraszthy V, Taheri S **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Lu YJ

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DOI: 10.12998/wjcc.v3.i1.58

World J Clin Cases 2015 January 16; 3(1): 58-64
ISSN 2307-8960 (online)

MINIREVIEWS

Vasopressors in obstetric anesthesia: A current perspective

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Received: July 26, 2014
Peer-review started: July 27, 2014
First decision: August 14, 2014
Revised: August 25, 2014
Accepted: October 23, 2014
Article in press: December 23, 2014
Published online: January 16, 2015

Abstract

Vasopressors are routinely used to counteract hypotension after neuraxial anesthesia in Obstetrics. The understanding of the mechanism of hypotension and the choice of vasopressor has evolved over the years to a point where phenylephrine has become the preferred vasopressor. Due to the absence of definitive evidence showing absolute clinical benefit of one over the other, especially in emergency and high-risk Cesarean sections, our choice of phenylephrine over the other vasopressors like mephentermine, metaraminol, and ephedrine is guided by indirect evidence on fetal acid-base status. This review article evaluates the present day evidence on the various vasopressors used in obstetric anesthesia today.

Key words: Vasopressor agents; Obstetrics; Cesarean section; Hypotension; Spinal anesthesia

Core tip: Phenylephrine has emerged as the vasopressor of choice in Obstetrics. However, the present recommendations are essentially based on studies conducted in elective Cesarean sections. Further studies are needed in emergency and high risk Cesarean sections in order to clarify whether there is a benefit of phenylephrine over other vasopressors.

Nag DS, Samaddar DP, Chatterjee A, Kumar H, Dembla A. Vasopressors in obstetric anesthesia: A current perspective. *World J Clin Cases* 2015; 3(1): 58-64 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i1/58.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i1.58

INTRODUCTION

Neuraxial anesthesia remains the preferred choice for Cesarean deliveries across the world. Hypotension is the physiologic consequence of spinal anesthesia and can have a potentially deleterious maternal and fetal impact. Vasopressors, which lead to an increase in systemic vascular resistance and rise in mean arterial pressures[1], have been traditionally used for the prevention and management of hypotension after neuraxial anesthesia. However, the understanding of hypotension after neuraxial anesthesia in obstetrics, and the use of vasopressors to counteract it, continues to evolve over the years. This review article briefly explores the present understanding of the mechanism causing hypotension before discussing the current use of

the various vasopressors in obstetric anesthesia today. The authors discuss the various vasopressors used in obstetric anesthesia and put the recent evidence into perspective to guide our clinical practice today.

HYPOTENSION AFTER NEURAXIAL ANESTHESIA

The sympathectomy resulting from the neuraxial blockade is exaggerated by the physiological changes of pregnancy and puerperium, leading to hypotension in as much as 55%-90% of the mothers receiving spinal anesthesia for Cesarean section[2]. Holmes *et al*[3] and Lees *et al*[4] indicated that the compression of the vena cava by gravid uterus impeded the venous return and caused hypotension. Marx[5] postulated that the subarachnoid block resulted in venous pooling of blood in the lower legs, leading to decreased venous return and reduced cardiac output. Although our present interpretation of the mechanism causing hypotension are still based on these principles, prophylactic therapeutic interventions based upon this understanding do not definitively prevent hypotension after neuraxial anaesthesia in Cesarean sections[6].

Based on studies on pre-eclamptic women, Sharwood-Smith *et al*[6] challenged the understanding that reduced central venous pressure led to decreased cardiac output and arterial pressures. They suggested that "venous capacitance" rather than venous pressure maybe the determinant in causing hypotension after spinal anesthesia in obstetrics. The "endothelium-dependent alteration of vascular smooth muscle function" and increased presence of "vasodilator prostaglandins and nitric oxide" during pregnancy have a vasodilatory effect which is counteracted by the intrinsic sympathetic vascular tone[6]. This intrinsic vascular tone is adversely impacted after spinal anesthesia, leading to exaggerated fall in blood pressure. Studies now show that cardiac output remains nearly unchanged even after sympathetic blockade[7], challenging the concept that in parturients, spinal anesthesia results in decrease in cardiac output[8]. Despite the varied understanding of hypotension following neuraxial anesthesia in pregnancy, vasopressors remain the cornerstone in restoring the arterial pressure and mitigating the possible adverse maternal and fetal impact.

VASOPRESSORS USED IN OBSTETRICS

Vasopressors which have been used in obstetrics primarily include the directly acting selective α_1 receptors agonists, phenylephrine and methoxamine, and both directly and indirectly acting mephentermine, metaraminol and ephedrine.

METHOXAMINE

Methoxamine is an $\alpha 1$ receptor agonist which causes intense vasoconstriction following parenteral administration, raising arterial blood pressure and may result in reflex vagal inhibition of the heart rate[9]. It is devoid of any inotropic or chronotropic effect[9] and has been used to counteract the hypotension caused by spinal anesthesia[10]. Tachyphylaxis has seldom been observed with methoxamine[11]. While the peak vasopressor effect after a single intravenous dose of 2-4 mg has been observed after 0.5-2 min, its duration of action has been reported to be 10-15 min[12]. Intramuscular administration of a 10-40 mg dose has its peak onset of action at 15-20 min and its action lasts for about 1.5 h[12]. Its use in clinical obstetrics has fallen out of favor decades ago owing to concerns regarding decreased uterine blood flow and adverse impact on fetal acid-base status in animal studies[12,13].

MEPHENTERMINE

It has a mixed α and β receptor agonist action with both direct and indirect effect due to release of norepinephrine and epinephrine[14]. Its impact on the heart rate is dependent on the vagal tone. Its use in hypotension after a neuraxial blockade in obstetrics is due to its ability to increase the blood pressures by augmenting the cardiac output[14]. Tachyphylaxis to the pressor action of mephentermine develops rapidly[15]. While there is immediate onset of action peaking at 5 min and lasting 15-30 min after an intravenous dose, an intramuscular dose starts acting after 5-15 min and has a variable duration of action from 1-4 h. It is commonly used as a 3-5 mg intravenous bolus or intravenous infusion of 2-5 mg/min[16], or 25-50 mg intramuscularly[17]. There is scarce literature evidence on the fetal metabolic effect and placental transfer of mephentermine[18]. However, a few studies have shown that mephentermine is as effective as phenylephrine in preventing maternal hypotension after spinal anesthesia and has similar effect on neonatal outcome[19]. It is being widely used in developing countries like India as it is much more economical[19] than phenylephrine. Moreover, unlike phenylephrine which needs multiple dilutions from the single use 10 mg/mL (1 mL) ampoules, mephentermine offers ease of use as it does not necessitates multiple dilutions.

METARAMINOL

Although it has both mixed α and β receptor agonist action, its primary clinical use is to counteract the hypotension after spinal anesthesia in obstetrics. It has significant direct effect on vascular α adrenergic receptors along with its indirect action due to the release of norepinephrine[20,21]. Tachyphylaxis develops due to the displacement of norepinephrine from the sympathetic nerve endings by metaraminol and its action as a false neurotransmitter having inhibited vasopressor effect[17]. While an intravenous bolus dose of 0.5-5 mg has its onset of action in 1-2 min, peak action is at 10 min and duration of action is 20-60 min. An intramuscular dose of 2-10 mg has its onset by 10 min and duration of action of 1-1.5 h[22].

PHENYLEPHRINE

At clinically relevant doses, it is a selective α1 receptor agonist and β agonist action is only seen at much higher doses[20]. It is frequently used in obstetric anesthesia to counteract the hypotension after spinal anesthesia due to marked arterial vasoconstriction caused by its α1 agonist action. Potential negative chronotropic effect is due to reflex bradycardia and decreased cardiac output might not adversely influence the fetus in elective cases[23], but during emergency Cesarean sections with presence of fetal acidosis, any fall in cardiac output may further jeopardize the compromised fetus[23]. However, definitive understanding on the effect of phenylephrine in emergency situations awaits further research[21]. Tachyphylaxis with phenylephrine is possibly caused by the down-regulation of α adrenergic receptors. Its potential to be reversed by hydrocortisone has not been evaluated in an obstetric setting[24].

An intravenous dose of phenylephrine has immediate onset and duration of action of 5-10 min[17]. The optimum regimen for administration of phenylephrine has not yet been defined[25]. Prophylactic administration is associated with a higher incidence of hypertension and bradycardia[26] and treatment after onset of hypotension is associated with higher "incidence and severity of maternal predelivery hypotension"[26]. Despite some studies suggesting that to prevent spinal anesthesia induced hypotension, as an intravenous intermittent bolus dose (ED95) of phenylephrine should be at least 122-147 μg[27,28], 40-100 μg bolus dose remains the common clinical practice[25].

Prophylactic infusions have been advocated in the range of 25-100 μg/min in various studies, but claims have been made that a fixed dose of 50 μg/min minimizes the risk of higher incidence of hypotension at lower doses and reactive hypertension, bradycardia and decreased cardiac output at higher doses[23,25,26].

However, prophylactic fixed dose concept has been challenged[26], necessitating further studies to find the advantages of phenylephrine infusion.

It was even suggested in 2010 that "prophylactic fixed rate infusions may have limited application in clinical practice" and further studies into variable rate of phenylephrine infusion is needed[26]. A recent study by Siddik-Sayyid *et al*[29] has failed to demonstrate any difference in neonatal outcome with a variable rate regimen adjusted in response to changes in arterial blood pressure, as compared to prophylactic fixed rate infusion regimen. However, with respect to limiting maternal symptoms, the variable rate regimen was more effective than relying on rescue phenylephrine[29].

Despite these studies, obstetric anesthesiologists are unable to arrive at a consensus opinion on the ideal regimen for administration of phenylephrine because other studies have demonstrated that with intermittent boluses, the total dose requirement is smaller, blood pressure was better maintained in the 1st 6 min after induction, and indeed, good blood pressure control is achievable by intermittent boluses[30], which is not only simple, but also does not need the setting up of a syringe pump[31].

Although not much literature is available on the efficacy of intramuscular phenylephrine, Ayorinde *et al*[32] reported that 4 mg of intramuscular pre-emptive phenylephrine decreased the severity of hypotension and the need for rescue vasopressors in spinal anesthesia induced hypotension.

EPHEDRINE

It has both direct α and β agonist action, but indirect action is more prominent due to the "release of norepinephrine from sympathetic neurons"[20]. It increases the blood pressure by β1 receptor stimulation with increased heart rate and cardiac contractility, whereas the α agonist action causes peripheral vasoconstriction[21,33]. Prophylactic doses of 30 mg intravenous ephedrine had been suggested by Ngan Kee *et al*[34] to achieve significant reduction in the incidence of hypotension, but it was associated with the risk of reactive hypertension in as much as 45% of the patients. Subsequent studies by Kol *et al*[35] also failed to demonstrate beneficial effect of prophylactic intravenous ephedrine at 0.5 mg/kg. Even for a reduction in the need for rescue boluses of ephedrine, at least 12 mg intravenous prophylactic dose of ephedrine is needed after spinal anesthesia for Cesarean sections[36]. Ephedrine's limited ability to prevent hypotension induced by neuraxial anesthesia is probably related to its slower onset of action[34]. As a rescue vasopressor, 5-15 mg intravenous boluses are most commonly advocated for the treatment of hypotension following neuraxial anesthesia. Its clinical effect is primarily due to its indirect action of releasing norepinephrine from postganglionic nerve endings. The drug not only has delayed onset of action, it also has a longer duration of action of about 60 min. Depletion of presynaptic norepinephrine stores also lead to tachyphylaxis[35]. Due to its delayed onset of action, it should only be repeated after 5-10 min as it was observed that larger doses of ephedrine were required in the first 10 min and often caused overshoot of the desired target systolic pressures after 10 min[37]. Intravenous boluses are therefore preferred to continuous intravenous infusions as the drug exhibits delayed onset of action and tachyphylaxis.

CHOICE OF VASOPRESSOR: THE RECENT EVIDENCE

The ideal vasopressor would be one which is reliable and easy to use, has rapid onset, short duration of action, easily titrable, can potentially be used prophylactically and lack any adverse maternal and fetal impact. A Comparative analysis of the commonly used vasopressors in obstetric anesthesia is illustrated in Table 1.

Table 1 Comparative analysis of vasopressors used in obstetric anesthesia

No.	Drug	Mechanism of Action	Advantage	Disadvantage
1	Methoxamine	α1 receptor agonist	No inotropic or chronotropic effect. Tachyphylaxis has seldom been observed	Reflex bradycardia. Adverse effect on fetal acid-base status
2	Mephentermine	α and β receptor agonist. Both direct and indirectly acting	Economical and does not need multiple dilutions as compared to Phenylephrine	Tachyphylaxis. Little evidence available on placental transfer and its fetal metabolic impact
3	Metaraminol	α and β receptor agonist. Both direct and indirectly acting	No adverse effect on fetal acid-base status as compared to ephedrine	Tachyphylaxis
4	Phenylephrine	Selective α1 receptor agonist at clinical doses	Immediate onset and short duration of action. Ideal for continuous infusion. No adverse effect on fetal acid-base status as compared to ephedrine	Tachyphylaxis. Reflex bradycardia and concerns regarding decreased maternal cardiac output
5	Ephedrine	α and β receptor agonist. Both direct and indirectly acting	Economical and does not need multiple dilutions as compared to Phenylephrine. No bradycardia	Tachyphylaxis. Adverse effect on fetal acid-base status as compared to Phenylephrine

In 2002, Lee *et al*[38] challenged the "traditional idea that ephedrine is the preferred choice". for use as a vasopressor to combat hypotension after spinal anesthesia for Cesarean sections. In a quantitative systemic review they concluded that for elective Cesarean sections, phenylephrine was associated with better fetal acid-base status, although no clinical outcome difference based on the Apgar scores could be established[38].

In patients treated with ephedrine, the cause of decreased pH, base excess and oxygen content in umbilical cord arterial blood is controversial. While earlier studies indicated towards differential action of various vasopressors on uteroplacental circulation[39], studies by Ngan Kee *et al*[40] showed that depressed fetal acid base status was possibly due to ephedrine crossing the placenta and causing depression of fetal pH by its "metabolic effects secondary to stimulation of fetal β-adrenergic receptors". A recent study by Landau *et al*[41] has given a new direction to this debate. They showed that the neonatal homozygosity for Arg16 of *ADRB2* protected from neonatal acidemia in mothers treated with ephedrine[41]. The presence of this genotype in greater that 30% of the Chinese cohort and the fact that their genotype differs considerably from their North Americans indicate that clinicians should be wary of extrapolating studies of one ethnic population group on another[41].

Despite evidence in favor of phenylephrine as a superior choice, there remains widespread variation in the "choice, dosing, and method of administration of vasopressors"[25]. The United Kingdom National Institute for Health and Care Excellence Guidelines state that ephedrine and phenylephrine are equally efficacious as vasopressors in obstetric anesthesia[42]. The American Society of Anesthesiologists Task Force on Obstetric Anesthesia states that while ephedrine and phenylephrine are both acceptable, "phenylephrine may be preferable because of improved fetal acid-base status in uncomplicated pregnancies"[43]. There is much more clarity in the Canadian guidelines which state that there is "general agreement among experts to recommend the use of phenylephrine" as the first line therapy[8]. Belgian guidelines also recommend phenylephrine as the preferred vasopressor in absence of maternal bradycardia (Grade 1, A)[44].

While there is abundant literature evidence claiming superiority of phenylephrine over ephedrine in healthy parturients undergoing elective Cesarean section based on fetal acid-base status, there is dearth of evidence showing benefit in clinical outcome. Meta-analysis of 142 studies comparing phenylephrine and ephedrine failed to show the superiority of one over the other while comparing the Apgar scores[45]. However recent systematic review and meta-analysis do show that fetal acidosis defined as pH < 7.20 was associated with four- and two-fold increase in mortality and morbidity, respectively[46].

Due to a dearth of studies on the vasopressor of choice during non-elective Cesarean sections[47], it is suggested that further research is needed in high-risk pregnancies, intra uterine growth retardation, placental insufficiency, pre-eclampsia[25] and in emergency Caesareans due to fetal distress.

In one study in 2008 by Ngan Kee *et al*[48] in non-elective Cesarean sections, there was "no differences in fetal acid-base status or clinical neonatal outcome" between 100 μg phenylephrine and 10 mg ephedrine boluses to manage spinal anesthesia induced hypotension. Similarly, a retrospective study by Cooper *et al*[49] on the choice of vasopressor between phenylephrine and ephedrine in high-risk Cesarean sections, there was no statistically significant difference in the umbilical artery pH between the two groups.

There is also scarce literature available on the other vasopressors[50]. Kansal *et al*[16] concluded that mephentermine can be used as safely as ephedrine in the management of spinal anesthesia-induced hypotension in Cesarean sections. Similarly, Mohta *et al*[19] concluded that phenylephrine and mephentermine are equally effective in preventing hypotension after a spinal anesthesia for Cesarean section. Both the studies compared the Apgar scores and the neonatal acid-base status while evaluating the vasopressors[16,19]. In 2014, studies by de Aragãoa *et al*[50] compared an infusion of metaraminol with phenylephrine and ephedrine and did not find any difference in the incidence of maternal hypotension or

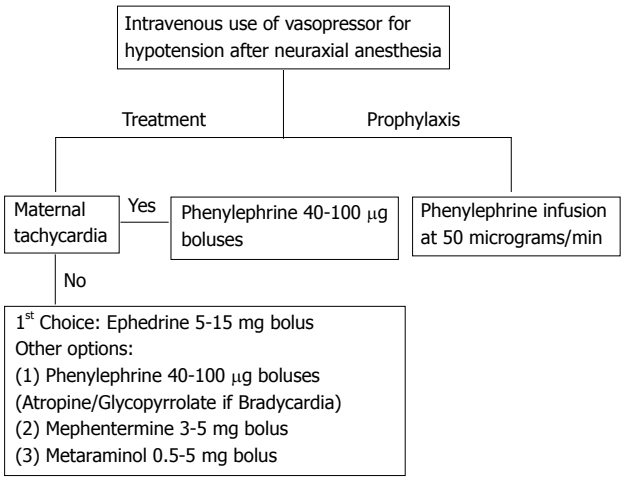

Figure 1 Suggested clinical protocol for intravenous use of vasopressor for Hypotension after Neuraxial Anaesthesia in Obstetrics.

neonatal Apgar scores. Comparison of phenylephrine, metaraminol and ephedrine showed that Ephedrine treated mothers had lower pH and base excess in their newborns[50]. However those treated with metaraminol needed fewer rescue boluses as compared to ephedrine, but not phenylephrine[50].

Combination of phenylephrine and ephedrine infusion has also demonstrated deterioration in fetal acid-base status and maternal hemodynamic control with the proportionate increase in the dose of ephedrine[51-53].

CONCLUSION

Current literature supports the use of phenylephrine as the vasopressors of choice while considering the influence on feto-maternal physiology[25,47]. However, this concept is mostly based on studies conducted in elective Cesarean sections. Therefore, this same principle cannot be extrapolated in emergency Cesarean sections and high-risk pregnancies.

Due to its potential for possible adverse impact on placental perfusion[25] when it causes bradycardia and decreased cardiac output, further studies on phenylephrine are needed, especially in presence of pre-existing fetal compromise.

Certain clinical protocols support the use of phenylephrine in the presence of maternal tachycardia (heart rate > 110/min) and ephedrine at lower heart rates (< 80/min)[54]. A suggested clinical protocol for intravenous use of vasopressor for hypotension after neuraxial anaesthesia in obstetrics is given in Figure 1.

Today, in obstetric anesthesia, both phenylephrine and ephedrine continue to be used in the "absence of relevant evidence, rather than any evidence of the absence of an effect"[55]. The same appears to be true for mephentermine and metaraminol also. Larger trials, especially in non-elective Cesarean sections, would be needed to give further direction to the obstetric anesthesiologists in choosing their preferred vasopressor.

REFERENCES

1 **Bangash MN**, Kong ML, Pearse RM. Use of inotropes and vasopressor agents in critically ill patients. *Br J Pharmacol* 2012; **165**: 2015-2033 [PMID: 21740415 DOI: 10.1111/j.1476-5381.2011.01588.x]

2 **Mercier FJ**, Bonnet MP, De la Dorie A, Moufouki M, Banu F, Hanaf A, Edouard D, Roger-Christoph S. [Spinal anaesthesia for caesarean section: fluid loading, vasopressors and hypotension]. *Ann Fr Anesth Reanim* 2007; **26**: 688-693 [PMID: 17590565 DOI: 10.1016/j.annfar.2007.05.003]

3 **Holmes F**. Spinal analgesia and caesarean section; maternal mortality. *J Obstet Gynaecol Br Emp* 1957; **64**: 229-232 [PMID: 13416987 DOI: 10.1111/j.1471-0528.1957.tb02626.x]

4 **Lees MM**, Scott DB, Kerr MG, Taylor SH. The circulatory effects of recumbent postural change in late pregnancy. *Clin Sci* 1967; **32**: 453-465 [PMID: 6067526]

5 **Marx GF**. Supine hypotension syndrome during cesarean section. *JAMA* 1969; **207**: 1903-1905 [PMID: 5818306 DOI: 10.1001/jama.1969.03150230117018]

6 **Sharwood-Smith G**, Drummond GB. Hypotension in obstetric spinal anaesthesia: a lesson from pre-eclampsia. *Br J Anaesth* 2009; **102**: 291-294 [PMID: 19218369 DOI: 10.1093/bja/aep003]

7 **Tamilselvan P**, Fernando R, Bray J, Sodhi M, Columb M. The effects of crystalloid and colloid preload on cardiac output in the parturient undergoing planned cesarean delivery under spinal anesthesia: a randomized trial. *Anesth Analg* 2009; **109**: 1916-1921 [PMID: 19923521 DOI: 10.1213/ANE.0b013e3181bbfdf6]

8 **Loubert C**. Fluid and vasopressor management for Cesarean delivery under spinal anesthesia: continuing professional development. *Can J Anaesth* 2012; **59**: 604-619 [PMID: 22528166 DOI: 10.1007/s12630-012-9705-9]

9 **Imai S**, Shigei T, Hashimoto K. Cardiac actions of methoxamine with special reference to its antagonistic action to epinephrine. *Circ Res* 1961; **9**: 552-560 [PMID: 13717556]

10 **Brienza A**, De Leonardis A. [The choice of the pressor drug in hypotension caused by peridural anesthesia. Observations with methoxamine, metaraminol and mephentermine]. *Acta Anaesthesiol* 1967; **18** Suppl 2: 11-27 [PMID: 5632249]

11 **Brewster RW,** Osgood PF, Isaacs JP, Goldberg LI, Chock RTW. Hemodynamic effects of a pressor amine (methoxamine) with a predominant vasoconstrictor activity. *Circ Res* 1960; **8:** 980-986 [DOI: 10.1161/01.RES.8.5.980]

12 **RxMed.** (Internet). VASOXYL®. Glaxo Wellcome. Methoxamine HCl. Vasopressor. [accessed 2014 Jul 10]. Available from: URL: http://www.rxmed.com/b.main/b2.pharmaceutical/b2.1.monographs/CPS-%20Monographs/CPS-%20-(General%20Monographs-%20V)/VASOXYL.html

13 **Ralston DH**, Shnider SM, DeLorimier AA. Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. *Anesthesiology* 1974; **40**: 354-370 [PMID: 4819091 DOI: 10.1097/00000542-197404000-00009]

14 **Hodge RL**, Dornhorst AC. The clinical pharmacology of vasoconstrictors. *Clin Pharmacol Ther* 1966; **7**: 639-647 [PMID: 5334234]

15 **Fawaz G**, Simaan J. The Tachyphylaxis Caused By Mephentermin And Tyramine. *Br J Pharmacol Chemother* 1965; **24**: 526-531 [PMID: 14320866 DOI: 10.1111/j.1476-5381.1965.tb01742.x]

16 **Kansal A**, Mohta M, Sethi AK, Tyagi A, Kumar P. Randomised trial of intravenous infusion of ephedrine or mephentermine for management of hypotension during spinal anaesthesia for Caesarean section. *Anaesthesia* 2005; **60**: 28-34 [PMID: 15601269 DOI: 10.1111/j.1365-2044.2004.03994.x]

17 **Glick DB.** The autonomic nervous system. In: Miller RD, Eriksson LI, Fleisher LA, editors. Miller's Anesthesia. 7th ed. Philadelphia: Elsevier, 2011: 261-304

18 **Mitra JK**, Roy J, Bhattacharyya P, Yunus M, Lyngdoh NM. Changing trends in the management of hypotension following spinal anesthesia in cesarean section. *J Postgrad Med* 2013; **59**: 121-126 [PMID: 23793313 DOI: 10.4103/0022-3859.113840]

19 **Mohta M**, Janani SS, Sethi AK, Agarwal D, Tyagi A. Comparison of phenylephrine hydrochloride and mephentermine sulphate for prevention of post spinal hypotension. *Anaesthesia* 2010; **65**: 1200-1205 [PMID: 21182601 DOI: 10.1111/j.1365-2044.2010.06559.x]

20 **Westfall TC,** Westfall DP. Adrenergic agonists and antagonists. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11 th ed. New York: McGraw Hill, 2006: 237-295

21 **Reidy J**, Douglas J. Vasopressors in obstetrics. *Anesthesiol Clin* 2008; **26**: 75-88, vi-vii [PMID: 18319181 DOI: 10.1016/j.anclin.2007.11.005]

22 **Smith S,** Scarth E, Sasada M. Metaraminol. In: Drugs in Anaesthesia and Intensive Care. 4th ed. Oxford: Oxford University Press, 2011: 214-215

23 **Stewart A**, Fernando R, McDonald S, Hignett R, Jones T, Columb M. The dose-dependent effects of phenylephrine for elective cesarean delivery under spinal anesthesia. *Anesth Analg* 2010; **111**: 1230-1237 [PMID: 20841418 DOI: 10.1213/ANE.0b013e3181f2eae1]

24 **Alhashemi JA**. Reduction of vasopressor requirement by hydrocortisone administration in a patient with cerebral vasospasm. *Br J Anaesth* 2001; **86**: 138-141 [PMID: 11575393 DOI: 10.1093/bja/86.1.138]

25 **Habib AS**. A review of the impact of phenylephrine administration on maternal hemodynamics and maternal and neonatal outcomes in women undergoing cesarean delivery under spinal anesthesia. *Anesth Analg* 2012; **114**: 377-390 [PMID: 22104076 DOI: 10.1213/ANE.0b013e3182373a3e]

26 **Allen TK**, George RB, White WD, Muir HA, Habib AS. A double-blind, placebo-controlled trial of four fixed rate infusion regimens of phenylephrine for hemodynamic support during spinal anesthesia for cesarean delivery. *Anesth Analg* 2010; **111**: 1221-1229 [PMID: 20495139 DOI: 10.1213/ANE.0b013e3181e1db21]

27 **Tanaka M**, Balki M, Parkes RK, Carvalho JC. ED95 of phenylephrine to prevent spinal-induced hypotension and/or nausea at elective cesarean delivery. *Int J Obstet Anesth* 2009; **18**: 125-130 [PMID: 19162468 DOI: 10.1016/j.ijoa.2008.09.008]

28 **George RB**, McKeen D, Columb MO, Habib AS. Up-down determination of the 90% effective dose of phenylephrine for the treatment of spinal anesthesia-induced hypotension in parturients undergoing cesarean delivery. *Anesth Analg* 2010; **110**: 154-158 [PMID: 19910625 DOI: 10.1213/ANE.0b013e3181c30b72.]

29 **Siddik-Sayyid SM**, Taha SK, Kanazi GE, Aouad MT. A randomized controlled trial of variable rate phenylephrine infusion with rescue phenylephrine boluses versus rescue boluses alone on physician interventions during spinal anesthesia for elective cesarean delivery. *Anesth Analg* 2014; **118**: 611-618 [PMID: 24299932 DOI: 10.1213/01.ane.0000437731.60260.ce]

30 **Doherty A**, Ohashi Y, Downey K, Carvalho JC. Phenylephrine infusion versus bolus regimens during cesarean delivery under spinal anesthesia: a double-blind randomized clinical trial to assess hemodynamic changes. *Anesth Analg* 2012; **115**: 1343-1350 [PMID: 23011562 DOI: 10.1213/ANE.0b013e31826ac3db]

31 **Ngan Kee WD**. Phenylephrine infusions for maintaining blood pressure during spinal anesthesia for cesarean delivery: finding the shoe that fits. *Anesth Analg* 2014; **118**: 496-498 [PMID: 24557093]

32 **Ayorinde BT**, Buczkowski P, Brown J, Shah J, Buggy DJ. Evaluation of pre-emptive intramuscular phenylephrine and ephedrine for reduction of spinal anaesthesia-induced hypotension during Caesarean section. *Br J Anaesth* 2001; **86**: 372-376 [PMID: 11573527 DOI: 10.1093/bja/86.3.372]

33 **Kee VR**. Hemodynamic pharmacology of intravenous vasopressors. *Crit Care Nurse* 2003; **23**: 79-82 [PMID: 12961786]

34 **Ngan Kee WD**, Khaw KS, Lee BB, Lau TK, Gin T. A dose-response study of prophylactic intravenous ephedrine for the prevention of hypotension during spinal anesthesia for cesarean delivery. *Anesth Analg* 2000; **90**: 1390-1395 [PMID: 10825326 DOI: 10.1097/00000539-200006000-00024]

35 **Kol IO**, Kaygusuz K, Gursoy S, Cetin A, Kahramanoglu Z, Ozkan F, Mimaroglu C. The effects of intravenous ephedrine during spinal anesthesia for cesarean delivery: a randomized controlled trial. *J Korean Med Sci* 2009; **24**: 883-888 [PMID: 19794988 DOI: 10.3346/jkms.2009.24.5.883]

36 **Loughrey JP**, Walsh F, Gardiner J. Prophylactic intravenous bolus ephedrine for elective Caesarean section under spinal anaesthesia. *Eur J Anaesthesiol* 2002; **19**: 63-68 [PMID: 11915786 DOI: 10.1017/S0265021502000108]

37 **Ngan Kee WD**, Lau TK, Khaw KS, Lee BB. Comparison of metaraminol and ephedrine infusions for maintaining arterial pressure during spinal anesthesia for elective cesarean section. *Anesthesiology* 2001; **95**: 307-313 [PMID: 11506099 DOI: 10.1097/00000542-200108000-00009]

38 **Lee A**, Ngan Kee WD, Gin T. A quantitative, systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. *Anesth Analg* 2002; **94**: 920-926, table of contents [PMID: 11916798 DOI: 10.1097/00000539-200204000-00028]

39 **Ngan Kee WD**. Prevention of maternal hypotension after regional anaesthesia for caesarean section. *Curr Opin Anaesthesiol* 2010; **23**: 304-309 [PMID: 20173633 DOI: 10.1097/ACO.0b013e328337ffc6]

40 **Ngan Kee WD**, Khaw KS, Tan PE, Ng FF, Karmakar MK. Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. *Anesthesiology* 2009; **111**: 506-512 [PMID: 19672175 DOI: 10.1097/ALN.0b013e3181b160a3]

41 **Landau R**, Liu SK, Blouin JL, Smiley RM, Ngan Kee WD. The effect of maternal and fetal β2-adrenoceptor and nitric oxide synthase genotype on vasopressor requirement and fetal acid-base status during spinal anesthesia for cesarean delivery. *Anesth Analg* 2011; **112**: 1432-1437 [PMID: 21613201 DOI: 10.1213/ANE.0b013e3182179424]

42 **Soltanifar S**, Russell R. The National Institute for Health and Clinical Excellence (NICE) guidelines for caesarean section, 2011 update: implications for the anaesthetist. *Int J Obstet Anesth* 2012; **21**: 264-272 [PMID: 22541846 DOI: 10.1016/j.ijoa.2012.03.004]

43 **American Society of Anesthesiologists Task Force on Obstetric Anesthesia.** Practice guidelines for obstetric anesthesia: an updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia. *Anesthesiology* 2007; **106**: 843-863 [PMID: 17413923 DOI: 10.1097/01.anes.0000264744.63275.10]

44 **Van De Velde M**. Belgian guidelines for safe regional anesthesia and obstetric anesthesia and analgesia. *Acta Anaesthesiol Belg* 2013; **64**: 95-96 [PMID: 24279197]

45 **Biddle C**. To press or not to press, and if so, with what? A single question-focused meta-analysis of vasopressor choice during regional anesthesia in obstetrics. *AANA J* 2013; **81**: 261-264 [PMID: 24133847]

46 **Malin GL**, Morris RK, Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: systematic review and meta-analysis. *BMJ* 2010; **340**: c1471 [PMID: 20466789 DOI: 10.1136/bmj.c1471]

47 **Dyer RA**, Biccard BM. Ephedrine for spinal hypotension during elective caesarean section: the final nail in the coffin? *Acta Anaesthesiol Scand* 2012; **56**: 807-809 [PMID: 22780437 DOI: 10.1111/j.1399-6576.2012.02719.x]

48 **Ngan Kee WD**, Khaw KS, Lau TK, Ng FF, Chui K, Ng KL. Randomised double-blinded comparison of phenylephrine

vs ephedrine for maintaining blood pressure during spinal anaesthesia for non-elective Caesarean section*. *Anaesthesia* 2008; **63**: 1319-1326 [PMID: 19032300 DOI: 10.1111/j.1365-2044.2008.05635.x]

49 **Cooper DW**, Sharma S, Orakkan P, Gurung S. Retrospective study of association between choice of vasopressor given during spinal anaesthesia for high-risk caesarean delivery and fetal pH. *Int J Obstet Anesth* 2010; **19**: 44-49 [PMID: 19945278 DOI: 1010.1016/j.ijoa.2009.06.002]

50 **de Aragãoa FF,** de Aragãob PW, de Souza Martins CA, Filho NS, de Souza Barcelos Barroqueiro E. Comparison of metaraminol, phenylephrine and ephedrine in prophylaxis and treatment of hypotension in cesarean section under spinal anesthesia. *Rev Bras Anestesiol* 2014; **64:** 299-306 [DOI: 10.1016/j.bjane.2013.07.014]

51 **Ngan Kee WD**, Lee A, Khaw KS, Ng FF, Karmakar MK, Gin T. A randomized double-blinded comparison of phenylephrine and ephedrine infusion combinations to maintain blood pressure during spinal anesthesia for cesarean delivery: the effects on fetal acid-base status and hemodynamic control. *Anesth Analg* 2008; **107**: 1295-1302 [PMID: 18806043 DOI: 10.1213/ane.0b013e31818065bc]

52 **Mercier FJ**, Riley ET, Frederickson WL, Roger-Christoph S, Benhamou D, Cohen SE. Phenylephrine added to prophylactic ephedrine infusion during spinal anesthesia for elective cesarean section. *Anesthesiology* 2001; **95**: 668-674 [PMID: 11575540 DOI: 10.1097/00000542-200109000-00020]

53 **Cooper DW**, Carpenter M, Mowbray P, Desira WR, Ryall DM, Kokri MS. Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. *Anesthesiology* 2002; **97**: 1582-1590 [PMID: 12459688 DOI: 10.1097/00000542-200212000-00034]

54 **Tulane Department of Anesthesiology.** Obstetric Anesthesia Guidelines. [accessed 2014 July 19]. Available from: URL: http: //tulaneanesthesiology.com/web/data/documents/Jul2009 TulOBAnesGuidelines.pdf

55 **Heesen M**, Kölhr S, Rossaint R, Straube S. Prophylactic phenylephrine for caesarean section under spinal anaesthesia: systematic review and meta-analysis. *Anaesthesia* 2014; **69**: 143-165 [PMID: 24588024 DOI: 10.1111/anae.12445]

P- Reviewer: Do SH, McCarthy RJ, Rasmussen S, Shi ZJ, Zafrakas M **S- Editor**: Tian YL **L- Editor**: A **E- Editor**: Lu YJ

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World J Clin Cases 2015 January 16; 3(1): 65-76
ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Posterior partially edentulous jaws, planning a rehabilitation with dental implants

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Author contributions: Monteiro DR and Silva EVF performed the computer search and wrote the paper; Pellizzer EP, Magro Filho O and Goiato MC designed the research, revised the paper and gave the final approval of the paper; all authors contributed equally to the work.
Ethics approval: None to declare.
Informed consent: None to declare.
Conflict-of-interest: The authors declare that they have no conflict of interest.
Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at goiato@foa.unesp.br. Participants gave informed consent for data sharing. No additional data are available.

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Received: June 19, 2014
Peer-review started: June 21, 2014
First decision: July 10, 2014
Revised: November 26, 2014
Accepted: December 3, 2014
Article in press: December 23, 2014
Published online: January 16, 2015

Abstract

AIM: To discuss important characteristics of the use of dental implants in posterior quadrants and the rehabilitation planning.

METHODS: An electronic search of English articles was conducted on MEDLINE (PubMed) from 1990 up to the period of March 2014. The key terms were dental implants and posterior jaws, dental implants/treatment planning and posterior maxilla, and dental implants/treatment planning and posterior mandible. No exclusion criteria were used for the initial search. Clinical trials, randomized and non randomized studies, classical and comparative studies, multicenter studies, *in vitro* and *in vivo* studies, case reports, longitudinal studies and reviews of the literature were included in this review.

RESULTS: One hundred and fifty-two articles met the inclusion criteria of treatment planning of dental implants in posterior jaw and were read in their entirety. The selected articles were categorized with respect to their context on space for restoration, anatomic considerations (bone quantity and density), radiographic techniques, implant selection (number, position, diameter and surface), tilted and pterygoid implants, short implants, occlusal considerations, and success rates of implants placed in the posterior region. The results derived from the review process were described under several different topic headings to give readers a clear overview of the literature. In general, it was observed that the use of dental implants in posterior region requires a careful treatment plan. It is important that the practitioner has knowledge about the theme to evaluate the treatment parameters.

CONCLUSION: The use of implants to restore the posterior arch presents many challenges and requires a detailed treatment planning.

Key words: Dental implants; Mandible; Maxilla; Edentulous jaw; Treatment

Core tip: The treatment plan for rehabilitation with dental implants in posterior quadrants of edentulous jaws must be meticulous. The professional must cautiously evaluate the treatment parameters to guarantee predictable and long-term restorations. The treatment plan includes detailed analysis of space for restoration, bone quantity and density, radiographic techniques, selection of number, diameter, and length of the implants, and occlusion.

Monteiro DR, Silva EVF, Pellizzer EP, Magro Filho O, Goiato MC. Posterior partially edentulous jaws, planning a rehabilitation with dental implants. *World J Clin Cases* 2015; 3(1): 65-76 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i1/65.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i1.65

INTRODUCTION

Implant-borne rehabilitation is a good option of treatment for patients with partial edentulism[1-3]. The validity of osseointegrated dental implants for the rehabilitation of posterior partially edentulous jaw had been related in the literature by several studies[4-7]. These rehabilitations offers substantial benefits when compared with removable partial dentures: improved occlusion and support, simplification of the prosthesis, less invasive restorative procedures, bone maintenance and, improvement in oral health[8,9].

However, to obtain excellent results in rehabilitations with dental implants meticulous attention must be paid to details[10]. In addition, the posterior quadrants of the mouth are challenging for rehabilitation with dental implants[6,11,12] due to their anatomical and occlusal features[6,9]. Thus, this article aimed to discuss important characteristics of the use of dental implants in posterior quadrants and the rehabilitation planning.

MATERIALS AND METHODS

An electronic search of English articles was conducted on MEDLINE (PubMed) from 1990 up to the period of March 2014. The Key terms were dental implants and posterior jaws, dental implants/treatment planning and posterior maxilla, and dental implants/treatment planning and posterior mandible. No exclusion criteria were used for the initial search. Titles and abstracts of the screened articles were reviewed and the full text was assessed for an appropriate analysis. Then, the articles were analyzed through inclusion and exclusion criteria. Clinical trials, randomized and non randomized studies, classical and comparative studies, multicenter studies, *in vitro* and *in vivo* studies, case reports, longitudinal studies and reviews of the literature were included in this review. Additionally, current and previous issues of the most relevant papers were inspected, intending to obtain other articles associated to the theme. Articles that were not related to the purpose of this study were excluded from further evaluation. Finally, one textbook was included for the review.

RESULTS

One hundred and fifty-two articles met the inclusion criteria of treatment planning of dental implants in posterior jaw and were read in their entirety. The selected articles were categorized with respect to their context on space for restoration, anatomic considerations, radiographic techniques, implant selection, tilted and pterygoid implants, short implants, occlusal considerations, and success rates. The results derived from the review process were described under several different topic headings to give readers a clear overview of the literature.

DISCUSSION

Space for restoration

The discussion about the space requirements for placing an implant is very important. The mesiodistal space required is related to the type and number of teeth that will be replaced[8]. According to Misch[13], the selection of implant size is influenced by the mesiodistal distance available for implant placement. These authors indicated a guideline for this selection: (1) a distance of at least 1.5 mm must be respected between the implant and the adjacent teeth; (2) a distance of at least 3.0 mm between the implant and an adjacent implant; and (3) for the replacement of a molar teeth, a implant with a wider diameter is indicated.

If the implant-supported proshtesis is positioned with a large distance from the adjacent tooth, critical contours and cantilever forces are generated on the implant. Since the mesiodistal dimension of molar teeth is greater when compared to other teeth, a distance of at least 2.5 mm between the implant and the adjacent implant has to be respected to assure a restoration proper contours[8].

According to Gastaldo *et al*[14], a distance of 3 mm between the bone crest adjacent implants and the proximal contact point is essential, and the implant should be placed 3-5 mm away from the tooth in order to guarantee a healthy interproximal papilla.

Simşek *et al*[15] evaluated, through finite element analysis (FEA), different distances between implants that retained three unit partial prosthesis and their effects on bone stress distribution in the posterior lower jaw. Axial, horizontal and oblique forces were applied and tensile and compressive bone stresses were evaluated. The authors observed that a space of 1.0 cm was the greatest distance between the inserted two implants.

Both the mesiodistal and the buccolingual dimensions from the crestal level to the apical part of the implant site should be evaluated[16]. At least, a 6 mm of bone buccolingual extension is necessary to insert a 4 mm-wide dental implant. For diameters higher than 5 mm, a 7 mm extension is required[8]. Additionally, the intermaxillary

space is an important source. A distance of 10 mm between the residual ridge and the antagonistic arch must be respected when substituting posterior teeth[8,17].

A multidisciplinary approach is considered when planning a dental implant treatment and involves orthodontics, surgery, and restorative, so that the function and aesthetics of those patients are improved[10,16,18-20]. Generally, over-eruption of opposite teeth occurs after a long period of tooth absence, which affects the restorative space. Therefore several treatment options to creat a sufficient space for restoration are available such as enameloplasty, minimal restorative therapy, orthodontic intrusion, tooth realignment, endodontic treatment and full crown preparation, segmental osteotomy for dentoalveolar extrusion and extraction[8,10,16,18,19].

Anatomic considerations: Bone quantity and density

The low-density and quantity of bone and the presence of sinus pneumatization in maxilla are relevant anatomic characteristics in the posterior region, since they can limit the implant height[21-31]. On the other hand, the mandibular canal is an important structure that could limit the installation of dental implants in lower jaws[21,32,33]. According to Jivraj *et al*[8] and Vazquez *et al*[34], a distance of at least 2 mm between the most apical part of the implant and vascular and neurologic structures must be respect.

Additionally, the mental foramen is an important mandibular structure when placing implants in the foraminal region. The mental foramen is either oval or round and is usually placed in the apical area of the second mandibular premolar or between apices of the premolars[35,36]. Nevertheless, its location may vary from the mandibular canine to the first molar[35,37].

Guidelines to evaluate the mental foramen position and the presence of mental nerve deviations have been proposed aiming to preserve the nerve, during surgeries in the foraminal area. Previously to implant insertion, a careful observation of mental nerve and foramen, through panoramic and periapical X-rays, is essential. In case of deficiency of this technique to observe the position of the nerve, the computadorized tomography scans are necessary. After the confirmation of the secure bone height, the professional can install the implants mesially or distally placed from the mental foramen or above it[34,35,37].

The lingual mandibular bone concavity is also another important factor since it increases the risks of fenestrations or perforations during implant insertion, in case of deficient buccal-lingual angulation[20,21,38].

Nevertheless, the bone density on the implant placement region affects the primary stability and in turns determines the implant treatment success[11,39,40]. Fuh *et al*[41] determined the density of trabecular bone at potential areas for implant placement. Chinese jawbones were evaluated through computed tomography (CT) in four different regions: anterior and posterior areas of maxilla and mandible. The bone densities differed between each region, being lower in the posterior area - maxilla (332 + 136 HU) and mandible (359 + 150 HU) - and higher in the anterior area -maxilla (516 + 132 HU) and mandible (530 + 161 HU). These results were similar to those of Sogo *et al*[42], who found that the bone in the posterior maxilla was classified as type Ⅲ (350-850 HU) and type Ⅳ bone (150-350 HU). These findings illustrated the necessity of choosing a specific implant design and surface treatment for the different bone density types owing to improvement of the bone-implant contact area[21]. Furthermore, cutting torque[40,43] and the resonance frequency[40,44] can be used to determine the bone quality and implant stability, respectively, and have a major effect on the osseointegration success.

Sakka *et al*[40], in a literature review, affirmed that to classify the bone quality it is important to evaluate bone morphology and characteristics of the constitutive cells. The cortical and trabecular bone ratio, and bone quantity and density have a great effect on the implant treatment longevity. Cells associated to bone quality, as macrophages, monocytes, fibroblasts, mesenchymal progenitors, osteoclasts, and cells related with angiogenesis, could influence the osseointegration of dental implants.

The implant placement is influenced by the form and contour of the edentulous alveolar ridge[21]. Infections, trauma during dental extraction, remodeling of alveolar bone after tooth extraction create localized defects on the bone[21,25,36,37,45], affecting its height and width, and consequently, influence the dental implant placement[21,28]. Some methods have been used to overcome these complications as guided bone regeneration with resorbable and nonresorbable barriers to enhance localized ridge deformities, the utilization of short-length implants, inclined implants, zygomatic or pterygoid implants, bone grafting surgeries and sinus lifting operations[21,46-52].

Del Fabbro *et al*[46] performed a systematic review of 39 selected studies in which 2046 patients underwent sinus grafting and received 6913 implants. After an accompaniment of 12 up to 75 mo, the reported survival rate was 92.5% (range, 61.2% to 100%). Results were also divided according to type of grafting materials. Overall, the survival rate of implants was 87.7% with autogenous bone, 94.9% when autogenous bone was mixed with other grafting materials, and 95.9% with nonautogenous grafting materials. Results were also reported according to type of implant surface. Overall, the survival rate was 85.6% for implants with smooth/machined surfaces, and 95.9% for implants with rough surfaces.

Radiographic techniques

Prior to implant insertion, intraoral and panoramic radiographies should be considered. But, since those techniques just provide information in a 2-dimensional view, the bucco-lingual bone width is missed[25,34,38,45,53-57].

The localization of the mandibular canal, the submandibular fossa, and the maxillary sinuses, in addition to the angulation of the alveolar crest and the bone volume are of primary importance during implant

treatment planning in the posterior jaw area[22,31,32,34,36,57-60]. Therefore, the use of CT in all sliced images is suggested to indicate the most convenient dimensions of the implant and its optimal position and inclination[25,38,42,45,54-57,61]. Spiral/helical CT scanners provide images with higher quality, with tridimensional view, associated with lower radiation exposure, than conventional computerized tomography[54,62]. Nevertheless, the CT scan is kind of expensive and requires large equipment. The radiation dose is relatively high[63].

In general, the conventional CT liberates a higher dose of radiation than another option of image scan, the cone-beam computed tomography (CBCT), which offers realistically tridimensional sliced images[31,54,57,58]. Therefore, this method is useful during implant treatment planning for partial edentulous patient[57,58,64,65].

Implant selection: Number, position, diameter, and surface

The selection of the ideal number of implants is related to the bone volume and density. Since the posterior region of upper jaw presents a soft bone tissue, it is recommended to insert 3 implants to replace 3 missing teeth[8,65]. In case of one implant failure, the previous prosthesis may still be used. And when the anterior or posterior implant fails, a cantilevered prosthesis could be fabricated[8].

The use of either two or three implants relies on the prosthesis biomechanical function and is influenced by load application during chewing[8]. In cases when it is possible to install three implants, a different configuration with a tripod effect of their distribution can be realized[8,66], which provides greater bone support versus linear placement[66]. Additionally, when possible, multiple implants in posterior quadrants should be splinted. Guichet *et al*[67] observed that splinted implant restorations exhibited optimal stress distribution than non-splinted prosthesis. However, Clelland *et al*[68] and Vigolo *et al*[69] observed that splinted prosthesis did not differ significantly from individual restorations, regarding strain distribution data and peri-implant marginal bone loss, respectively.

Regarding the implant diameter, implants with small (from 3.0 up to 3.5 mm) or regular (from 3.75 up to 4.5 mm) diameters should be used for pre-molar teeth and are not indicated in molar region due to the high occlusion force transmission[21,70]. Prosthesis that does not respect the long axis of the implant tends to develop inappropriate biomechanical forces on the restoration/implant assembly[71,72]. In this case, screw loosening and implant or abutment fatigue may occur[71,73]. Moreover, the cantilever force may induce peri-implant stress and bone resorption[74,75].

Increased mechanical stability and bone-implant contact are achieved using implants with a large diameter (from 5.0 up to 6.0 mm)[21,76-78]. In addition, their use provide an effective counter acting occlusal force of the magnitude that may be observed in molar areas[21,79-81]. Finally, the wide-diameter implants mimic the emergence profile of the molar tooth[8,81].

Nonetheless, due to the presence of a soft bone tissue at posterior jaw, two implants can be indicated in the first molar area[82,83]. Two implants placed very close simulate an anatomical condition of the roots, which increase in two folds the anchorage surface area. Additionally, it eliminates antero-posterior cantilevers, decreases rotational forces and screw loosening. Nevertheless, the routine oral hygiene may be more difficult and insufficient mesiodistal space limits the placement of two implants[8,21].

According to Carvalho *et al*[21], different factors can influence when making a decision between one implant with a large diameter (5 mm) or two implants with a small or regular diameter. These factors are: bone volume and density, bone height between the residual rigde and important structures such as sinus and neurovascular canals and, the availableness of bone in a mesiodistal direction.

In relation to the surface of the implant, the use of rough surface implants has outnumbered machined implants[84-88], and it is supported by evidence of earlier and greater implant stability[84-87,89]. It is also argued that this fact prevents the necessity of a second surgical stage, and even encourages earlier or immediate loading in specific cases[80,90]. But, longitudinal studies comparing the two different surfaces using identical protocols in matched population groups and surgical sites have not been accessed. Therefore, the remaining question rises if the assumed improved longitudinal clinical findings are really the result of better science or the product promotion[89].

Tilted and pterygoid implants

The insertion of tilted implants may be an important alternative to bone grafting, guided bone regeneration, nerve lateralization, short implants, or height deficient atrophic posterior jaw[23,33,50,56,59,75,91-93]. Additionally, it allows for bicortical stabilization of the implants which reduces implant micromotion during osseointegration and enhances the implant success rate[93].

Krekmanov *et al*[94] and Aparicio *et al*[95] evaluated alternatives for implant insertion in severely atrophic maxillas. The authors suggested that a mesiodistal inclination of the implant, associated or not with a bucco-palatal direction, respects the maxillary sinus and are a treatment option for reabsorbed posterior upper jaws. More recently, in a report[93] comprising 196 tilted implants in 64 atrophic posterior mandible edentulous, an absence of osseointegration resulted in failure of only two implants, and the neurovascular structures were intact.

The pterygoid implant was first introduced to be placed in the bone pillar, that is formed by the three structures: pyramidal process of the palatine bone, pterygoid process of the sphenoid bone and maxillary tuberosity[96]. While the first two are formed by dense

cortical bone, the maxillary tuberosity is based on poorer bone quality[22,24,51,96-98]. The surgeon should be aware that the maxillary artery and its branches passess through the posterior and medial regions of the maxillary tuberosity[99]. In case of full-arch implant supported restorations, the use of pterygomaxillary implants gives support and retention for the restorations and eliminate the cantilever's length that may be necessary when just anterior implants are placed[47,51,98,100].

Bahat[101] reported that 7% of the 72 implants inserted with a modified technique in the tuberosity area failed after a follow-up period of 21.4 mo, while Ridell *et al*[99] did not observe failures of any of the 22 implants placed in the same area after an accompaniment of 8 years. Peñarrocha *et al*[47] evaluated 68 pterygoid implants over 1 year of loading and found a success rate of 97.05% and a peri-implant bone loss of 0.71 mm. After that period, the patients were satisfied with the functional and esthetical aspects of the oral rehabilitation.

On the other hand, Balshi *et al*[98] found a cumulative survival rate of 90.8% of 1.608 implants placed into the pterygomaxillary region. These authors compared two-stage freehand, single-stage freehand and single-stage guided protocols. They observed that single-stage protocol exhibited higher cumulative survival rate (96.45%) than two-stage protocol (85.94%) and guided surgery (93.38%). Therefore, immediate loading of those implants is beneficial to treatment.

When implants are inserted into the tuber area, normally it is necessary to tilt the implant, which is unfavorable to the biomechanical point of view, increasing the peri-implant bone resorption and reducing implant success rates. On the other hand, previous studies showed appropriated results with tilted implants *vs* straight ones[33,59,92,95]. Maybe it occurs because the tilted implants can be longer than axial ones[99].

The use of splinted implants has been indicated to reduce the stress on tilted implants[93]. This recommendation has been originated from studies that demonstrated that splinted implants showed better stress distribution when compared to non-splinted prosthesis[67]. On the other hand, Lan *et al*[12] observed, through finite element study, that tilted implants with splinted crowns exhibited greater stress concentration, specially in implants with distal tilting. Nevertheless, additional follow-up and long-term evaluations are warranted.

Short implants

Some authors[91,102-105] have defined short implants as implants no longer than 7 mm. Others[29,106-109] have considered short implants to be implants up to 10 mm long.

The length of implants is limited to the presence of some anatomical structures as the intra-alveolar canal and the maxillary sinus, and bone resorption. In these cases, the use of short implants has been recommended[3,23,29,72,97,104,105,109-112]. From a biomechanical point of view, when an implant is loaded, the peri-implant crestal bone receives the stress from the first few threads of the implant; therefore, once a minimum implant height is osseointegrated, implant diameter is more relevant when compared to an increase in length[23,28,86,108,113-116].

To Grant *et al*[117], short implants are convenient due to: (1) usually, this technique does not require a bone grafting procedure, which results in a faster and less expensive treatment and improves the patient's confort; (2) risks during the surgery, such as nerve damage, osteotomy heat and lesions on the adjacent tooth, are reduced; and (3) there is a surgical ease, in cases of insufficient interarch spaces. However, several controversies still exist to their indication owing to: (1) reduced implant surface; thus leading to less bone-to-implant contact after osseointegration; (2) reduced surface of force distribution after loading; more pressure at the crestal bone; more resorption leading to more threads exposed, decreasing the surface of osseointegrated implant; and (3) compromised crown-to-implant ratio[118].

In case of increased crown-to-implant (C/I) ratio, the crown works as a lever arm, transferring the stress to the crestal bone around the implant[115,119], which can result in peri-implant bone loss[119,120] and problems with components of the prosthesis[66,121].

Blanes[121] found that, when the C/I ratio was higher than 2, the survival rate of the implant-retained prosthesis was 94.1%. Apparently, according to these authors, the C/I ratio did not influence the marginal bone loss. Also, Rokni *et al*[122] observed that the C/I ratio did not interfere on crestal bone loss around dental implants. Similarly, Urdaneta *et al*[73] identified the same results on single-tooth implants. However, these authors noted an increase in prosthetic complications, such as implant abutment and fracture.

Crown/Implant ratios ranging from 0.5 to 1 are important to avoid stress and bone loss at a crestal bone level, which could result in implant loss[116,123,124]. Nevertheless, Tawil *et al*[125] stated that high C/I ratios are not the most relevant agent that affect load distribution and Schneider *et al*[126] added that this increase may be used successfully in implants for single-tooth replacement in posterior jaws, except for smoking patients.

Short implants are feasible solutions in case of insufficient bone height and provide favorable force orientation and distribution[111,125]. In case of full-arch fixed dental prosthesis, short implants can be an alternative in posterior jaws to give support for the cantilever, reducing lever arms and stress loading on implants[72].

Although short implants exhibited greater failure rates that longer ones[127], some studies[3,113,128] demonstrated similar outcomes for both types of implants. Probably, these divergences resulted from other variables, such as implant surface, professional ability, bone characteristics, implant primary stability and prosthodontic protocol, which also affects the implant survival[86].

Atieh *et al*[112] performed a systematic review of 33 selected studies concerning 2573 short implants inserted in posterior upper and /or lower jaws to retain fixed partial

Table 1 Cumulative success rates of short implants placed in posterior region

Ref.	Implant surface	Implant length	N implants	Period of evaluation	Success rate (%)
Bahat[127]	Machined-surface	7 mm	-	5 to 70 mo	90.50
Winkler *et al*[130]	Machined-surface	< 10 mm	181	3 yr	93.40
Friberg *et al*[103]	Machined-surface	< 10 mm	247	8 yr	93.70
Deporter *et al*[84]	Porous-surface	7 or 9 mm	48	8.2 to 50.3 mo	100.00
Tawil *et al*[107]	Machined-surface	⩽ 10 mm	269	12 to 92 mo	95.50
Griffin *et al*[113]	Hydroxyapatite-coated	8 mm	168	Up to 68 mo	100.00
Renouard *et al*[151]	Machined or oxidized surface	6 to 8.5 mm	96	2 yr	94.60
Goené *et al*[110]	Acid-etched surface	7 or 8.5 mm	311	3 yr	95.80
Misch *et al*[85]	Roughened surface	7 or 9 mm	745	6 yr	98.90
Anitua *et al*[86]	Micro-rough acid-etched surface; bioactive surface	7 to 8.5 mm	532	5 yr	99.20
Grant *et al*[117]	-	8 mm	335	up to 2 yr	99.00
Anitua *et al*[114]	-	< 8.5 mm	1.287	1 to 8 yr	99.30
De Santis *et al*[97]	Oxidized surface	< 8.5 mm	107	1 to 3 yr	98.10
Maló *et al*[104]	Oxidized surface	7 mm	217	12 mo	95.00
Pieri *et al*[111]	-	6 mm	61	2 yr	96.80
Perelli *et al*[27]	Porous-surface	5 or 7 mm	110	5 yr	90.00
Jiansheng *et al*[109]	Hydroxyapatite-coated and ankylos	5.7 to 8 mm	162	2 yr	99.40
Slotte *et al*[29]	Acid-etched surface	4 mm	100	2 yr	92.30
Deporter *et al*[88]	Porous-surface	7 or 9 mm	48	10 yr	95.50

prosthesis. A survival rate of 98% was reported, after an accompaniment period of 5 years. When comparing short and long implants, no important differences were observed. The authors affirmed that short implants represents a viable treatment option than longer ones and that the survival rate is not related to implant surface, design or width.

Morand *et al*[118] reported that the one improvement that had the most dramatic effect in improving implant treatments was the evolution of implant surfaces from machined/polished to rough-textured surfaces. Table 1 confirms this information, evidencing higher success rates for rough surfaced implants. The percentage of bone-implant contact can be modified by the surface condition of the implant. This is important because the greater the percentage of bone contact, the lesser stress is applied to the bone-implant interface[86]. Therefore, it is possible to assure that with careful case selection criteria, the longevity of short implants is greater than 90%.

Nevertheless, besides the high success rates, the most important aspect of treatment with short implants is the case selection[23,118]. Facing severe bone resorption associated with poor bone quality and overload, bone grafting techniques could prevent failure in such associations. The success rate of short implants in patients with more favorable conditions is greater which makes it the best treatment option[129].

Occlusal considerations

The excess of loading in posterior jaws associated with the functional activity of the mandible in a buccal-lingual direction and with cusp inclination can create lateral forces onto implants[9,130-132]. Thus, during implant treatment planning, a broad evaluation of the loading is essential, since a bending moment at the peri-implant bone can result in prosthesis components damages and/or crestal bone loss[20,66,115,132,133].

Various factors can overload an implant. Rangert *et al*[134] identified two principal factors that justify this excess of loading: geometric and occlusal load reasons. The first one is related with the implant number and position, and with the prosthesis configuration. The second factor includes lateral occlusal force components and parafunctional habits, which increase the loading onto implant surfaces. If forces are higher than normal, the implant can be overloaded.

Ogawa *et al*[135] affirmed that a decrease in number of supporting implants is to promote an increase in implant loading. The bending moments were higher when prosthesis were supported by three implants than four or five implants. Additionally, concerning the implant position, the smallest implant distribution increased the bending moments.

The prevention of occlusal overload should be the focus of any treatment planning[66,136]. In case of no alternative, the prosthesis should be protected from injuries with an inter-occlusal device[67,93]. Some guidelines were reported aiming to respect physiologic limits for occlusal loading: optimized passive fit, reduction of cantilevers, adequate selection of the dimensions and number of implants, presence of a correct preload in the abutment screw and a proper buccal-lingual dimension and cusp inclination of the crown[66,132,133,137-139].

Furthermore, the principles of implant occlusion are mostly based on the traditional principles of conventional restoration. Anterior guidance should be presented and during lateral excursion, a posterior disclusion is indicated for working and non working sides. Group function disocclusion is indicated when the canine is compromised[8].

Payer *et al*[140] evaluated the outcome of edentulous posterior mandible treated with implant-retained immediate provisional prosthesis. According to these authors, immediately loaded implants exhibited similar results when

Table 2 Cumulative success rates of implants placed in posterior region

Ref.	N implants	Posterior zone	Period of evaluation	Implant systems	Success rate (%)
Jemt *et al*[4]	259	Maxilla and mandible	5 yr	Nobelpharma	97.20
Zarb *et al*[144]	105	Maxilla and mandible	2.6-7.4 yr	Nobelpharma	94.30
Block *et al*[142]	443	Mandible	10 yr		79.30
Becker *et al*[143]	282	Maxilla and mandible	6 yr	Branemark	89.40
Bahat[145]	660	Maxilla	10 yr	Branemark	93.40
Attard *et al*[5]	106	Maxilla and Mandible	10 yr	Nobel biocare	94.00
Attard *et al*[152]	432	Maxilla and Mandible	15 yr	Nobel biocare	91.60
Jebreen *et al*[7]	141	Maxilla and Mandible	12-69 mo	ITI	96.45
Blanes *et al*[6]	192	Maxilla and Mandible	10 yr	ITI	97.90
Huynh-Ba *et al*[153]	273	Maxilla	8 yr	-	94.90
Maló *et al*[70]	247	Maxilla and Mandible	11 yr	Nobel biocare	95.10
Schneider *et al*[126]	100	Maxilla and Mandible	5 yr	Nobel biocare and straumann standard	95.80

compared to conventionally loaded implants. During a follow-up period of 5 years, the survival rate was 95%.

Similarly, Degidi *et al*[136] performed a randomized clinical trial that aimed to evaluate the effect of immediately loaded and immediately restored implants for edentulous posterior lower jaws. The authors found that both procedures are predictable. No differences in marginal bone loss or survival rate were observed.

Nonetheless, concerning the conditions of early-loaded implants in the posterior upper and lower jaws, Kim *et al*[141] observed that, although early loading is a predictable procedure, it is important to be careful with maxillary implants.

Success rates

Table 2 illustrates the success rates of implants inserted in the posterior jaws of patients with partial edentulism. Favorable success rates were observed when edentulous areas were replaced with implants, except for the study of Block *et al*[142], which related lower success rates for implants inserted in posterior inferior jaws (78.5% for first molars and 71.8% for second molars). Some studies showed distinct success rates for those implants placed in the posterior regions of maxilla and mandible, with lower success rates for the posterior maxilla[4,6,7,143]. However, Zarb *et al*[144] obtained a success rate of 97.6% for the 41 implants placed in the upper jaw and, of 92.2% for the 64 implants placed in the lower jaw, after a loading period of 2.6 to 7.4 years.

The non-standardization between and within studies has increased the range in success rates, *e.g.*, 79.3% to 97.9%. The differences in study design may be the driven force toward those results. Factors such as length, number, diameter and surface of the implants, bicortical fixation, and extended healing periods contribute to a good long-term success rate[4,143,145]. When the implants are placed into soft bone tissues or inserted in regions with insufficient bone height that demands grafting procedures such as sinus lifting, lack of osseointegration[11,25,146] and failure after loading[147] are prone to occur. The same problem occurs in case of smoking patients[11,148]. Additionally, the lack of oral hygiene may be another initial factor of implant loss[133,145,149], while bicortical fixation may improve osseointegration and reduce bone resorption[116,145,150].

COMMENTS

Background

The osseointegrated implants allow a functional rehabilitation for patients with partial edentulism, since they improve the occlusion and retention of the prosthesis and the bone maintenance. However, the posterior region of the maxilla and mandible requires special attention due to their anatomical and occlusal characteristics.

Research frontiers

Implant-retained prosthesis is a common procedure for posterior partially edentulous jaw rehabilitations. The knowledge regarding this topic involves maxillofacial anatomy, physiology and radiology, oral implantology, occlusion and prosthodontics, and is directly related with patient's psychological aspects.

Innovations and breakthroughs

This review of the literature presents an accurate description of the main articles that evaluated a rehabilitation with dental implants in the posterior maxilla or mandible. Different topics, such as space for restoration, anatomic considerations, radiographic techniques, selection of number, diameter, position and length of implants, occlusal considerations and success rates, were carefully discussed in this article.

Applications

The study findings suggest that professionals need to minutely evaluate the treatment parameters to guarantee the longevity and success of the rehabilitation.

Terminology

Crown-to-implant (C/I) ratio is a guideline related with the longevity and survival of the prosthesis, since a higher C/I ratio represents a lever arm of the crown over the peri-implant bone area, which can result in bone loss.

Peer review

The work is interesting,and useful to the clinicians.

REFERENCES

1 **Ozkan Y**, Akoğlu B, Kulak-Ozkan Y. Five-year treatment outcomes with four types of implants in the posterior maxilla and mandible in partially edentulous patients: a retrospective study. *Int J Oral Maxillofac Implants* 2011; **26**: 639-647 [PMID: 21691612]

2 **Aglietta M**, Iorio Siciliano V, Blasi A, Sculean A, Brägger U, Lang NP, Salvi GE. Clinical and radiographic changes at implants supporting single-unit crowns (SCs) and fixed dental prostheses (FDPs) with one cantilever extension. A retrospective study. *Clin Oral Implants Res* 2012; **23**: 550-555 [PMID: 22250868 DOI: 10.1111/j.1600-0501.2011.02391.x]

3 **Dam HG**, Najm SA, Nurdin N, Bischof M, Finkelman M, Nedir R. A 5- to 6-year radiological evaluation of titanium

plasma sprayed/sandblasted and acid-etched implants: results from private practice. *Clin Oral Implants Res* 2014; **25**: e159-e165 [PMID: 23360220 DOI: 10.1111/clr.12083]
4 **Jemt T**, Lekholm U. Oral implant treatment in posterior partially edentulous jaws: a 5-year follow-up report. *Int J Oral Maxillofac Implants* 1993; **8**: 635-640 [PMID: 8181825]
5 **Attard N**, Zarb GA. Implant prosthodontic management of posterior partial edentulism: long-term follow-up of a prospective study. *J Can Dent Assoc* 2002; **68**: 118-124 [PMID: 11869502]
6 **Blanes RJ**, Bernard JP, Blanes ZM, Belser UC. A 10-year prospective study of ITI dental implants placed in the posterior region. I: Clinical and radiographic results. *Clin Oral Implants Res* 2007; **18**: 699-706 [PMID: 17991252]
7 **Jebreen SE**, Khraisat A. Multicenter retrospective study of ITI implant-supported posterior partial prosthesis in Jordan. *Clin Implant Dent Relat Res* 2007; **9**: 89-93 [PMID: 17535332]
8 **Jivraj S**, Chee W. Treatment planning of implants in posterior quadrants. *Br Dent J* 2006; **201**: 13-23 [PMID: 16829878]
9 **Chang SH**, Lin CL, Hsue SS, Lin YS, Huang SR. Biomechanical analysis of the effects of implant diameter and bone quality in short implants placed in the atrophic posterior maxilla. *Med Eng Phys* 2012; **34**: 153-160 [PMID: 21807548 DOI: 10.1016/j.medengphy.2011.07.005]
10 **Jivraj S**, Corrado P, Chee W. An interdisciplinary approach to treatment planning in implant dentistry. *Br Dent J* 2007; **202**: 11-17 [PMID: 17220847]
11 **Chrcanovic BR**, Albrektsson T, Wennerberg A. Reasons for failures of oral implants. *J Oral Rehabil* 2014; **41**: 443-476 [PMID: 24612346 DOI: 10.1111/joor.12157]
12 **Lan TH**, Pan CY, Lee HE, Huang HL, Wang CH. Bone stress analysis of various angulations of mesiodistal implants with splinted crowns in the posterior mandible: a three-dimensional finite element study. *Int J Oral Maxillofac Implants* 2010; **25**: 763-770 [PMID: 20657872]
13 **Misch CE.** Dental implant prosthetics. St Louis: Mosby, 2005: 281-307
14 **Gastaldo JF**, Cury PR, Sendyk WR. Effect of the vertical and horizontal distances between adjacent implants and between a tooth and an implant on the incidence of interproximal papilla. *J Periodontol* 2004; **75**: 1242-1246 [PMID: 15515340]
15 **Simşek B**, Erkmen E, Yilmaz D, Eser A. Effects of different inter-implant distances on the stress distribution around endosseous implants in posterior mandible: a 3D finite element analysis. *Med Eng Phys* 2006; **28**: 199-213 [PMID: 15979921]
16 **Smidt A**, Venezia E, Tandlich M. Teeth realignment for enhanced posterior single implant restorations. *J Oral Maxillofac Surg* 2007; **65**: 40-46 [PMID: 17586348]
17 **Cooper LF**, Limmer BM, Gates WD. "Rules of 10"--guidelines for successful planning and treatment of mandibular edentulism using dental implants. *Compend Contin Educ Dent* 2012; **33**: 328-334; quiz 335-336 [PMID: 22616215]
18 **Basa S**, Varol A, Sener ID, Sertgoz A. Posterior maxillary segmental osteotomy for restoring the mandible with dental implants: a clinical report. *J Prosthet Dent* 2008; **99**: 340-343 [PMID: 18456044 DOI: 10.1016/S0022-3913(08)60080-3]
19 **Lee HE**, Lee KT, Tseng YC, Huang IY, Chen CM. Interdisciplinary management of unfavorable posterior intermaxillary space. *Br J Oral Maxillofac Surg* 2008; **46**: 413-415 [PMID: 18420318 DOI: 10.1016/j.bjoms.2007.10.009]
20 **Chan HL**, Benavides E, Yeh CY, Fu JH, Rudek IE, Wang HL. Risk assessment of lingual plate perforation in posterior mandibular region: a virtual implant placement study using cone-beam computed tomography. *J Periodontol* 2011; **82**: 129-135 [PMID: 20653440 DOI: 10.1902/jop.2010.100313]
21 **Carvalho W**, Casado PL, Caúla AL, Barboza EP. Implants for single first molar replacement: important treatment concerns. *Implant Dent* 2004; **13**: 328-335 [PMID: 15591994]
22 **Okumura N**, Stegaroiu R, Kitamura E, Kurokawa K, Nomura S. Influence of maxillary cortical bone thickness, implant design and implant diameter on stress around implants: a three-dimensional finite element analysis. *J Prosthodont Res* 2010; **54**: 133-142 [PMID: 20153281 DOI: 10.1016/j.jpor.2009.12.004]
23 **Raviv E**, Turcotte A, Harel-Raviv M. Short dental implants in reduced alveolar bone height. *Quintessence Int* 2010; **41**: 575-579 [PMID: 20614044]
24 **de Almeida EO**, Rocha EP, Freitas AC, Freitas MM. Finite element stress analysis of edentulous mandibles with different bone types supporting multiple-implant superstructures. *Int J Oral Maxillofac Implants* 2010; **25**: 1108-1114 [PMID: 21197486]
25 **Conrad HJ**, Jung J, Barczak M, Basu S, Seong WJ. Retrospective cohort study of the predictors of implant failure in the posterior maxilla. *Int J Oral Maxillofac Implants* 2011; **26**: 154-162 [PMID: 21365051]
26 **Barone A**, Orlando B, Tonelli P, Covani U. Survival rate for implants placed in the posterior maxilla with and without sinus augmentation: a comparative cohort study. *J Periodontol* 2011; **82**: 219-226 [PMID: 20831372 DOI: 10.1902/jop.2010.100177]
27 **Perelli M**, Abundo R, Corrente G, Saccone C. Short (5 and 7 mm long) porous implants in the posterior atrophic maxilla: a 5-year report of a prospective single-cohort study. *Eur J Oral Implantol* 2012; **5**: 265-272 [PMID: 23000710]
28 **Li T**, Yang X, Zhang D, Zhou H, Shao J, Ding Y, Kong L. Analysis of the biomechanical feasibility of a wide implant in moderately atrophic maxillary sinus region with finite element method. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; **114**: e1-e8 [PMID: 22769414 DOI: 10.1016/j.oooo.2011.08.010]
29 **Slotte C**, Grønningsaeter A, Halmøy AM, Öhrnell LO, Stroh G, Isaksson S, Johansson LÅ, Mordenfeld A, Eklund J, Embring J. Four-millimeter implants supporting fixed partial dental prostheses in the severely resorbed posterior mandible: two-year results. *Clin Implant Dent Relat Res* 2012; **14** Suppl 1: e46-e58 [PMID: 21599827 DOI: 10.1111/j.1708-8208.2011.00346.x]
30 **Kopecka D**, Simunek A, Brazda T, Rota M, Slezak R, Capek L. Relationship between subsinus bone height and bone volume requirements for dental implants: a human radiographic study. *Int J Oral Maxillofac Implants* 2012; **27**: 48-54 [PMID: 22299078]
31 **Nunes LS**, Bornstein MM, Sendi P, Buser D. Anatomical characteristics and dimensions of edentulous sites in the posterior maxillae of patients referred for implant therapy. *Int J Periodontics Restorative Dent* 2013; **33**: 337-345 [PMID: 23593627 DOI: 10.11607/prd.1475]
32 **Lautner N**, McCoy M, Gaggl A, Krenkel C. Intramandibular course of the mandibular nerve; clinical significance for distraction and implantology. *Rev Stomatol Chir Maxillofac* 2012; **113**: 161-168 [PMID: 22483343 DOI: 10.1016/j.sto-max.2012.02.002]
33 **Peñarrocha Diago M**, Maestre Ferrín L, Peñarrocha Oltra D, Canullo L, Calvo Guirado JL, Peñarrocha Diago M. Tilted implants for the restoration of posterior mandibles with horizontal atrophy: an alternative treatment. *J Oral Maxillofac Surg* 2013; **71**: 856-864 [PMID: 23415467 DOI: 10.1016/j.joms.2012.12.016]
34 **Vazquez L**, Nizam Al Din Y, Christoph Belser U, Combescure C, Bernard JP. Reliability of the vertical magnification factor on panoramic radiographs: clinical implications for posterior mandibular implants. *Clin Oral Implants Res* 2011; **22**: 1420-1425 [PMID: 21435009 DOI: 10.1111/j.1600-0501.2010.02131.x]
35 **Greenstein G**, Tarnow D. The mental foramen and nerve: clinical and anatomical factors related to dental implant placement: a literature review. *J Periodontol* 2006; **77**: 1933-1943 [PMID: 17209776]
36 **Perelli M**, Abundo R, Corrente G, Saccone C. Short (5 and 7 mm long) porous implant in the posterior atrophic mandible: a 5-year report of a prospective study. *Eur J Oral Implantol* 2011; **4**: 363-368 [PMID: 22282732]
37 **Massey ND**, Galil KA, Wilson TD. Determining position

of the inferior alveolar nerve via anatomical dissection and micro-computed tomography in preparation for dental implants. *J Can Dent Assoc* 2013; **79**: d39 [PMID: 23920072]
38 **Leong DJ**, Chan HL, Yeh CY, Takarakis N, Fu JH, Wang HL. Risk of lingual plate perforation during implant placement in the posterior mandible: a human cadaver study. *Implant Dent* 2011; **20**: 360-363 [PMID: 21811168 DOI: 10.1097/ID.0b013e3182263555]
39 **Turkyilmaz I**, McGlumphy EA. Influence of bone density on implant stability parameters and implant success: a retrospective clinical study. *BMC Oral Health* 2008; **8**: 32 [PMID: 19025637 DOI: 10.1186/1472-6831-8-32]
40 **Sakka S**, Coulthard P. Bone quality: a reality for the process of osseointegration. *Implant Dent* 2009; **18**: 480-485 [PMID: 20009601 DOI: 10.1097/ID.0b013e3181bb840d]
41 **Fuh LJ**, Huang HL, Chen CS, Fu KL, Shen YW, Tu MG, Shen WC, Hsu JT. Variations in bone density at dental implant sites in different regions of the jawbone. *J Oral Rehabil* 2010; **37**: 346-351 [PMID: 20113389 DOI: 10.1111/j.1365-2842.2010.02061.x]
42 **Sogo M**, Ikebe K, Yang TC, Wada M, Maeda Y. Assessment of bone density in the posterior maxilla based on Hounsfield units to enhance the initial stability of implants. *Clin Implant Dent Relat Res* 2012; **14** Suppl 1: e183-e187 [PMID: 22176704 DOI: 10.1111/j.1708-8208.2011.00423.x]
43 **Friberg B**, Sennerby L, Gröndahl K, Bergström C, Bäck T, Lekholm U. On cutting torque measurements during implant placement: a 3-year clinical prospective study. *Clin Implant Dent Relat Res* 1999; **1**: 75-83 [PMID: 11359301]
44 **Meredith N**, Alleyne D, Cawley P. Quantitative determination of the stability of the implant-tissue interface using resonance frequency analysis. *Clin Oral Implants Res* 1996; **7**: 261-267 [PMID: 9151590]
45 **Pramstraller M**, Farina R, Franceschetti G, Pramstraller C, Trombelli L. Ridge dimensions of the edentulous posterior maxilla: a retrospective analysis of a cohort of 127 patients using computerized tomography data. *Clin Oral Implants Res* 2011; **22**: 54-61 [PMID: 20831759 DOI: 10.1111/j.1600-0501.2010.01984.x]
46 **Del Fabbro M**, Testori T, Francetti L, Weinstein R. Systematic review of survival rates for implants placed in the grafted maxillary sinus. *Int J Periodontics Restorative Dent* 2004; **24**: 565-577 [PMID: 15626319]
47 **Peñarrocha M**, Carrillo C, Boronat A, Peñarrocha M. Retrospective study of 68 implants placed in the pterygomaxillary region using drills and osteotomes. *Int J Oral Maxillofac Implants* 2009; **24**: 720-726 [PMID: 19885414]
48 **Chiapasco M**, Zaniboni M. Methods to treat the edentulous posterior maxilla: implants with sinus grafting. *J Oral Maxillofac Surg* 2009; **67**: 867-871 [PMID: 19304048 DOI: 10.1016/j.joms.2008.11.023]
49 **Migliorança RM**, Coppedê A, Dias Rezende RC, de Mayo T. Restoration of the edentulous maxilla using extrasinus zygomatic implants combined with anterior conventional implants: a retrospective study. *Int J Oral Maxillofac Implants* 2011; **26**: 665-672 [PMID: 21691615]
50 **Bedrossian E**. Rescue implant concept: the expanded use of the zygoma implant in the graftless solutions. *Oral Maxillofac Surg Clin North Am* 2011; **23**: 257-276, vi [PMID: 21492800 DOI: 10.1016/j.coms.2011.01.009]
51 **Candel E**, Peñarrocha D, Peñarrocha M. Rehabilitation of the atrophic posterior maxilla with pterygoid implants: a review. *J Oral Implantol* 2012; **38** Spec No: 461-466 [PMID: 21568718 DOI: 10.1563/AAID-JOI-D-10-00200]
52 **Testori T**, Weinstein RL, Taschieri S, Del Fabbro M. Risk factor analysis following maxillary sinus augmentation: a retrospective multicenter study. *Int J Oral Maxillofac Implants* 2012; **27**: 1170-1176 [PMID: 23057031]
53 **Bou Serhal C**, Jacobs R, Persoons M, Hermans R, van Steenberghe D. The accuracy of spiral tomography to assess bone quantity for the preoperative planning of implants in the posterior maxilla. *Clin Oral Implants Res* 2000; **11**: 242-247 [PMID: 11168215]
54 **Parnia F**, Fard EM, Mahboub F, Hafezeqoran A, Gavgani FE. Tomographic volume evaluation of submandibular fossa in patients requiring dental implants. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; **109**: e32-e36 [PMID: 20123366 DOI: 10.1016/j.tripleo.2009.08.035]
55 **Schropp L**, Stavropoulos A, Gotfredsen E, Wenzel A. Comparison of panoramic and conventional cross-sectional tomography for preoperative selection of implant size. *Clin Oral Implants Res* 2011; **22**: 424-429 [PMID: 21054555 DOI: 10.1111/j.1600-0501.2010.02006.x]
56 **Fortin T**, Camby E, Alik M, Isidori M, Bouchet H. Panoramic images versus three-dimensional planning software for oral implant planning in atrophied posterior maxillary: a clinical radiological study. *Clin Implant Dent Relat Res* 2013; **15**: 198-204 [PMID: 21477064 DOI: 10.1111/j.1708-8208.2011.00342.x]
57 **Kamrun N**, Tetsumura A, Nomura Y, Yamaguchi S, Baba O, Nakamura S, Watanabe H, Kurabayashi T. Visualization of the superior and inferior borders of the mandibular canal: a comparative study using digital panoramic radiographs and cross-sectional computed tomography images. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013; **115**: 550-557 [PMID: 23522648 DOI: 10.1016/j.oooo.2013.01.001]
58 **Lofthag-Hansen S**, Gröndahl K, Ekestubbe A. Cone-beam CT for preoperative implant planning in the posterior mandible: visibility of anatomic landmarks. *Clin Implant Dent Relat Res* 2009; **11**: 246-255 [PMID: 18783419 DOI: 10.1111/j.1708-8208.2008.00114.x]
59 **Agliardi E**, Clericò M, Ciancio P, Massironi D. Immediate loading of full-arch fixed prostheses supported by axial and tilted implants for the treatment of edentulous atrophic mandibles. *Quintessence Int* 2010; **41**: 285-293 [PMID: 20305862]
60 **Mehra A**, Pai KM. Evaluation of dimensional accuracy of panoramic cross-sectional tomography, its ability to identify the inferior alveolar canal, and its impact on estimation of appropriate implant dimensions in the mandibular posterior region. *Clin Implant Dent Relat Res* 2012; **14**: 100-111 [PMID: 19673959 DOI: 10.1111/j.1708-8208.2009.00226.x]
61 **Daróz SR**, Cardoso ES, Manso MC, Vidigal GM. Evaluation of bone width lateral to the mandibular canal as an alternative approach for implant installation. *Implant Dent* 2013; **22**: 97-101 [PMID: 23303270 DOI: 10.1097/ID.0b013e31827e8640]
62 **Kawamata A**, Ariji Y, Langlais RP. Three-dimensional computed tomography imaging in dentistry. *Dent Clin North Am* 2000; **44**: 395-410 [PMID: 10740775]
63 **Ito K**, Gomi Y, Sato S, Arai Y, Shinoda K. Clinical application of a new compact CT system to assess 3-D images for the preoperative treatment planning of implants in the posterior mandible A case report. *Clin Oral Implants Res* 2001; **12**: 539-542 [PMID: 11564116]
64 **Maloney K**, Bastidas J, Freeman K, Olson TR, Kraut RA. Cone beam computed tomography and SimPlant materialize dental software versus direct measurement of the width and height of the posterior mandible: an anatomic study. *J Oral Maxillofac Surg* 2011; **69**: 1923-1929 [PMID: 21496995 DOI: 10.1016/j.joms.2011.01.003]
65 **Chen XY**, Zhang CY, Nie EM, Zhang MC. Treatment planning of implants when 3 mandibular posterior teeth are missing: a 3-dimensional finite element analysis. *Implant Dent* 2012; **21**: 340-343 [PMID: 22814561 DOI: 10.1097/ID.0b013e31825cbc67]
66 **Rangert B**, Krogh PH, Langer B, Van Roekel N. Bending overload and implant fracture: a retrospective clinical analysis. *Int J Oral Maxillofac Implants* 1995; **10**: 326-334 [PMID: 7615329]
67 **Guichet DL**, Yoshinobu D, Caputo AA. Effect of splinting

and interproximal contact tightness on load transfer by implant restorations. *J Prosthet Dent* 2002; **87**: 528-535 [PMID: 12070516]

68 **Clelland NL**, Seidt JD, Daroz LG, McGlumphy EA. Comparison of strains for splinted and nonsplinted implant prostheses using three-dimensional image correlation. *Int J Oral Maxillofac Implants* 2010; **25**: 953-959 [PMID: 20862409]

69 **Vigolo P**, Zaccaria M. Clinical evaluation of marginal bone level change of multiple adjacent implants restored with splinted and nonsplinted restorations: a 5-year prospective study. *Int J Oral Maxillofac Implants* 2010; **25**: 1189-1194 [PMID: 21197497]

70 **Maló P**, de Araújo Nobre M. Implants (3.3 mm diameter) for the rehabilitation of edentulous posterior regions: a retrospective clinical study with up to 11 years of follow-up. *Clin Implant Dent Relat Res* 2011; **13**: 95-103 [PMID: 19681926 DOI: 10.1111/j.1708-8208.2009.00188.x]

71 **Becker W**, Becker BE. Replacement of maxillary and mandibular molars with single endosseous implant restorations: a retrospective study. *J Prosthet Dent* 1995; **74**: 51-55 [PMID: 7674191]

72 **Ogawa T**, Dhaliwal S, Naert I, Mine A, Kronstrom M, Sasaki K, Duyck J. Effect of tilted and short distal implants on axial forces and bending moments in implants supporting fixed dental prostheses: an in vitro study. *Int J Prosthodont* 1995; **23**: 566-573 [PMID: 21209995]

73 **Urdaneta RA**, Rodriguez S, McNeil DC, Weed M, Chuang SK. The effect of increased crown-to-implant ratio on single-tooth locking-taper implants. *Int J Oral Maxillofac Implants* 2010; **25**: 729-743 [PMID: 20657868]

74 **Sullivan DY**. Wide implants for wide teeth. *Dent Econ* 1994; **84**: 82-83 [PMID: 8612905]

75 **Balleri P**, Ferrari M, Veltri M. One-year outcome of implants strategically placed in the retrocanine bone triangle. *Clin Implant Dent Relat Res* 2010; **12**: 324-330 [PMID: 19438960 DOI: 10.1111/j.1708-8208.2009.00170.x]

76 **Schincaglia GP**, Marzola R, Giovanni GF, Chiara CS, Scotti R. Replacement of mandibular molars with single-unit restorations supported by wide-body implants: immediate versus delayed loading. A randomized controlled study. *Int J Oral Maxillofac Implants* 2008; **23**: 474-480 [PMID: 18700371]

77 **Ivanoff CJ**, Sennerby L, Johansson C, Rangert B, Lekholm U. Influence of implant diameters on the integration of screw implants. An experimental study in rabbits. *Int J Oral Maxillofac Surg* 1997; **26**: 141-148 [PMID: 9151173]

78 **Ivanoff CJ**, Gröndahl K, Sennerby L, Bergström C, Lekholm U. Influence of variations in implant diameters: a 3- to 5-year retrospective clinical report. *Int J Oral Maxillofac Implants* 1999; **14**: 173-180 [PMID: 10212533]

79 **Matsushita Y**, Kitoh M, Mizuta K, Ikeda H, Suetsugu T. Two-dimensional FEM analysis of hydroxyapatite implants: diameter effects on stress distribution. *J Oral Implantol* 1990; **16**: 6-11 [PMID: 2074593]

80 **Calandriello R**, Tomatis M. Immediate occlusal loading of single lower molars using Brånemark System® Wide Platform TiUnite™ implants: a 5-year follow-up report of a prospective clinical multicenter study. *Clin Implant Dent Relat Res* 2011; **13**: 311-318 [PMID: 19673926 DOI: 10.1111/j.1708-8208.2009.00214.x]

81 **Fugazzotto PA**, Hains FO. Immediate implant placement in posterior areas: the mandibular arch. *Compend Contin Educ Dent* 2012; **33**: 494-496, 498, 500 passim; quiz 507, 510 [PMID: 22908599]

82 **Balshi TJ**, Wolfinger GJ. Two-implant-supported single molar replacement: interdental space requirements and comparison to alternative options. *Int J Periodontics Restorative Dent* 1997; **17**: 426-435 [PMID: 9497731]

83 **Sato Y**, Shindoi N, Hosokawa R, Tsuga K, Akagawa Y. Biomechanical effects of double or wide implants for single molar replacement in the posterior mandibular region. *J Oral Rehabil* 2000; **27**: 842-845 [PMID: 11065018]

84 **Deporter D**, Pilliar RM, Todescan R, Watson P, Pharoah M. Managing the posterior mandible of partially edentulous patients with short, porous-surfaced dental implants: early data from a clinical trial. *Int J Oral Maxillofac Implants* 2001; **16**: 653-658 [PMID: 11669247]

85 **Misch CE**, Steignga J, Barboza E, Misch-Dietsh F, Cianciola LJ, Kazor C. Short dental implants in posterior partial edentulism: a multicenter retrospective 6-year case series study. *J Periodontol* 2006; **77**: 1340-1347 [PMID: 16937587]

86 **Anitua E**, Orive G, Aguirre JJ, Andía I. Five-year clinical evaluation of short dental implants placed in posterior areas: a retrospective study. *J Periodontol* 2008; **79**: 42-48 [PMID: 18166091 DOI: 10.1902/jop.2008.070142]

87 **Bratu EA**, Tandlich M, Shapira L. A rough surface implant neck with microthreads reduces the amount of marginal bone loss: a prospective clinical study. *Clin Oral Implants Res* 2009; **20**: 827-832 [PMID: 19508341 DOI: 10.1111/j.1600-0501.2009.01730.x]

88 **Deporter DA**, Kermalli J, Todescan R, Atenafu E. Performance of sintered, porous-surfaced, press-fit implants after 10 years of function in the partially edentulous posterior mandible. *Int J Periodontics Restorative Dent* 2012; **32**: 563-570 [PMID: 22754904]

89 **Zarb G**, Attard N. Implant management of posterior partial edentulism. *Int J Prosthodont* 2007; **20**: 371-373 [PMID: 17695865]

90 **Fung K**, Marzola R, Scotti R, Tadinada A, Schincaglia GP. A 36-month randomized controlled split-mouth trial comparing immediately loaded titanium oxide-anodized and machined implants supporting fixed partial dentures in the posterior mandible. *Int J Oral Maxillofac Implants* 2011; **26**: 631-638 [PMID: 21691611]

91 **Friberg B**. The posterior maxilla: clinical considerations and current concepts using Brånemark System implants. *Periodontol 2000* 2008; **47**: 67-78 [PMID: 18412574 DOI: 10.1111/j.1600-0757.2007.00238.x]

92 **Bevilacqua M**, Tealdo T, Menini M, Pera F, Mossolov A, Drago C, Pera P. The influence of cantilever length and implant inclination on stress distribution in maxillary implant-supported fixed dentures. *J Prosthet Dent* 2011; **105**: 5-13 [PMID: 21194582 DOI: 10.1016/S0022-3913(10)60182-5]

93 **Pancko F**, Dyer J, Weisglass S, Kraut RA. Use of tilted implants in treatment of the atrophic posterior mandible: a preliminary report of a novel approach. *J Oral Maxillofac Surg* 2010; **68**: 407-413 [PMID: 20116715 DOI: 10.1016/j.joms.2009.08.003]

94 **Krekmanov L**, Kahn M, Rangert B, Lindström H. Tilting of posterior mandibular and maxillary implants for improved prosthesis support. *Int J Oral Maxillofac Implants* 2000; **15**: 405-414 [PMID: 10874806]

95 **Aparicio C**, Perales P, Rangert B. Tilted implants as an alternative to maxillary sinus grafting: a clinical, radiologic, and periotest study. *Clin Implant Dent Relat Res* 2001; **3**: 39-49 [PMID: 11441542]

96 **Lee SP**, Paik KS, Kim MK. Anatomical study of the pyramidal process of the palatine bone in relation to implant placement in the posterior maxilla. *J Oral Rehabil* 2001; **28**: 125-132 [PMID: 11298260]

97 **De Santis D**, Cucchi A, Longhi C, Vincenzo B. Short threaded implants with an oxidized surface to restore posterior teeth: 1- to 3-year results of a prospective study. *Int J Oral Maxillofac Implants* 2011; **26**: 393-403 [PMID: 21483893]

98 **Balshi TJ**, Wolfinger GJ, Slauch RW, Balshi SF. A retrospective comparison of implants in the pterygomaxillary region: implant placement with two-stage, single-stage, and guided surgery protocols. *Int J Oral Maxillofac Implants* 2013; **28**: 184-189 [PMID: 23377065 DOI: 10.11607/jomi.2693]

99 **Ridell A**, Gröndahl K, Sennerby L. Placement of Brånemark implants in the maxillary tuber region: anatomical considerations, surgical technique and long-term results.

Clin Oral Implants Res 2009; **20**: 94-98 [PMID: 19126113 DOI: 10.1111/j.1600-0501.2007.01491.x]
100 **Balshi TJ**, Wolfinger GJ, Balshi SF. Analysis of 356 pterygomaxillary implants in edentulous arches for fixed prosthesis anchorage. *Int J Oral Maxillofac Implants* 1999; **14**: 398-406 [PMID: 10379114]
101 **Bahat O**. Osseointegrated implants in the maxillary tuberosity: report on 45 consecutive patients. *Int J Oral Maxillofac Implants* 1992; **7**: 459-467 [PMID: 1299641]
102 **Johns RB**, Jemt T, Heath MR, Hutton JE, McKenna S, McNamara DC, van Steenberghe D, Taylor R, Watson RM, Herrmann I. A multicenter study of overdentures supported by Brånemark implants. *Int J Oral Maxillofac Implants* 1992; **7**: 513-522 [PMID: 1299648]
103 **Friberg B**, Gröndahl K, Lekholm U, Brånemark PI. Long-term follow-up of severely atrophic edentulous mandibles reconstructed with short Brånemark implants. *Clin Implant Dent Relat Res* 2000; **2**: 184-189 [PMID: 11359277]
104 **Maló P**, Nobre Md, Lopes A. Short implants in posterior jaws. A prospective 1-year study. *Eur J Oral Implantol* 2011; **4**: 47-53 [PMID: 21594219]
105 **Srinivasan M**, Vazquez L, Rieder P, Moraguez O, Bernard JP, Belser UC. Efficacy and predictability of short dental implants (& lt; 8 mm): a critical appraisal of the recent literature. *Int J Oral Maxillofac Implants* 2012; **27**: 1429-1437 [PMID: 23189293]
106 **Testori T**, Wiseman L, Woolfe S, Porter SS. A prospective multicenter clinical study of the Osseotite implant: four-year interim report. *Int J Oral Maxillofac Implants* 2001; **16**: 193-200 [PMID: 11324207]
107 **Tawil G**, Younan R. Clinical evaluation of short, machined-surface implants followed for 12 to 92 months. *Int J Oral Maxillofac Implants* 2003; **18**: 894-901 [PMID: 14696666]
108 **Telleman G**, Raghoebar GM, Vissink A, Meijer HJ. Impact of platform switching on inter-proximal bone levels around short implants in the posterior region; 1-year results from a randomized clinical trial. *J Clin Periodontol* 2012; **39**: 688-697 [PMID: 22540412 DOI: 10.1111/j.1600-051X.2012.01887.x]
109 **Jiansheng H**, Dongying X, Xianfeng W, Baoyi X, Qiong L, Jincai Z. Clinical evaluation of short and wide-diameter implants immediately placed into extraction sockets of posterior areas: a 2-year retrospective study. *J Oral Implantol* 2012; **38**: 729-737 [PMID: 23317299 DOI: 10.1563/AAID-JOI-D-11-00168]
110 **Goené R**, Bianchesi C, Hüerzeler M, Del Lupo R, Testori T, Davarpanah M, Jalbout Z. Performance of short implants in partial restorations: 3-year follow-up of Osseotite implants. *Implant Dent* 2005; **14**: 274-280 [PMID: 16160574]
111 **Pieri F**, Aldini NN, Fini M, Marchetti C, Corinaldesi G. Preliminary 2-year report on treatment outcomes for 6-mm-long implants in posterior atrophic mandibles. *Int J Prosthodont* 2012; **25**: 279-289 [PMID: 22545259]
112 **Atieh MA**, Zadeh H, Stanford CM, Cooper LF. Survival of short dental implants for treatment of posterior partial edentulism: a systematic review. *Int J Oral Maxillofac Implants* 2012; **27**: 1323-1331 [PMID: 23189281]
113 **Griffin TJ**, Cheung WS. The use of short, wide implants in posterior areas with reduced bone height: a retrospective investigation. *J Prosthet Dent* 2004; **92**: 139-144 [PMID: 15295322]
114 **Anitua E**, Orive G. Short implants in maxillae and mandibles: a retrospective study with 1 to 8 years of follow-up. *J Periodontol* 2010; **81**: 819-826 [PMID: 20450361 DOI: 10.1902/jop.2010.090637]
115 **Sotto-Maior BS**, Senna PM, da Silva WJ, Rocha EP, Del Bel Cury AA. Influence of crown-to-implant ratio, retention system, restorative material, and occlusal loading on stress concentrations in single short implants. *Int J Oral Maxillofac Implants* 2012; **27**: e13-e18 [PMID: 22616067]
116 **Chang SH**, Lin CL, Lin YS, Hsue SS, Huang SR. Biomechanical comparison of a single short and wide implant with monocortical or bicortical engagement in the atrophic posterior maxilla and a long implant in the augmented sinus. *Int J Oral Maxillofac Implants* 2012; **27**: e102-e111 [PMID: 23189315]
117 **Grant BT**, Pancko FX, Kraut RA. Outcomes of placing short dental implants in the posterior mandible: a retrospective study of 124 cases. *J Oral Maxillofac Surg* 2009; **67**: 713-717 [PMID: 19304026 DOI: 10.1016/j.joms.2008.11.004]
118 **Morand M**, Irinakis T. The challenge of implant therapy in the posterior maxilla: providing a rationale for the use of short implants. *J Oral Implantol* 2007; **33**: 257-266 [PMID: 17987857]
119 **Kitamura E**, Stegaroiu R, Nomura S, Miyakawa O. Biomechanical aspects of marginal bone resorption around osseointegrated implants: considerations based on a three-dimensional finite element analysis. *Clin Oral Implants Res* 2004; **15**: 401-412 [PMID: 15248874]
120 **Misch CE**, Suzuki JB, Misch-Dietsh FM, Bidez MW. A positive correlation between occlusal trauma and peri-implant bone loss: literature support. *Implant Dent* 2005; **14**: 108-116 [PMID: 15968181]
121 **Blanes RJ**. To what extent does the crown-implant ratio affect the survival and complications of implant-supported reconstructions? A systematic review. *Clin Oral Implants Res* 2009; **20** Suppl 4: 67-72 [PMID: 19663952 DOI: 10.1111/j.1600-0501.2009.01762.x]
122 **Rokni S**, Todescan R, Watson P, Pharoah M, Adegbembo AO, Deporter D. An assessment of crown-to-root ratios with short sintered porous-surfaced implants supporting prostheses in partially edentulous patients. *Int J Oral Maxillofac Implants* 2005; **20**: 69-76 [PMID: 15747676]
123 **Haas R**, Mensdorff-Pouilly N, Mailath G, Watzek G. Brånemark single tooth implants: a preliminary report of 76 implants. *J Prosthet Dent* 1995; **73**: 274-279 [PMID: 7760277]
124 **Glantz PO**, Nilner K. Biomechanical aspects of prosthetic implant-borne reconstructions. *Periodontol 2000* 1998; **17**: 119-124 [PMID: 10337319]
125 **Tawil G**, Aboujaoude N, Younan R. Influence of prosthetic parameters on the survival and complication rates of short implants. *Int J Oral Maxillofac Implants* 2006; **21**: 275-282 [PMID: 16634499]
126 **Schneider D**, Witt L, Hämmerle CH. Influence of the crown-to-implant length ratio on the clinical performance of implants supporting single crown restorations: a cross-sectional retrospective 5-year investigation. *Clin Oral Implants Res* 2012; **23**: 169-174 [PMID: 21689162 DOI: 10.1111/j.1600-0501.2011.02230.x]
127 **Bahat O**. Treatment planning and placement of implants in the posterior maxillae: report of 732 consecutive Nobelpharma implants. *Int J Oral Maxillofac Implants* 1993; **8**: 151-161 [PMID: 8359870]
128 **Nedir R**, Bischof M, Briaux JM, Beyer S, Szmukler-Moncler S, Bernard JP. A 7-year life table analysis from a prospective study on ITI implants with special emphasis on the use of short implants. Results from a private practice. *Clin Oral Implants Res* 2004; **15**: 150-157 [PMID: 15085870]
129 **das Neves FD**, Fones D, Bernardes SR, do Prado CJ, Neto AJ. Short implants--an analysis of longitudinal studies. *Int J Oral Maxillofac Implants* 2006; **21**: 86-93 [PMID: 16519186]
130 **Winkler S**, Morris HF, Ochi S. Implant survival to 36 months as related to length and diameter. *Ann Periodontol* 2000; **5**: 22-31 [PMID: 11885179]
131 **Tagger Green N**, Machtei EE, Horwitz J, Peled M. Fracture of dental implants: literature review and report of a case. *Implant Dent* 2002; **11**: 137-143 [PMID: 12078595]
132 **Conrad HJ**, Schulte JK, Vallee MC. Fractures related to occlusal overload with single posterior implants: a clinical report. *J Prosthet Dent* 2008; **99**: 251-256 [PMID: 18395533 DOI: 10.1016/S0022-3913(08)00041-3]
133 **Mattheos N**, Schittek Janda M, Zampelis A, Chronopoulos V. Reversible, non-plaque-induced loss of osseointegration

of successfully loaded dental implants. *Clin Oral Implants Res* 2013; **24**: 347-354 [PMID: 22931471 DOI: 10.1111/clr.12009]
134 **Rangert BR**, Sullivan RM, Jemt TM. Load factor control for implants in the posterior partially edentulous segment. *Int J Oral Maxillofac Implants* 1997; **12**: 360-370 [PMID: 9197101]
135 **Ogawa T**, Dhaliwal S, Naert I, Mine A, Kronstrom M, Sasaki K, Duyck J. Impact of implant number, distribution and prosthesis material on loading on implants supporting fixed prostheses. *J Oral Rehabil* 2010; **37**: 525-531 [PMID: 20236236 DOI: 10.1111/j.1365-2842.2010.02076.x]
136 **Degidi M**, Nardi D, Piattelli A. A comparison between immediate loading and immediate restoration in cases of partial posterior mandibular edentulism: a 3-year randomized clinical trial. *Clin Oral Implants Res* 2010; **21**: 682-687 [PMID: 20412091 DOI: 10.1111/j.1600-0501.2009.01910.x]
137 **Bakaeen LG**, Winkler S, Neff PA. The effect of implant diameter, restoration design, and occlusal table variations on screw loosening of posterior single-tooth implant restorations. *J Oral Implantol* 2001; **27**: 63-72 [PMID: 12498429]
138 **Assunção WG**, Gomes EA, Rocha EP, Delben JA. Three-dimensional finite element analysis of vertical and angular misfit in implant-supported fixed prostheses. *Int J Oral Maxillofac Implants* 2011; **26**: 788-796 [PMID: 21841989]
139 **Bacchi A**, Consani RL, Mesquita MF, dos Santos MB. Stress distribution in fixed-partial prosthesis and peri-implant bone tissue with different framework materials and vertical misfit levels: a three-dimensional finite element analysis. *J Oral Sci* 2013; **55**: 239-244 [PMID: 24042591]
140 **Payer M**, Heschl A, Wimmer G, Wegscheider W, Kirmeier R, Lorenzoni M. Immediate provisional restoration of screw-type implants in the posterior mandible: results after 5 years of clinical function. *Clin Oral Implants Res* 2010; **21**: 815-821 [PMID: 20465555 DOI: 10.1111/j.1600-0501.2010.01919.x]
141 **Kim JH**, Yang JY, Kim YK, Heo YK, Yeo IS. Retrospective results of implants for partially edentulous posterior jaws according to time points of early loading. *Int J Oral Maxillofac Implants* 2013; **28**: 1293-1299 [PMID: 24066320 DOI: 10.11607/jomi.2884]
142 **Block MS**, Gardiner D, Kent JN, Misiek DJ, Finger IM, Guerra L. Hydroxyapatite-coated cylindrical implants in the posterior mandible: 10-year observations. *Int J Oral Maxillofac Implants* 1996; **11**: 626-633 [PMID: 8908861]
143 **Becker W**, Becker BE, Alsuwyed A, Al-Mubarak S. Long-term evaluation of 282 implants in maxillary and mandibular molar positions: a prospective study. *J Periodontol* 1999; **70**: 896-901 [PMID: 10476898]
144 **Zarb GA**, Schmitt A. The longitudinal clinical effectiveness of osseointegrated dental implants in posterior partially edentulous patients. *Int J Prosthodont* 1993; **6**: 189-196 [PMID: 8329097]
145 **Bahat O**. Brånemark system implants in the posterior maxilla: clinical study of 660 implants followed for 5 to 12 years. *Int J Oral Maxillofac Implants* 2000; **15**: 646-653 [PMID: 11055131]
146 **Truhlar RS**, Morris HF, Ochi S, Winkler S. Second-stage failures related to bone quality in patients receiving endosseous dental implants: DICRG Interim Report No. 7. Dental Implant Clinical Research Group. *Implant Dent* 1994; **3**: 252-255 [PMID: 7663467]
147 **Jaffin RA**, Berman CL. The excessive loss of Branemark fixtures in type IV bone: a 5-year analysis. *J Periodontol* 1991; **62**: 2-4 [PMID: 2002427]
148 **Bain CA**. Smoking and implant failure--benefits of a smoking cessation protocol. *Int J Oral Maxillofac Implants* 1996; **11**: 756-759 [PMID: 8990637]
149 **Boutros SM**, Michalowicz BS, Smith QT, Aeppli DM. Crevicular fluid enzymes from endosseous dental implants and natural teeth. *Int J Oral Maxillofac Implants* 1996; **11**: 322-330 [PMID: 8752553]
150 **Ivanoff CJ**, Sennerby L, Lekholm U. Influence of mono- and bicortical anchorage on the integration of titanium implants. A study in the rabbit tibia. *Int J Oral Maxillofac Surg* 1996; **25**: 229-235 [PMID: 8872230]
151 **Renouard F**, Nisand D. Short implants in the severely resorbed maxilla: a 2-year retrospective clinical study. *Clin Implant Dent Relat Res* 2005; **7** Suppl 1: S104-S110 [PMID: 16137095]
152 **Attard NJ**, Zarb GA. Implant prosthodontic management of partially edentulous patients missing posterior teeth: the Toronto experience. *J Prosthet Dent* 2003; **89**: 352-359 [PMID: 12690347]
153 **Huynh-Ba G**, Friedberg JR, Vogiatzi D, Ioannidou E. Implant failure predictors in the posterior maxilla: a retrospective study of 273 consecutive implants. *J Periodontol* 2008; **79**: 2256-2261 [PMID: 19053914 DOI: 10.1902/jop.2008.070602]

P- Reviewer: Chen S, Ferreira MM, Vieyra J **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Clinical Cases

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.12998/wjcc.v3.i1.77

World J Clin Cases 2015 January 16; 3(1): 77-80
ISSN 2307-8960 (online)

CASE REPORT

Giant xanthogranuloma of the pelvis with S1 origin: Complete removal with only posterior approach, technical note

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Received: June 30, 2014
Peer-review started: July 1, 2014
First decision: August 14, 2014
Revised: October 14, 2014
Accepted: October 23, 2014
Article in press: December 23, 2014
Published online: January 16, 2015

Abstract

Xanthogranulomas (XG) are benign proliferative disorder of histiocytes, a non-Langerhans cell histiocytosis. Whose etiology is unknown. The nature of these lesions is controversial and could be either reactive or neoplastic; the presence of monoclonal cells does, however, favor the second hypothesis. Xanthogranuloma is frequently found in young adults and children (under 20 years old), mainly in the skin. In about 5%-10% of all Juvenile XG (JXG) cases xanthogranuloma are extracutaneous. Within this group, the site most frequently involved is the eye. Other involved organs are heart, liver, adrenals, oropharynx, lung, spleen, central nervous system and subcutaneous tissue, although involvement of the spine is uncommon. Isolated lesions involving the sacral region are extremely rare. To date, this is the first reported case of a giant JXG arising from S1 with extension into the pelvic region in an adult spine.

Key words: Xanthogranulomas; Non-Langerhans cell histiocytosis; Touton giant cells; Congenital xanthoma; Neurofibromatosis

Core tip: Xanthogranulomas (XG) are benign lesions derived by histiocytes, also called histiocytosis with non-Langerhans cell. Isolated xanthogranuloma involving the sacral region are unique. We report the unique giant Juvenile XG arising from S1 with extension into the pelvic region in an adult spine. Complete surgical removal is the goal of the treatment and usually curative even if there is not a study in the literature with a long follow up able to confirm this. If total resection is not possible, the patients must be followed by strictly clinical examination or should undergo adjuvant radiotherapy.

Marotta N, Landi A, Mancarella C, Rocco P, Pietrantonio A, Galati G, Bolognese A, Delfini R. Giant xanthogranuloma of the pelvis with S1 origin: Complete removal with only posterior approach, technical note. *World J Clin Cases* 2015; 3(1): 77-80 Available

from: URL: http://www.wjgnet.com/2307-8960/full/v3/i1/77.htm
DOI: http://dx.doi.org/10.12998/wjcc.v3.i1.77

INTRODUCTION

Xanthogranulomas (XG) are benign proliferative disorder of histiocytes, a non-Langerhans cell histiocytosis[1]. Whose etiology is unknown. The nature of these lesions is controversial and could be either reactive or neoplastic; the presence of monoclonal cells does, however, favor the second hypothesis[2]. Xanthogranuloma is frequently found in the skin of young population, especially under 20 years old. In about 5%-10% of all Juvenile XG (JXG) cases xanthogranuloma is extracutaneous. Within this group, the eye appears to be the site most frequently involved. Other involved organs include the oropharynx, heart, liver, lung, spleen, adrenals, muscles , central nervous system and the subcutaneous tissues, although involvement of the spine is uncommon[1]. Isolated xanthogranuloma of the sacral region are extremely rare[1,3]. To date, this is the first case of a giant JXG arising from S1 with extension into the pelvic region in an adult spine.

CASE REPORT

Anamnestic data and neurologic examination

A 44-year-old man was referred to our hospital with a 9 mo history of pollakiuria, stypsis, and sciatica along the S2 left dermatome, the symptoms appeared slowly worsening. The patient underwent lumbosacral magnetic resonance imaging (MRI) with gadolinium that demonstrated the presence of a presacral, giant, well-circumscribed round formation. The lesion compressed the left S4, S3 and S2 roots and dislocated the urinary bladder, rectum, and iliac artery, and it extended ventrally from the left articular mass of S1 to the pelvic region. The lesion was hypointense on T1 weighted images and isointense on T2 ones with dishomogeneous contrast enhancement after gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) (Figure 1). The computed tomography (CT) bone scanning showed the erosion of S3-S4 foramen and bone involvement of left sacral wing. On physical examination, the patient had a positive right Lasegue sign. Rectal inspection revealed the presence of a posterior hard-elastic lesion.

Treatment

The patient underwent CT-guided biopsy at the division of general surgery of the Policlinico Umberto I. A juvenile xantogranuloma was diagnosed at the histological examination. The patient was then referred to our attention and underwent surgery performing a posterior approach: the patient was placed in prone position; Intraoperative neurophysiological monitoring has been utilized. A standard electromyography monitoring of L4, L5 and S1 was conducted bilaterally. Moreover the insertion of electrodes in the urethra and anal sphincter during the surgical procedure helps to discriminate between nerve root and tumor. A U shaped skin incision was performed, followed by a complete exposure of the spinal column and partially of the sacro-iliac region with prevalent lateral extension on the left side. A complete laminectomy and partial left sacrectomy (25% of left sacrum removal) was performed. Because of the benign nature of the lesion and the space formed by tumor growth, we performed a less invasive procedure with intralesional posterior tumor removal, obtaining enough space without total sacrectomy that could be destabilizing for spine. We used the posterior approach to easily reach the lesion right after the opening of the subcutaneous layer and because it was easier to reach the origin point of the lesion and to control the S2, S3 and S4 root. Intraoperatively, the lesion appeared xanthochromic, friable, moderately bloody and presented a discontinuous capsule. The consistency was really flabby so that the cranial part of the tumor was easily mobilization and the removal was safe for structures as like as rectum and sacral plexus. The lesion was very adherent to the surrounding tissues. The lesion was macroscopically total removed. Immediately after surgery, the patient had relief of pain and had a progressive resolution of sphincter disturbances, with complete recovery after 15 d from surgery. A complete removal of the tumor was shown in the postoperative spine MRI (Figure 2). The patient was discharged on the tenth postoperative day. Clinical follow-up at 1 year showed the stability of symptoms. Radiological follow up using MRI (3T, T1, T2, STIR, T1 sequences with contrast) at 3, 6 and 12 mo showed no signs of recurrent disease.

Pathology

Gross examination showed a 13 cm × 10 cm × 13 cm round lesion, discontinuously encapsulated and adherent to surrounding tissues. The cut surface was homogeneous, yellow and of gelatinous consistency. Microscopic examination revealed the presence of typical touton giant cells. In general, a finding of such cells is sufficient for a diagnosis of xanthogranuloma. Immunohistochemical studies, in one of Dehner's series, showed an immunopositive response for CD68, factor XIIIa and Vimentin of the tumor cells, and are not reactive for S100 and CD1a (Figure 3)[4].

DISCUSSION

Proliferative disorders of histiocytes were described in 1905 by Adamson[5]. Those diseases comprehend a group of pathologies in which the main hstological patterns are dendritic cells and macrophages. The xanthogranuloma has called a non-Langerhans cell histiocytosis as soon as other entities as: Rosai-Dorfman disease (if associated with lymphadenopathy), benign cephalic histiocytosis, the papular xanthoma, and hemophagocytic histiocytosis. Xanthogranuloma is usually benign and is also known as juvenile because it occurs predominantly in young people under the age of twenty years[1]. Etiology of JXG

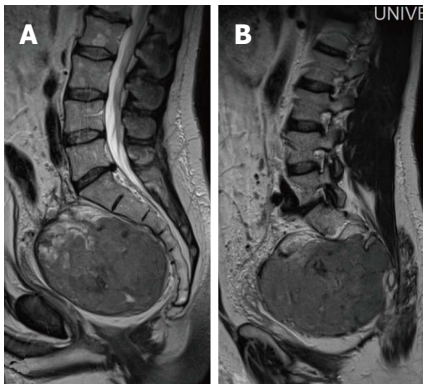

Figure 1 lumbosacral magnetic resonance imaging showing a giant, well-circumscribed round formation hypointense on T1 weighted images and isointense on T2 ones with dishomogeneous contrast enhancement after Gd-DTPA. A: A sagittal T2-wieghted midline image; B: A sagittal T2-weighted lateral image. Gd-DTPA: Gadolinium diethylenetriaminepentaacetic acid.

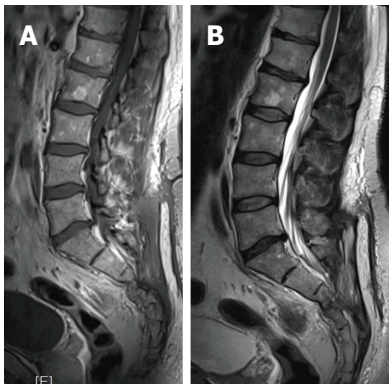

Figure 2 Postoperative spine magnetic resonance imaging showing complete removal of the tumor. A: A sagittal T1-wheighted image after Gd–DTPA; B: A sagittal T2-weighted midline image showing macroscopical total tumor removal. Gd-DTPA: Gadolinium diethylenetriaminepentaacetic acid.

is unknown, but probably is the result of alteration in macrophagic response to an aspecific injury, resulting in a granuloma.

On the other hand, the recent discovery of the monoclonal nature of the cell population of these lesions, has suggested a possible neoplastic origin[2]. The skin of neck and head are the most frequent location of the JXG 67%[3]. It can be multiple or solitary with red-to-yellowish nodules and papules. The involvement of extracutaneous tisuues occurs in about 5%-10% and mainly involves eyes (uvea). Involvement has been reported in other organs including the lung, heart, liver, oropharynx, central nervous system, spleen, adrenals, muscles and subcutaneous tissues, although spinal involvement is extremely rare[3]. The lesions are self-limiting regressing over several years and predominantly occur in childhood. In these cases, conservative treatment and clinical observation is therefore indicated. Adults do not usually experience spontaneous resolution[3] and injuries may present invasive characteristics, meaning that surgical procedures become the treatment of choice. The gold standard radiological examination is MRI, useful

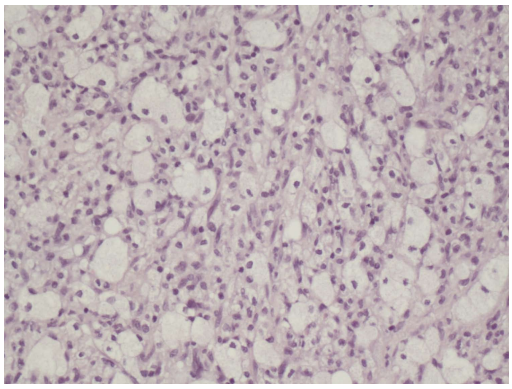

Figure 3 Histological picture: Microscopic examination revealed the presence of typical touton giant cells.

for defining the localization and relation to the other structures. Today a standard treatment for extracutaneous JXG is not defined. However, literature indicates that total removal of the tumor is the treatment of choice and it is important the excision of the origin of the tumor. According to some authors, *en-bloc* excision of the lesion to healthy margins could be a curative treatment option. If total resection is not possible, the patients should be followed under medical observation or be submitted to adjuvant radiotherapy[3]: if the symptoms recur, the patients should be re-operated[1]. On the other hand, radiation treatment, besides not being free from complications, poses the lesion at risk of malignant transformation. To date, this is the first case of giant JXG arising S1 with extension into the pelvic region in an adult spine. All spinal surgeons know and understand the risk of vascular injury because iliac arteries, aorta, and other vascular structures are strictly related to the anterior lumbar spine. We used the posterior approach to reduce the risk of vascular injury, to easily reach the lesion right after the opening of the subcutaneous layer and the origin point of the lesion and to control the S2, S3 and S4 root. Although the depth of the cable and the relationships with the adjacent vascular structures made it particularly difficult to remove the lesion, total removal was achieved by a posterior approach. The placing of neurophysiological electrodes monitor during the surgical procedure in the urethra sphincter and anal sphincter allows surgeons to distinguish between nerve roots and tumor, and to prevent urinary dysfunctions.

The follow-up at one year showed an improvement in reported preoperatively symptoms and confirmed radical removal, without any signs of disease recurrence.

A standard treatment for extracutaneous JXG is not still accepted. However, complete surgical removal is the goal of treatment although the size and the aggressive behavior of the tumor may condition the procedure. Complete surgical removal is usually curative even if there is not a study in the literature with a long follow up able to confirm this. If total resection is not possible, the patients have to be followed under close medical observation or should undergo adjuvant radiotherapy. Important is the

use of neurophysiological monitoring especially of the pelvic region to prevent any neurological dysfunction.

COMMENTS

Case characteristics

Pollakiuria, stypsis, and sciatica along the S2 left dermatome.

Clinical diagnosis

On physical examination, the patient had a positive right Lasegue sign. Rectal inspection revealed a posterior hard-elastic lesion.

Imaging diagnosis

Lumbosacral magnetic resonance imaging with gadolinium demonstrated the presence of a presacral, giant, well-circumscribed round formation. A computed tomography bone scanning showed erosion of the left sacral wing at S3-S4 foramen.

Pathological diagnosis

Microscopic examination revealed the presence of typical touton giant cells. In general, a finding of such cells is sufficient for a diagnosis of xanthogranuloma.

Treatment

Surgical treatment.

Related reports

The recent discovery of the monoclonal nature of the cell population of these lesions, has suggested a possible neoplastic origin. The lesions are self-limiting and predominantly occur in infancy and childhood, and typically regress over several years. In these cases, conservative treatment and clinical observation is therefore indicated. Adults do not usually experience spontaneous resolution and injuries may present invasive characteristics, meaning that surgical procedures become the treatment of choice.

Term explanation

Xanthogranuloma, a proliferative histiocytic disorders.

Experiences and lessons

Complete surgical removal is the gold standard for the treatment of this pathology.

Peer review

The paper describes a rare (probably unique) case of symptomatic giant xanthogranulomas of the pelvis in a 40 years old male. Authors explain clearly why they decided to manage surgically the lesion. Excision was successfully performed trough a posterior route to avoid damages to the surrounding neurovascular structures. Symptoms relief was immediate and preserved one year after surgery. The paper is really interesting.

REFERENCES

1 **Cao D**, Ma J, Yang X, Xiao J. Solitary juvenile xanthogranuloma in the upper cervical spine: case report and review of the literatures. *Eur Spine J* 2008; **17** Suppl 2: S318-S323 [PMID: 18228052 DOI: 10.1007/s00586-008-0606-0]

2 **Janssen D**, Fölster-Holst R, Harms D, Klapper W. Clonality in juvenile xanthogranuloma. *Am J Surg Pathol* 2007; **31**: 812-813 [PMID: 17460468 DOI: 10.1097/PAS.0b013e318030a3b3]

3 **Agabegi SS**, Iorio TE, Wilson JD, Fischgrund JS. Juvenile xanthogranuloma in an adult lumbar spine: a case report. *Spine* (Phila Pa 1976) 2011; **36**: E69-E73 [PMID: 21192217 DOI: 10.1097/BRS.0b013e318201b7f5]

4 **Dehner LP**. Juvenile xanthogranulomas in the first two decades of life: a clinicopathologic study of 174 cases with cutaneous and extracutaneous manifestations. *Am J Surg Pathol* 2003; **27**: 579-593 [PMID: 12717244 DOI: 10.1097/00000478-200305000-00003]

5 **Adamson HG**. Congenital xanthoma multiplex. *Br J Dermatol* 1905; **17**: 222

P- Reviewer: Naselli A, Soria F **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.12998/wjcc.v3.i1.81

World J Clin Cases 2015 January 16; 3(1): 81-84
ISSN 2307-8960 (online)

CASE REPORT

Conservative management of cervical pregnancy with intramuscular administration of methotrexate and KCl injection: Case report and review of the literature

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Received: July 29, 2014
Peer-review started: July 30, 2014
First decision: September 16, 2014
Revised: October 9, 2014
Accepted: October 28, 2014
Article in press: December 23, 2014
Published online: January 16, 2015

Abstract

We report the case of a cervical pregnancy successfully treated with intramuscular injection of methotrexate (MTX) and intramniotic administration of potassium chloride. A 41-year-old woman was admitted to our Department with the suspicion of ectopic pregnancy. Transvaginal ultrasound revealed empty endometrial cavity, gestational sac within the cervical canal and embryonic echo measuring crown rump length 1.5 mm. Serum beta human chorionic gonadotropine (β-HCG) was measured 28590 IU/L. No cardiac activity was detected. The diagnosis of a cervical pregnancy was made. Patient was treated with intramuscular administration of methotrexate (50 mg/m^2) in combination with ultrasound-guided intramniotic injection of KCl (2 meq/mL). Gradual decrease of β-HCG levels as well as ultrasound observation of collapsed gestational sac was observed. No curettage was necessitated. Patient was discharged on day 10th and was set in follow-up on a weekly basis. β-HCG values were measured < 10 IU/L on 56th day after MTX administration. Intramuscular administration of MTX may be effective in treatment of cervical pregnancy without additional interventional measures.

Key words: Cervical pregnancy; Methotrexate; Effectiveness; Conservative treatment; Intramuscular

Core tip: This case of cervical pregnancy is one amongst few treated successfully with intramuscular administration of methotrexate and intramniotic KCl, without demanding additional interventional treatment. Our paper also summarizes the basic conclusions about conservative treatment of cervical pregnancy, a challenging issue in which no consensus still exists.

Petousis S, Margioula-Siarkou C, Kalogiannidis I, Karavas G, Palapelas V, Prapas N, Rousso D. Conservative management of cervical pregnancy with intramuscular administration of methotrexate and KCl injection: Case report and review of the literature. *World J Clin Cases* 2015; 3(1): 81-84 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i1/81.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i1.81

INTRODUCTION

Cervical pregnancy represents < 1% of ectopic gestations with its estimated frequency ranging between 1:1000-1:18000 pregnancies[1]. It consists a rather challenging clinical condition that may even lead to life-threatening complications. Diagnosis is based on ultrasound imaging and may frequently present difficulties; however, it should be made as early as possible in order to avoid the risk of severe vaginal hemorrhage which may even necessitate emergency hysterectomy[2,3].

No consensus has yet been achieved regarding the optimal therapeutic approach of cervical pregnancy. Review of literature demonstrates lack of randomized clinical trials comparing the effectiveness of various therapeutic protocols as the rarity of cases poses reasonable scientific limitations. However, the trend of modern clinical practice is rather destinated to conservative management mainly based on the usage of methotrexate (MTX)[1,3,4]. MTX may be administrated intramuscularly (*i.m.*) or intramniotically (*i.a.*) and may also be combined with other therapeutic means, such as intramniotic administration of potassium chloride, vaginal mifepristone or uterine artery embolization (UAE)[4-11]. In any case, close follow-up is demanded in order to diagnose incompletely treated cases and perform additional interventions such as curettage, hysteroscopy or even hysterectomy[7,12,13].

We present the case of a cervical pregnancy which was successfully treated with intramuscular injection of MTX plus intramniotic administration of potassium chloride, without necessitating further treatment with curettage. Furthermore, a narrative review is also provided regarding the various therapeutic options regarding the optimal treatment of cervical pregnancy.

CASE REPORT

A 41-year-old woman was admitted to our Department with the suspicion of ectopic pregnancy. The woman was followed-up by a private physician, being on her 54th day of amenorrhea, with reported beta human chorionic gonadotropine (β-HCG) ranging within normal values, based on her reported last menstrual cycle. Conception was reported to be spontaneous. The patient had an obstetrical history of three pregnancies, of which the first one was delivered vaginally and the consequent two with caesarean section. Regarding medical-gynecological history, patient reported no severe additional pathology. During her physical and gynecological examination patient was haemodynamically stable. Pelvic examination was normal and cervix itself was closed.

Transvaginal ultrasound imaging at the time of admission revealed empty endometrial cavity, gestational sac within the cervical canal and embryonic echo measuring CRL 1.5 mm (Figure 1). Cardiac activity was detected at the time of diagnosis. Serum β-HCG was measured 28590 IU/L, while no other remarkable findings were observed from her blood test examination. The diagnosis of a cervical pregnancy was therefore made and patient was hospitalized for further treatment.

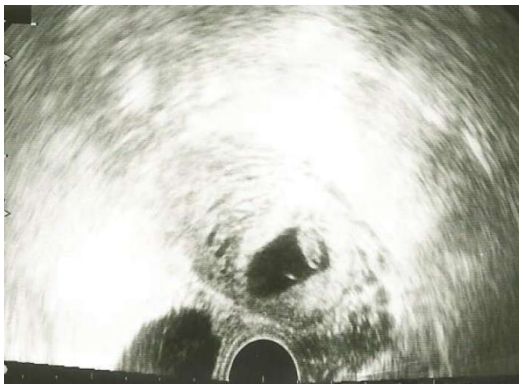

Figure 1 Ultrasound imaging of cervical pregnancy at the time of admission.

Because of patient's stable clinical condition, without signs of vaginal bleeding or pain, patient was decided to be treated with intramuscular administration of methotrexate (50 mg/m^2) in combination with ultrasound-guided intramniotic injection of KCl (2 meq/mL). Injection of KCL was well tolerated by patient without need for anesthesia administration, despite the presence of anesthesiologist during the whole procedure.

Considering that the day of medication was day 1, β-HCG was measured 25.100 IU/L on day 4, 8400 IU/L on day 7 and 1351 IU/L on day 10. Gradual decrease of β-HCG levels was also combined with ultrasound observation of collapsed gestational sac (Figure 2). No additional intervention such as curettage was decided to be performed. During hospitalization period, patient reported only minimal vaginal spotting, without reporting pain or other suspicious signs or symptoms and was therefore discharged on day 10th with the recommendation of follow-up on a weekly basis until β-HCG values are measured lower than 10 IU/L. She was also advised to use contraceptive methods of choice for the next 6 mo in order to avoid conception. Her follow-up period was totally uncomplicated, β-HCG values getting < 10 IU/L on 56th day after MTX administration. Patient was also reexamined 3 mo after cervical pregnancy diagnosis, the gynaecological examination revealing absence of residual pregnancy.

DISCUSSION

We described the case of a cervical pregnancy treated successfully with intramuscular administration of methotrexate and intramniotic injection of KCl, without necessitating additional interventional treatment.

MTX administration has been reported as an effective therapeutic option for the treatment of cervical pregnancy. However, there have been several therapeutic patterns proposed, without consensus regarding their comparative effectiveness. Ben Hamouda *et al*[14] as well as Api *et al*[15] have reported that exclusively single-dose intramuscular administration of MTX may be effective on treating cervical pregnancy without additional need for curettage[14,15]. Intramuscular MTX may also be combined

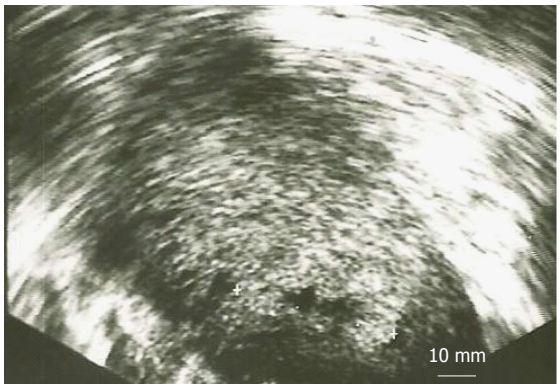

Figure 2 Ultrasound imaging of collapsed gestational sac after methotrexate treatment.

effectively with intramniotic injection of KCl[4,16], while oral mifepristone may also be co-administered effectively as reported by Shresthra *et al*[10]. Kochi *et al*[17], in another case series including 4 cervical pregnancies, have also discussed the alternative of UAE with methotrexate, a method that has been reported to be effective either as monotherapy or in combination with other medication[17]. Furthermore, apart from intramuscular injection and UAE, there is still the option of intramniotic (*i.a.*) administration of methotrexate either as mono-therapy or in combination with intramniotic injection of KCl, as characteristically described by Júnior *et al*[5] in a series of 8 successfully treated cervical pregnancies[5,18-20]. In our case, the choice of intramuscular administration of MTX was based on clinician's relative experience on this certain method of administration, given the fact of the non consensus of optimal method of treatment.

A basic endpoint of the present case report may be the fact that conservative management including *i.m.* MTX and *i.a.* KCl may be effective in treatment of cervical pregnancy without need for performing curettage. Indeed, effectiveness of exclusive administration of MTX has been reported to be as high as 81.3%, while the percentage is increased to 90% when MTX is combined with additional conservative methods[2]. However, conservative treatment with MTX may not definitely exclude the possibility of incomplete treatment, with the underlying possibility of hemorrhage still being potential[21]. Song *et al*[8], in a retrospective study including 50 cases, report that out of 30 cases being treated with *i.m.* MTX, there were only 9 cases that did not necessitate further treatment with curettage[8]. Cipullo *et al*[22], in a case series including 5 cervical pregnancies treated with im MTX + UAE reported that, because of late diagnosis, emergency hysterectomy could not be avoided in a case[22]. Furthermore, there are also reports of unsuccessful intramniotic MTX administration, such as that of Mangino *et al*[11], in which hysteroscopy was finally performed in order to effectively treat cervical pregnancy[11]. Pereira *et al*[7] have also reported the case of a residual pregnancy 3 mo after *i.m.* MTX + *i.a.* injection of KCl + UAE, therefore demonstrating that close follow-up is demanded in order to confirm definite treatment[7]. Thus, conservative treatment with MTX should definitely be combined with close follow-up, including measure of serum β-HCG levels every 3 d after the initial i.m. administration and the possibility of additional 2nd or 3rd dose or even interventional treatment should always be re-evaluated in order to avoid risk of severe hemorrhage. Besides, non-conservative treatment has also been proposed as the basic therapeutic approach by other researchers with satisfying results[23].

The most crucial point, however, regarding treatment of cervical pregnancy with MTX may be to identify patients eligible to be treated conservatively. MTX administration should be preferred in case of haemodynamically stable patients with unruptured ectopic pregnancy, without severe complaint for pelvic pain or vaginal bleeding and mainly in case the size of ectopic mass does not exceed 3-3.5 cm[24,25]. Serum β-HCG levels should always been taken into consideration as there have been implications of improved correspondence in case β-HCG levels are lower than 5000 IU/L. Compliance of patient with close follow-up is also demanded while all potential risks and side-effects should also be explained to the patient[26].

In conclusion, conservative treatment of MTX seems to be the most reasonable therapeutic approach in cases of early diagnosed cervical pregnancies. Intramuscular administration of MTX in combination with intramniotic KCL injection may be effective in the treatment of cervical pregnancy However, further multi-center observational or even randomized studies should be performed in order to assess comparative effectiveness of various therapeutic protocols. Besides, the issue of cost-effectiveness of invasive *vs* conservative management, especially taking into consideration the follow-up necessitated after MTX administration, has to be further elucidated in order to achieve definite conclusions regarding a clinical entity that still poses severe diagnostic and mainly therapeutic challenges.

COMMENTS

Case characteristics

A 41-years-old woman on her 8th gestational week with the suspicion of cervical pregnancy.

Clinical diagnosis

No specific signs or symptoms during typical gynecological examination. Cervix closed.

Differential diagnosis

Other kinds of ectopic pregnancies.

Laboratory diagnosis

Beta human chorionic gonadotropine levels measured 28590 IU/L.

Imaging diagnosis

Empty endometrial cavity, gestational sac within the cervical canal and embryonic echo measuring CRL 1.5 mm.

Treatment

The patient was treated with intramuscular administration of methotrexate and intramniotic injection of KCl. No additional interventional treatment was performed.

Related reports

Successful conservative treatment of cervical pregnancy has been reported by only a few other studies. No consensus has yet been made regarding the various therapeutic options' comparative effectiveness.

Term explanation

Cervical pregnancy accounts for < 1% of ectopic pregnancies with frequency

between 1:1000-1:18000.

Experiences and lessons

Early diagnosis and close follow-up may permit successful conservative treatment with methotrexate, potentially avoiding curettage. However, the risk of severe hemorrhage should always been taken into consideration.

Peer review

This is an interesting study. The case report is well and clearly described and the discussion is concise.

REFERENCES

1 **Yitzhak M**, Orvieto R, Nitke S, Neuman-Levin M, Ben-Rafael Z, Schoenfeld A. Cervical pregnancy--a conservative stepwise approach. *Hum Reprod* 1999; **14**: 847-849 [PMID: 10221725 DOI: 10.1093/humrep/14.3.847]

2 **Vela G**, Tulandi T. Cervical pregnancy: the importance of early diagnosis and treatment. *J Minim Invasive Gynecol* 2007; **14**: 481-484 [PMID: 17630167 DOI: 10.1016/j.jmig.2006.11.012]

3 **Sijanović S**, Vidosavljević D, Topolovec Z, Milostić-Srb A, Mrčela M. Management of cervical ectopic pregnancy after unsuccesful methotrexate treatment. *Iran J Reprod Med* 2014; **12**: 285-288 [PMID: 24976825]

4 **Guzowski G**, Sieroszewski P. Invasive ultrasound in the management of cervical ectopic pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2014; **172**: 7-9 [PMID: 24287286 DOI: 10.1016/j.ejogrb.2013.10.016]

5 **Júnior JE**, Musiello RB, Araujo Júnior E, Souza E, Fava JL, Guerzet EA, Camano L. Conservative management of cervical pregnancy with embryonic heart activity by ultrasound-guided local injection: an eight case series. *J Matern Fetal Neonatal Med* 2014; **27**: 1378-1381 [PMID: 24134459]

6 **Chaudhary V**, Sachdeva P, Kumar D, Arora R, Banavaliker J, Khan M. Conservative management of cervical pregnancy: a report of two cases. *J Reprod Med* 2013; **58**: 451-457 [PMID: 24050038]

7 **Pereira N**, Grias I, Foster SE, Della Badia CR. Acute hemorrhage related to a residual cervical pregnancy: management with curettage, tamponade, and cerclage. *J Minim Invasive Gynecol* 2013; **20**: 907-911 [PMID: 23876387 DOI: 10.1016/j.jmig.2013.05.011]

8 **Song MJ**, Moon MH, Kim JA, Kim TJ. Serial transvaginal sonographic findings of cervical ectopic pregnancy treated with high-dose methotrexate. *J Ultrasound Med* 2009; **28**: 55-61 [PMID: 19106357]

9 **Kofinas** JD, Purisch SE, Brandt JS, Montes M. Hysteroscopic Removal of Cervical Ectopic Pregnancy Following Failed Intramuscular/Intra-Sac Methotrexate: A Case Report. *J Gynecol Surg* 2012; **28**: 369-371 [PMID: 24761129 DOI: 10.1089/gyn.2012.0006]

10 **Shrestha E**, Yang Y, Li X, Zhang Y. Successful conservative management with methotrexate and mifepristone of cervical pregnancy. *J Biomed Res* 2011; **25**: 71-73 [PMID: 23554674 DOI: 10.1016/S1674-8301(11)60009-2]

11 **Mangino FP**, Ceccarello M, Di Lorenzo G, D'Ottavio G, Bogatti P, Ricci G. Successful rescue hysteroscopic resection of a cervical ectopic pregnancy previously treated with methotrexate with no combined safety precautions. *Clin Exp Obstet Gynecol* 2014; **41**: 214-216 [PMID: 24779256]

12 **Tinelli A**, Malvasi A, Vergara D, Casciaro S. Emergency surgical procedure for failed methotrexate treatment of cervical pregnancy: a case report. *Eur J Contracept Reprod Health Care* 2007; **12**: 391-395 [PMID: 17853169 DOI: 10.1080/13625180701502351]

13 **Lin CY**, Chang CY, Chang HM, Tsai EM. Cervical pregnancy treated with systemic methotrexate administration and resectoscopy. *Taiwan J Obstet Gynecol* 2008; **47**: 443-447 [PMID: 19126514 DOI: 10.1016/S1028-4559(09)60015-2]

14 **Ben Hamouda S**, Ouerdiane N, Daaloul W, Masmoudi A, Bouguerra B, Sfar R. Conservative management of cervical pregnancy. A case-report. *Tunis Med* 2008; **86**: 827-829 [PMID: 19472784]

15 **Api O**, Unal O, Api M, Ergin B, Alkan N, Kars B, Turan C. Ultrasonographic appearance of cervical pregnancy following successful treatment with methotrexate. *Ultrasound Obstet Gynecol* 2006; **28**: 845-847 [PMID: 17063447 DOI: 10.1002/uog.3846]

16 **Polak G**, Stachowicz N, Morawska D, Kotarski J. [Treatment of cervical pregnancy with systemic methotrexate and KCI solution injection into the gestational sac--case report and review of literature]. *Ginekol Pol* 2011; **82**: 386-389 [PMID: 21851040]

17 **Kochi K**, Hidaka T, Yasoshima K, Yoneda K, Arai K, Arai T. Cervical pregnancy: a report of four cases. *J Obstet Gynaecol Res* 2014; **40**: 603-606 [PMID: 24118279 DOI: 10.1111/jog.12185]

18 **Moon HS**, Hyun JH, Kim KS, Kim HJ, Moon SE, Koo JS. Use of Tuohy needle for intraamniotic methotrexate injection through the cervical canal in a cervical pregnancy after failure of systemic methotrexate treatment. *Am J Obstet Gynecol* 2010; **202**: e4-e6 [PMID: 20452477 DOI: 10.1016/j.ajog.2010.01.081]

19 **Ferrara L**, Belogolovkin V, Gandhi M, Litton C, Jacobs A, Saltzman D, Rebarber A. Successful management of a consecutive cervical pregnancy by sonographically guided transvaginal local injection: case report and review of the literature. *J Ultrasound Med* 2007; **26**: 959-965 [PMID: 17592059]

20 **Jeng CJ**, Ko ML, Shen J. Transvaginal ultrasound-guided treatment of cervical pregnancy. *Obstet Gynecol* 2007; **109**: 1076-1082 [PMID: 17470585 DOI: 10.1097/01.AOG.0000262052.09350.52]

21 **Saeng-anan U**, Sreshthaputra O, Sukpan K, Tongsong T. Cervical pregnancy with massive bleeding after treatment with methotrexate. *BMJ Case Rep* 2013; **2013**: bcr2013200440 [PMID: 23929636 DOI: 10.1136/bcr-2013-200440]

22 **Cipullo L**, Cassese S, Fasolino L, Fasolino MC, Fasolino A. Cervical pregnancy: a case series and a review of current clinical practice. *Eur J Contracept Reprod Health Care* 2008; **13**: 313-319 [PMID: 18821465 DOI: 10.1080/13625180802254571]

23 **De La Vega GA**, Avery C, Nemiroff R, Marchiano D. Treatment of early cervical pregnancy with cerclage, carboprost, curettage, and balloon tamponade. *Obstet Gynecol* 2007; **109**: 505-507 [PMID: 17267874 DOI: 10.1097/01.AOG.0000220599.74326.94]

24 **Hajenius PJ**, Mol F, Mol BW, Bossuyt PM, Ankum WM, van der Veen F. Interventions for tubal ectopic pregnancy. *Cochrane Database Syst Rev* 2007; **1**: CD000324 [PMID: 17253448]

25 **Lipscomb GH**. Medical management of ectopic pregnancy. *Clin Obstet Gynecol* 2012; **55**: 424-432 [PMID: 22510624 DOI: 10.1097/GRF.0b013e3182510a48]

26 **Fernandez H**, Bourget P, Lelaidier C, Doumerc S, Frydman R. Methotrexate treatment of unilateral twin ectopic pregnancy: case report and pharmacokinetic considerations. *Ultrasound Obstet Gynecol* 1993; **3**: 357-359 [PMID: 12797262 DOI: 10.1046/j.1469-0705.1993.03050357.x]

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DOI: 10.12998/wjcc.v3.i1.85

World J Clin Cases 2015 January 16; 3(1): 85-88
ISSN 2307-8960 (online)

CASE REPORT

Unusual disposition of lateral circumflex femoral artery: Anatomical description and clinical implications

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Received: August 29, 2014
Peer-review started: August 30, 2014
First decision: September 28, 2014
Revised: October 8, 2014
Accepted: November 7, 2014
Article in press: December 23, 2014
Published online: January 16, 2015

Abstract

The anatomical knowledge of arterial variations of lower limb is of utmost significance for the present day surgeons and interventional radiologists for minimizing complications during vascular reconstructive procedures, catheterization procedures and surgical intervention for embolism. Lateral Circumflex Femoral Artery (LCFA) is an important branch of Profunda Femoris artery and precise knowledge of its variations can be of great relevance during surgical and radiological procedures in femoral region. The present study reports a unique case of anomalous route taken by LCFA posterior to femoral nerve associated with a prominent muscular branch from Femoral artery mimicking the course of LCFA. Documentation of such variations is highly significant. It may serve as guideline for surgeons in reducing the incidence of postoperative complications where LCFA is used as a long vascular pedicle in anterolateral perforator thigh flap and in breast reconstruction after mastectomy. Ignorance of such variations can lead to fatal intraoperative haemorrhage and incapacitating sensory and motor deficit due to injury to femoral nerve branches which are closely related to these vessels.

Key words: Lateral circumflex femoral artery; Femoral nerve; Femoral artery; Angiography; Reconstructive surgical procedures; Surgical flaps

Core tip: The knowledge of variations in site of origin and course of the Profunda femoris artery and its circumflex branches is of utmost clinical significance during diagnostic imaging procedures and surgeries performed in the femoral triangle. The present study highlights an abnormal course of the lateral circumflex femoral artery (LCFA) posterior to the femoral nerve associated with a significant muscular branch of femoral artery which mimicked the course of LCFA. Knowledge of such variations maybe of great help to surgeons, interventional radiologists and physicians in reducing the chances of intraoperative secondary haemorrhage and postoperative complications.

Goel S, Arora J, Mehta V, Sharma M, Suri RK, Rath G. Unusual disposition of lateral circumflex femoral artery: Anatomical

description and clinical implications. *World J Clin Cases* 2015; 3(1): 85-88 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i1/85.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i1.85

INTRODUCTION

Arterial variations of lower limb have always been of utmost importance due to their involvement in vascular reconstructive surgeries, catheterization procedures and in raising myocutaneous flaps with vascular pedicles. The recent use of lateral circumflex femoral artery (LCFA) in coronary artery bypass grafting as well as anterolateral thigh cutaneous flaps for oral and oropharyngeal reconstructions has further enhanced the relevance of normal and variant anatomy of LCFA. In view of anatomical variations, preoperative angiographic evaluation of femoral arterial system becomes mandatory in surgical procedures involving the LCFA. Literature reports several variations in origin of LCFA[1,2]. However reports of variant course of LCFA as described in the present study are few.

CASE REPORT

In a unique case, during cadaveric dissection, variant course of LCFA was detected in the right lower extremity of a 53 years old adult Indian male cadaver.

The Profunda Femoris Artery (PFA) took origin as usual from the Femoral Artery (FA), at a distance of 5 cm from the mid inguinal point. At a distance of 7 cm from the same anatomical landmark, LCFA was seen to arise from PFA (Figure 1). LCFA traversed deep to the posterior division of femoral nerve unlike its usual course anterior to the latter. Coursing for 2 cm, the LCFA divided into ascending, transverse and descending branches each of which also traversed behind the posterior division of femoral nerve (Figure 2). The trifurcation of LCFA was immediately posterior to the site where the posterior division of Femoral Nerve (FN) divided into multiple muscular branches.

A prominent muscular branch was given off from FA, 3 cm distal to origin of PFA and 1.5 cm distal to LCFA. This branch traversed parallel to LCFA, mimicked the usual course of latter and passed laterally between the branches of posterior division of Femoral Nerve. The proximal part of the muscular branch was deep to the posterior division of femoral nerve while the terminal branches coursed between the saphenous nerve (SN) and never to vastus lateralis (NVL). Interestingly, this muscular branch arising from FA, appeared to take the course normally taken by LCFA, between divisions of femoral nerve before it terminated by supplying the Vastus Lateralis muscle (Figures 1 and 2).

DISCUSSION

Anatomical knowledge of LCFA including its variations has gained significant importance with the involvement of LCFA in anterolateral thigh free flap[3], aortopopliteal bypass[4] and extracranial intracranial bypass surgery[5]. With the advent of novel harvesting and reconstructive techniques, precise anatomical knowledge of LCFA becomes further important.

The LCFA, commonly a branch of PFA, traverses between divisions of FN, posterior to Sartorius and Rectus Femoris muscles. Coursing behind these structures it divides into ascending, transverse and descending branches. The LCFA contributes blood supply to head and neck of femur, greater trochanter, vastus lateralis and knee joint[6].

Literature reports the use of descending branch of LCFA as a collateral[7] and use of ascending branch in vascularised iliac transplantation[8]. Variations in the origin of LCFA have been reported in cadaveric[9] as well as angiographic studies[10]. However our study is unique as it reports an unusual route taken by LCFA, posterior to the posterior division of femoral nerve and additional presence of a prominent muscular branch of FA which mimics the normal route of LCFA, coursing between the branches of femoral nerve to terminate in vastus lateralis.

Anomalous route of LCFA is of utmost importance to surgeons while raising free rectus femoris muscle flaps with a branch of posterior division of FN, for one stage reconstruction of facial paralysis[11]. Awareness of such anatomical variations as reported in our case may prevent inadvertent injury to LCFA while handling the branches of femoral nerve.

Preoperative anatomical assessment of LCFA through arteriographic study is also essential. The LCFA is frequently explored for its use as new arterial graft for coronary artery bypass grafting[12]. During such surgical procedures, an atypical course of LCFA may lead to an unfortunate sequel of injury to branches of femoral nerve traversing in front of LCFA.

The femoral nerve block is routinely given at a site just above the origin of PFA during knee replacement surgery. Ignorance of the presence of LCFA behind the posterior division of femoral nerve may lead to misinterpretation of absence of LCFA behind the latter and hence consequential accidental injury to LCFA. Exploration of femoral nerve for anaesthetic procedures, therefore, requires awareness of variant course of LCFA in relation to femoral nerve.

Racial differences in direct origin of LCFA from FA have been reported[13]. Studies also report anatomic pattern and calibre of both LCFA and perforators nourishing the anterolateral thigh flap[1]. However, variations in course of LCFA are few. Knowledge of arterial variations is extremely important as these may be the source of intraoperative iatrogenic haemorrhage or post operative complications. Arterial variations of lower extremity as reported in the present case are also important because of their close association with repair of femoral hernias.

Literature reports cadaveric and angiographic studies involving LCFA. Angiographic studies are of utmost importance although difficulties may be encountered

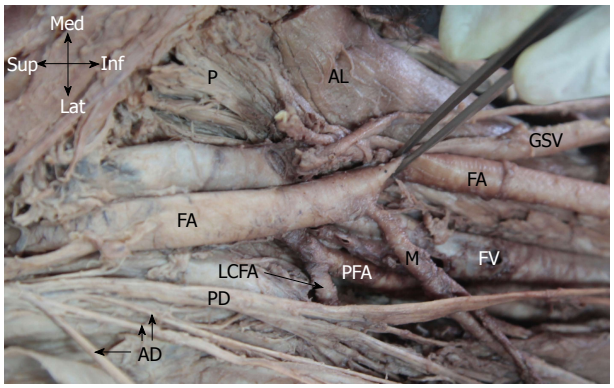

Figure 1 Right femoral region showing. Med: Medial; Lat: Lateral; Sup: Superior; Inf: Inferior; FA: Femoral Artery; FV: Femoral Vein; GSV: Great Saphenous Vein; AL: Adductor longus; P: Pectineus; PFA: Profunda femoris artery; LCFA: Lateral circumflex femoral artery; PD: Posterior division of femoral nerve; AD: Anterior division of femoral nerve; M: Muscular branch of FA.

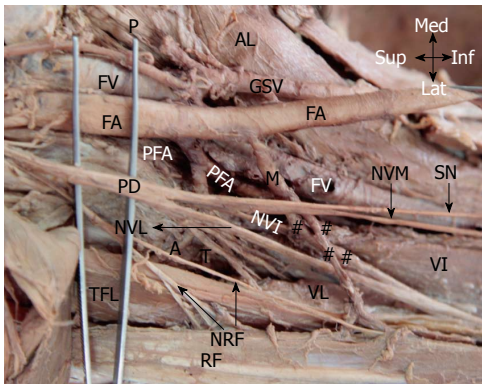

Figure 2 Right femoral region showing. Med: Medial; Lat: Lateral; Sup: Superior; Inf: Inferior; FA: Femoral Artery; FV: Femoral Vein; GSV: Great Saphenous Vein; AL: Adductor longus; P: Pectineus; PFA: Profunda femoris artery; LCFA: Lateral circumflex femoral artery; PD: Posterior division of femoral nerve; M: Muscular branch of FA; TFL: Tensor fascia lata; RF: Rectus femoris; VI: Vastus intermedialis; VL: Vastus lateralis; NVM: Nerve to vastus medialis; SN: Saphenous nerve; NVL: Nerve to vastus lateralis; NVI: Nerve to vastus intermedius; NRF: Nerve to rectus femoris; #: Terminal branches of M; A: Ascending branch of LCFA; T: transverse branch of LCFA.

while defining route and branches of LCFA on angiography. Our study describes variant course of LCFA associated with a prominent muscular branch from FA mimicking the usual route of LCFA. Reports of such cases may be of great importance in bridging the gap between cadaveric and angiographic studies of LCFA.

In aortoiliac occlusive diseases, bypass to the PFA or FA has emerged as a suitable mode of treatment. But in patients with total occlusion of femoral artery as well as profunda femoris artery, bypass to the LCFA was found to be successful[14]. Hence, knowledge of course and branching pattern of LCFA, as reported in our case is extremely important in management of patients with multilevel occlusive diseases of iliac and femoral arteries.

Anatomical knowledge of branches of LCFA is also important while using sharp ended version guidewires during hip fracture surgery[15]. Such surgical procedures, involving exploration of branches of LCFA, may lead to iatrogenic injury to the ascending branch of LCFA because of its variant course behind the femoral nerve.

In the present case, the main trunk of LCFA, as well as its ascending, transverse and descending branches coursed behind the posterior division of femoral nerve. At the same time a prominent muscular branch of FA was seen mimicking the usual course of LCFA, by coursing between the branches of posterior division femoral nerve. Knowledge of such variations is important in surgical transplantation procedures where the branches of LCFA are of utmost use. It may simplify the procedure of flap dissection involving LCFA, especially when anterolateral thigh flap is the easiest and has the least morbidity[16].

Developmental arrests at different stages may lead to anatomical variations related to branches of femoral artery. Vasculature development in the lower limb is preceded by morphological and molecular changes that occur in the limb mesenchyme, therefore variations in vascular pattern are often recorded[17].

With increasing challenges in the field of surgery and occurrence of uncommon anatomic variations, it becomes imperative for the present day surgeons, interventional radiologists and anatomists to be aware of anatomical variations of LCFA - its variant course and muscular branches mimicking the normal course of LCFA. Ignorance of such variations can not only lead to fatal intraoperative haemorrhage but also injury to the branches of femoral nerve which are in close relation to these vessels. Such avoidable femoral nerve lesions can lead to incapacitating sensory and motor deficit. Our study is a sincere effort in this field for minimizing injury to vital structures of lower limb like the femoral nerve and the lateral circumflex femoral artery. We, as anatomists, humbly submit that awareness of vascular variations as encountered in our study is of tremendous significance for successful reconstructive procedures of the region.

COMMENTS

Case characteristics

Anomalous route taken by lateral circumflex femoral artery (LCFA) posterior to femoral nerve and presence of a prominent muscular branch from Femoral artery mimicking the course of LCFA.

Clinical diagnosis

Arterial variants as reported in the present study are of utmost significance in anterolateral thigh flap surgeries, coronary artery bypass grafting and femoral nerve block in knee surgeries.

Differential diagnosis

Anatomical awareness of variant course of LCFA associated with a prominent muscular branch from Femoral Artery (FA) mimicking the course of LCFA is imperative for vascular surgeons and interventional radiologists. The muscular branch of FA can be mistaken for LCFA leading to the accidental ligation of the wrong vessel.

Related reports

Literature reports several variations in origin of LCFA. However reports of variant course of LCFA as described in the present study are few. This vessel as well as its branches are now extensively used in reconstructive and bypass surgeries.

Term explanation

LCFA normally courses in between the branches of Femoral Nerve.

Experiences and lessons

Ignorance of such variations can lead to fatal intraoperative haemorrhage and incapacitating sensory and motor deficit.

Peer review

This article highlights the importance of vascular variations of lower limb encountered in cadaveric studies and its application in surgery, anaesthesiology and interventional radiology.

REFERENCES

1 **Valdatta L**, Tuinder S, Buoro M, Thione A, Faga A, Putz R. Lateral circumflex femoral arterial system and perforators of the anterolateral thigh flap: an anatomic study. *Ann Plast Surg* 2002; **49**: 145-150 [PMID: 12187341 DOI: 10.1097/00000637-200208000-00006]

2 **Voboril R**. Note on variability of the arteries of the lower extremities in man. *Folia Morphol* (Praha) 1990; **38**: 265-272 [PMID: 2269453]

3 **Park CW**, Miles BA. The expanding role of the anterolateral thigh free flap in head and neck reconstruction. *Curr Opin Otolaryngol Head Neck Surg* 2011; **19**: 263-268 [PMID: 21900855 DOI: 10.1097/MOO.0b013e328347f845]

4 **Sugawara Y**, Sato O, Miyata T, Kimura H, Namba T, Makuuchi M. Utilization of the lateral circumflex femoral artery as a midway outflow for aorto-popliteal grafting: report of a case. *Surg Today* 1998; **28**: 967-970 [PMID: 9744412 DOI: 10.1007/s005950050264]

5 **Başkaya MK**, Kiehn MW, Ahmed AS, Ateş O, Niemann DB. Alternative vascular graft for extracranial-intracranial bypass surgery: descending branch of the lateral circumflex femoral artery. *Neurosurg Focus* 2008; **24**: E8 [PMID: 18275304 DOI: 10.3171/FOC/2008/24/2/E8]

6 **Standring S,** editor. Gray's anatomy – the anatomical basis of clinical practice. 40th ed. Edinburgh: Elsevier Churchill Livingstone, 2008: 1379-1380

7 **Hage JJ**, Woerdeman LA. Lower limb necrosis after use of the anterolateral thigh free flap: is preoperative angiography indicated? *Ann Plast Surg* 2004; **52**: 315-318 [PMID: 15156989 DOI: 10.1097/01.sap.0000100422.66597.13]

8 **Xu DC**, Kong JM, Zhong SZ. The ascending branch of the lateral circumflex femoral artery. A new supply for vascularized iliac transplantation. *Surg Radiol Anat* 1989; **11**: 263-264 [PMID: 2617407 DOI: 10.1007/BF02098692]

9 **Uzel M**, Tanyeli E, Yildirim M. An anatomical study of the origins of the lateral circumflex femoral artery in the Turkish population. *Folia Morphol* (Warsz) 2008; **67**: 226-230 [PMID: 19085859]

10 **Fukuda H**, Ashida M, Ishii R, Abe S, Ibukuro K. Anatomical variants of the lateral femoral circumflex artery: an angiographic study. *Surg Radiol Anat* 2005; **27**: 260-264 [PMID: 15682274 DOI: 10.1007/s00276-004-0312-5]

11 **Koshima I**, Moriguchi T, Soeda S, Hamanaka T, Tanaka H, Ohta S. Free rectus femoris muscle transfer for one-stage reconstruction of established facial paralysis. *Plast Reconstr Surg* 1994; **94**: 421-430 [PMID: 8047592 DOI: 10.1097/00006534-199409000-00001]

12 **Gaiotto FA**, Vianna CB, Busnardo FF, Parga JR, Dallan LA, Cesar LA, Stolf NA, Jatene FB. The descending branch of the lateral femoral circumflex artery is a good option in CABG with arterial grafts. *Rev Bras Cir Cardiovasc* 2013; **28**: 317-324 [PMID: 24343680 DOI: 10.5935/1678-9741.20130050]

13 **Williams GD,** Martin CH, McIntire LR. Origins of the deep and circumflex group of arteries. *Anat Rec* 1934; **60:** 189-196 [DOI: 10.1002/ar.1090600206]

14 **Gradman WS**. Bypass to the lateral circumflex femoral artery. *Ann Vasc Surg* 1992; **6**: 344-346 [PMID: 1390022 DOI: 10.1007/BF02008791]

15 **Davda K**, Pollard TC, Graham AJ. Delayed presentation of lateral femoral circumflex artery injury post cannulated hip screw surgery--a case report. *Ann R Coll Surg Engl* 2009; **91**: W3-W5 [PMID: 19416578 DOI: 10.1308/147870809X401001]

16 **Chen HC**, Tang YB. Anterolateral thigh flap: an ideal soft tissue flap. *Clin Plast Surg* 2003; **30**: 383-401 [PMID: 12916595 DOI: 10.1016/S0094-1298(03)00040-3]

17 **Keen JA**. A study of the arterial variations in the limbs, with special reference to symmetry of vascular patterns. *Am J Anat* 1961; **108**: 245-261 [PMID: 14454801 DOI: 10.1002/aja.1001080303]

P- Reviewer: Alimehmeti R, Boffano P **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Lu YJ

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