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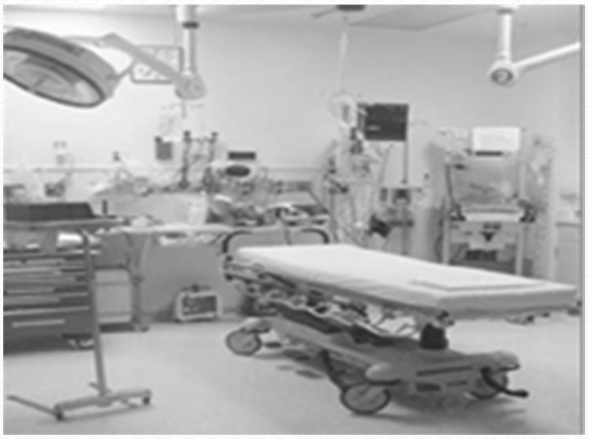

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Review

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Stevens-Johnson Syndrome without Skin Lesions: A Rare and Clinically Challenging Disease in the Urgent Setting

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ABSTRACT

Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme are life threatening diseases causing mucocutaneous eruptions and can be difficult to manage medically. When oral tissues are involved, airway management can be of critical importance. Fluid and electrolyte imbalance are common and protocols to prevent secondary infection are initiated. All three conditions are rapidly evolving. Stevens-Johnson syndrome is more commonly associated with *Mycoplasma pneumoniae* in the pediatric population and drug hypersensitivity in adults, whereas erythema multiforme is mostly associated with herpes simplex virus in the adult population. These diseases are T-cell-mediated immune reactions, thought to represent a spectrum of the same disease. Clinical and immunohistochemical techniques are capable of differentiating Stevens-Johnson syndrome from erythema multiforme and provide insight into the possible underlying pathology creating the disease. Rare cases of Stevens-Johnson syndrome without skin manifestations have been associated with *Mycoplasma pneumoniae* and predominantly occur in males. In-hospital management is recommended to provide airway support, maintain fluid intake, electrolyte balance, obtain multi-speciality consultation, and to perform diagnostic testing. We describe a case of a 14 year old male with atypical Stevens-Johnson syndrome and a review of the literature.

KEYWORDS: Stevens-Johnson syndrome; Toxic epidermal necrolysis; Erythema multiforme; Immunohistochemical; Episcleritis; Ulcerative stomatitis; *Mycoplasma pneumoniae* associated mucositis (MPAM); Fuchs syndrome; Major histocompatibility class; Non-MPAM atypical Stevens-Johnson syndrome.

ABBREVIATIONS: MPAM: Mycoplasma pneumonia-associated mucositis; SJS: Stevens-Johnson syndrome; TEN: Toxic Epidermal Necrolysis; EM: Erythema Multiforme; HSV: Herpes Simplex Virus; MP: Mycoplasma Pneumonia; IVIg: Intravenous immunoglobulins; HLA: Human Leukocyte Antigen; TNF-alpha: Tumor Necrosis Factor-alpha.

INTRODUCTION

Stevens-Johnson syndrome (SJS), Toxic Tpidermal Necrolysis (TEN) and Erythema Multiforme (EM) are immune hypersensitivity disorders associated with drug or infectious exposure, which can be life threatening. SJS and TEN are believed to be the same disease, with TEN representing the more severe form of the disease spectrum. Historical information such as exposure to specific drugs or infections, and clinical information such as the characteristics of skin lesions and their distribution have been useful in differentiating between and SJS, TEN, or

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EM. Histologic and histochemical analyses remain the optimal methods of differentiating these diseases.[1-4] SJS, TEN, and EM are felt to be cytotoxic-mediated, and various strategies are used for management with newer treatment protocols being devised. Recent case reports describe rare variants of SJS without skin manifestations.

CASE REPORT

A 14 year old previously healthy male with mild fever and malaise was seen by his primary care doctor for bilateral conjunctivitis and cough, for which he was prescribed azithromycin. After two doses he developed painful mouth swelling and the azithromycin was discontinued. This was similar to a previous reaction he had with penicillin three years earlier which resolved spontaneously after discontinuation. His symptoms worsened despite being off the azithromycin and he was prescribed oral prednisone, which was ineffective and discontinued after three days. He was referred to an ophthalmologist who felt his conjunctivitis represented a herpetic infection, and was started on ganciclovir ophthalmic gel and prednisolone acetate drops which he used for three days. He was subsequently seen by ENT who noted a new development of bleeding oral lesions and multiple blisters of the lips and oral mucosa (Figure 1). Magic mouthwash was prescribed. The patient experienced increasing difficulty with sustaining oral fluid intake and breathing due to his throat swelling, and was admitted to the hospital. On admission, the patient presented with dehydration, a non-productive cough, sensitivity to light, and blurred vision. A chest X-ray was performed and showed no abnormalities. On ophthalmologic examination, visual acuity was 20/20 in the right eye and 20/40 in the left eye. Pupils were equal, round and reactive to light. There was extensive ulceration of the conjunctiva of both eyes and diffuse fluorescein staining across the conjunctiva and cornea, with the left eye worse than the right. Focal episcleral injection in the right eye was noted (Figure 2). No adhesions or symblepharon were appreciated although inferior conjunctiva pseudomembrane formation was noted, right eye greater than the left. Funduscopic examination disclosed no abnormalities of the optic nerve, macula, or retinal vasculature.

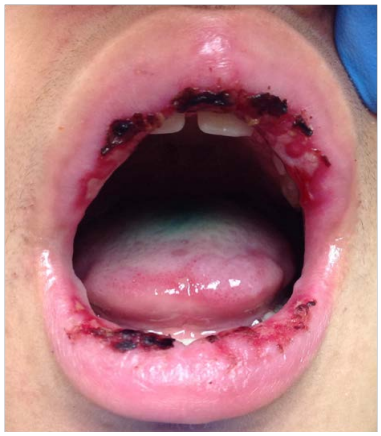

Figure 1: Oral lesions seen in a 14 year old patient with Stevens-Johnson syndrome without skin lesions.

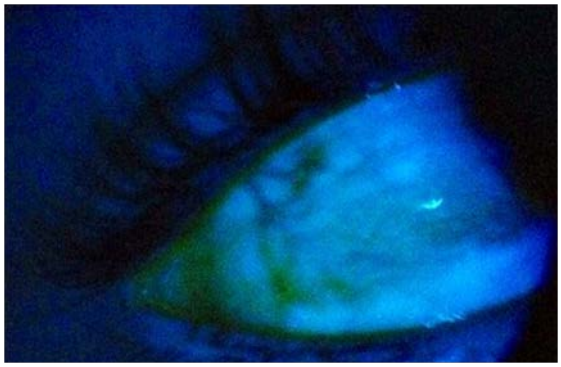

Figure 2: Episcleritis of the right eye show by fluorescein ophthalmic examination.

Blood serology disclosed a C-reactive protein of 1.61 mg/dL, white blood cell count of 8.6 K/UL, and was negative for mononucleosis, Herpes Simplex Virus (HSV) 1 and 2, human immunodeficiency virus, influenzae, and *Mycoplasma Pneumoniae* (MP) IgM antibody. MP IgG was mildly elevated at 0.65 U/L (0.09-0.33 U/L) and degressed to 0.35 U/L after one day. Mycoplasma PCR was negative in oral cavity lavage. Epstein Barr virus nuclear and capsid antigen IgG were positive with values of >8.0 (<0.91). Coxsackie B Virus Titers were negative with values <1:10 for Types 1,2,3,4, and 6. Coxsackie B Type 5 had a value of 1:20 (<1:10). Coxsackie A Type 9 titer was negative with a value of <1:8 (<1:8). The presumed diagnosis was SJS without skin lesions due to azithromycin hypersensitivity with concurrent Epstein-Barr infection.

The patient was discharged within four days of admission in stable condition. Ophthalmological follow-up disclosed healing of his episcleritis and conjunctival and corneal lesions after continued use of lubricant eye drops. Subsequent clinical follow ups showed complete resolution after one month.

METHODS

We performed a systematic electronic literature search using the PubMed and Ovid MEDLINE databases. The last search was performed on April 7, 2015. The keywords used were: atypical Stevens Johnson syndrome, incomplete Stevens-Johnson syndrome, Stevens-Johnson syndrome without skin lesions, *Mycoplasma pneumoniae* associated mucositis, and Fuchs syndrome. All literature was limited to the English language.

Titles and abstracts were read to determine eligibility. Patients were included if they met the criteria for atypical SJS which included: lesions involving at least two mucous membranes (mouth, ocular, or genital), no skin involvement, and positive infection or suspected drug reaction.

RESULTS

Our search yielded 1,192 publications that included the keywords listed in our methods section. 24 articles met the criteria for atypical SJS. In total, there were 32 patients described

including our reported patient. Patients were separated into two categories: children ages 3 to 16 years of age (17 patients, Table 1) and adults 18 to 44 years of age (15 patients, Table 2). Information for each case includes age, sex, chest involvement, genital involvement, etiology, diagnosis, diagnostic testing, and treatment. No patients under the age of 3 or over the age of 44 were reported in the literature.

Of the pediatric cases (Table 1), fifteen patients were male (88%), ten patients had chest involvement (59%), ten patients had genital involvement (59%), and fourteen patients had positive MP infection (82%). One was treated with immunosuppressants, all were treated with antibiotics (mainly macrolides), and one was treated with intravenous immunoglobulins (IVIg). All patients had a favorable outcome and all had complete resolution to their baseline health.

A prior review of atypical SJS by Vujic, et al. in 2014 yielded 818 search results, of which only 11 articles (13 patients) met their criteria.[26] The review was limited to adult patients between the ages of 18 to 38 years of age. Ten patients were male (77%), six patients had chest involvement (46%), nine patients had genital involvement (69%), and all patients had positive MP infection (100%). Nine were treated with immunosuppressants and ten were treated with antibiotics, which were mainly macrolides and fluoroquinolones.

For the adult cases, one case was excluded from Vujic, et al. for minimal skin involvement, and three more were included. Of those three additional cases, 2 were male, 2 had chest involvement, none had genital involvement, and two had positive MP infection. All were treated with immunosuppressants, two were treated with antibiotics, and one was treated with IVIg. All patients had a favorable outcome.

Four cases were not associated with MP (Table 1-2). Of the pediatric cases, one cause was unknown and two were from a suspected drug reaction. The presumed cause in the adult case was from MP despite having negative serological testing, although she did test positive for influenza type B.

DISCUSSION

Erythema Multiforme

EM, SJS, and TEN are acute, immune-mediated, hypersensitivity reactions to certain medications or infections, which are believed to trigger a cytotoxic response. EM was previously thought to be part of the spectrum of SJS and TEN, but today it is recognized as a distinct entity with different clinical and epidemiological characteristics.[29,30] EM is manifested by characteristically raised, bullous skin lesions that are palpable. Epidermal detachment occurs in less than 10% of the body surface area and there is minimal mucous membrane involvement. Oral lesions are described as polymorphic, erosive, ampullary, and erythematosus.[29] EM occurs mostly in adults between 20 to 40 years old[31] and is most often caused by HSV.[3,29,30]

Stevens-Johnson Syndrome

SJS was first described in 1922 by Albert Mason Stevens and Frank Chambliss Johnson.[32] It is considered to be a single disease entity with TEN, with less severity. The process begins with fever and flu-like symptoms, followed by a breakout of severe mucosal erosions and diffuse, flat atypical skin lesions that are non-palpable. SJS has a prevalence of 1.2-6 /million cases per year, with a mortality rate of 5-10%.[4,33] The most commonly identified cause of SJS in children is infection and drug sensitivity for adults.[28,10,34,35] Viral agents associated with SJS include coxsackie virus, HSV, AIDS, influenza, hepatitis, mumps, and Epstein-Barr. Associated bacterial agents include group A beta-hemolytic streptococci, diphtheria, brucellosis, lymphogranuloma venereum, mycobacteria, MP, rickettsia, tularemia, and typhoid.

Atypical Stevens-Johnson Syndrome/*Mycoplasma Pneumoniae*-Associated Mucositis

The first case of atypical SJS was described by Maj Otto F. Sieber in 1967.[11,19,23] Most cases of this disorder have a better prognosis and recovery time than typical SJS, and to date there have been no mortalities from this condition. It is difficult to determine at the onset of this disorder if it will proceed to complete SJS or TEN. Ocular involvement occurs in every case and can include diffuse bullous conjunctival edema, pseudomembranes of the conjunctiva, corneal epithelial defects and episcleritis.[14] In 2005, Schalock and Dinulos proposed that the diagnosis of atypical SJS be classified as *Mycoplasma pneumoniae*-associated mucositis (MPAM) due to the striking feature that atypical cases of SJS are associated with MP.[11] MP is the most common cause of childhood pneumonia and is a self-limiting disease managed without antibiotics, which can explain why there is a better prognosis for MPAM.

In our review of the literature, four atypical cases were not associated with MP, therefore not fitting the criteria for MPAM (Tables 1 and 2). Of the pediatric cases, one cause was unknown and two were from a suspected drug reaction. The adult case was more complicated because the presumed cause was from MP despite having negative serological testing, only because the more likely cause of atypical SJS is from MP. The patient tested positive for influenza type B, which we suspect was the actual triggering factor. This suggests there may be other variant forms of atypical SJS, which we feel is the case for our patient. We suspect our patient developed a reaction to the azithromycin, which similarly occurred after a dose of penicillin three years prior with the exception of the mucosal necrosis. A similar case is described by Lamireau et al., of a 7-year-old boy that initially presented with non-MPAM atypical SJS, which recurred and resulted in a complete SJS.[8]

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Author et al.	Age	Sex	Chest Involved	Genital Involved	Etiology	Diagnosis	Diagnostic Testing	Treatment*
Alter[5]	13	M	N	N	MP	MPAM	Complement fixation titer	Erythromycin
	10	M	Y	Y	MP	MPAM	Complement fixation titer	Erythromycin
	12	M	Y	Y	MP	MPAM	Complement fixation titer	Erythromycin
Bressan[6]	9	F	N/A	Y	MP	MPAM	IgM, agglutination assays	IVIg
Fearon[7]	8	M	Y	N	MP	MPAM w/ RSV	Agglutination assays	Roxithromycin
Lamireau[8]	6	M	Y	N	MP	SJS	Mouth culture, oral PCR, IgG, - cold agglutinin	Erythromycin, thalidomide
	7	M	N	N	Not Stated	SJS	Serology, - PCR	Rovamycin, prednisone
Latsch[4]	13	F	Y	Y	MP	SJS w/o skin lesions	Throat swab PCR, microparticle agglutination assay, IgM, -IgA, -IgG	Clarithromycin
	11	M	N	N	MP	SJS w/o skin lesions	Sputum specimen, microparticle agglutination assay, IgM, IgA, IgG	Clarithromycin
Meyer Sauteur[9]	7	M	Y	Y	MP	Fuchs	Throat swab PCR, complement fixation titer	Azithromycin
Ravin[10]	14	M	Y	Y	MP	Atypical SJS	Throat swab PCR	Cefuroxime, azithromycin
	16	M	Y	Y	MP	Atypical SJS	Throat swab PCR	Ceftriaxone, azithromycin
Schalock[11]	17	M	N/A	N	MP	MPAM	IgG	Azithromycin
Strawn[12]	15	M	Y	Y	Drug	Atypical SJS	N/A	Cefdinir, azithromycin
Trapp[13]	13	M	N/A	Y	MP	MPAM	IgM, - cold agglutinin	Azithromycin
Vanfleteren[14]	14	M	Y	Y	MP	SJS w/o skin lesions	IgG, IgM	Clarithromycin, amoxicillin-clavulanic acid, acyclovir
Ours	14	M	N	N	Drug	SJS w/o skin lesions w/ EBV	IgG, -IgM, - oral PCR, EBV NA IgG and CA IgG	Doxycycline

EBV: Epstein Barr Virus; RSV: Respiratory Syncytial Virus.
Age, sex, chest involvement, genital involvement, etiology, diagnosis, diagnostic methods, and treatment for 17 pediatric cases of atypical Stevens-Johnson syndrome. *The literature shows a variability in initial treatment, with the ultimate treatment being focused on treating *Mycoplasma pneumonia* or inflammation which is shown in this table.

Table 1: Pediatric cases of atypical Stevens-Johnson syndrome.

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Author et al.	Age	Sex	Chest Involved	Genital Involved	Etiology	Diagnosis	Diagnostic Testing	Treatment*
Birch[15]	21	F	N/A	Y	MP	Atypical SJS	Esophageal biopsy, - PCR, IgM	IVIg, levofloxacin
Havliza[16]	32	F	N/A	N	MP	Fuchs	Antibody titers	Prenisolone, acyclovir, cefuroxime, levofloxacin
	38	F	N/A	N	MP	Fuchs	Antibody titers	Prenisolone, acyclovir, cefuroxime, levofloxacin
Hillebrand[17]	23	M	Y	Y	MP	Incomplete SJS	Throat swab PCR, agglutination IgM IgG titer	Amoxicillin-clavulanic acid, azithromycin
Kirke[18]	18	M	N	Y	MP	SJS	Oral biopsy, - immunofluorescence, IgM, complement fixation titer, cold agglutinin	Prednisolone
Li[19]	26	M	N	Y	MP	Fuchs	Oral biopsy, IgM, -cold agglutinin	Amoxicillin, oseltamivir, methylprednisolone, clarithromycin
Majima[20]	44	F	Y	N	Presumed MP	SJS-like mucositis w/o skin lesions	-IgM, + influenza B from nasal swab	Methylprednisolone, prednisolone, ampicillin, azithromycin
McGouran[21]	18	M	N	Y	MP	Atypical SJS	IgM	Methylprednisolone
Ramasamy[22]	19	M	Y	N	MP	Incomplete SJS	Complement fixation titer, agglutination assays, convalescent serum sample	Co-amoxiclav, erythromycin
Sieber[23]	22	M	Y	Y	MP	SJS	Throat swab, MP hemagglutination-inhibition, complement fixation titer	Prednisone, sodium cephalothin, tetracycline
Sternbersky[24]	22	M	N/A	Y	MP	Fuchs	IgG, IgM	Clarithromycin
Varghese[25]	20	M	Y	N	MP	MPAM	IgG, IgM, immunofluorescence	Levofloxacin, clindamycin, IVIg, methylprednisolone
Vujic[26]	23	M	Y	N	MP	MPAM	Oral mucosa biopsy, IgA, IgG, IgM, -immunofluorescence	Doxycycline, prednisolone
Walicka[27]	28	M	Y	Y	MP	SJS	Immunoenzymatic examination	Ceftriaxone, fluconazole, ciprofloxacin, cyclosporine A, fenoterol and ipratropium bromide (nebulizer), doxycycline, ambroxol, fenoterol
Yachoui[28]	29	M	N/A	Y	MP	Atypical SJS	IgM	Solumedrol

Age, sex, chest involvement, genital involvement, etiology, diagnosis, diagnostic methods, and treatment for 15 adult cases of atypical Stevens-Johnson syndrome. *The literature shows a variability in initial treatment, with the ultimate treatment being focused on treating *Mycoplasma pneumonia* or inflammation which is shown in this table.

Table 2: Adult cases of atypical Stevens-Johnson syndrome.

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To our knowledge, there are only four reports of SJS associated with azithromycin,[35-37] with our case being the first described for atypical SJS. The first reported case describes a 5-year-old boy who developed oral pain and skin eruptions three days after taking azithromycin. Initial HSV testing was unremarkable, but showed an increase in IgM antibody after retesting. They suspected the HSV was reactivated after the use of steroids, which may explain the positivity for Epstein-Barr in our case.

Genetic Predisposition

The underlying root for the spectrum of disease presentation and treatment responses between atypical SJS, MPAM, SJS, TEN and EM may have some underlying genetic influences. A strong genetic association can be formed by examining Human Leukocyte Antigen (HLA) typing, occurrences in family members, and recurrence. HLA-B*5701, HLA-B*5801, HLA-B*1502, HLA-A*3101, HLA-A*0206, HLA-B*4403, HLA-A29, HLA-B12, HLA-DR7, and HLA-A2 are linked to SJS drug hypersensitivity reactions.[38-41] HLA-DQB1*0601, HLA-DQA1*0103, DQB1*0301, and HLA-A*0206 are linked to ocular manifestations in SJS.[42] Genetic influences can explain why SJS occurs in multiple family members even though it is a rare condition[43] or why it recurs in certain individuals. Finkelstein, et al. reported 55 cases of SJS/TEN, of which 10 were reported to have a recurrence of SJS up to seven years after the initial episode.[35] The suspected initial triggers were from medication (5 cases), MP infections (3 cases), HSV infection (1 case), and influenza (1 case). Recurrences were from medication (2 cases), MP infection (4 cases), HSV infection (2 cases), and unknown (2 cases). Three patients had more than two recurrent episodes.

Mechanism

SJS/TEN hypersensitivity reactions are mediated by cytotoxic T lymphocyte and natural killer cell responses resulting in keratinocyte death.[44] CD8+ T-cells recognize antigens bound to major histocompatibility complex I molecules, which activates two different types of cytotoxic signals. The first signal releases perforin, granzyme B, and granulysin which go into the cytosol of the target cell to eventually trigger apoptosis. The second signal includes the expression of FAS ligand which binds to FAS molecules on the surface of the target cell, leading to apoptosis. Keratinocyte death causes separation of the epidermis from the dermis, resulting in the blistering and classic skin lesions of typical SJS. This triggers cytokines (TNF-alpha), creating more inflammation and eventual necrosis.

Diagnostic Methods

The diagnosis of MP is demonstrated by immunoglobulin diagnostic work up and PCR. The use of PCR is rapid and enables physicians to quickly diagnose and treat patients, although one case of positive MPAM by IgM and esophageal biopsy described a negative PCR report.[15] False negatives can occur as the sensitivity of PCR ranges from 78-100%, while serology ranges from 50-66%.[10]

Skin biopsies are a definitive way to differentiate SJS/TEN from EM. Histopathological analyses typically show subepidermal blistering, widespread keratinocyte apoptosis, and full-thickness epidermal necrosis and detachment with a sparse dermal mononuclear infiltrate.[44] Differences can also be distinguished in their early stages. The number of granulysin- and perforin-expressing CD8+ cells are greater in SJS than EM, while the number of Foxp3 and CD4+ cells are lower.[1] However, this technique is unavailable in atypical cases where there are no skin lesions present. Oral biopsies have been performed for atypical SJS/MPAM, which show highly necrotic mucosa with extensive inflammatory infiltrate consistent with SJS.[26]

Management and Treatment

There is a complexity of the treatment for a condition which may in the long run be self-limiting, however may evolve due to its complexity. Treatment with antibiotics and immunosuppressive agents remains the mainstay of management for patients with a suspected infectious cause. There are questions about efficacy and safety regarding the use of corticosteroids, however, an improvement in the disease indicates that there is an inflammatory component that needs to be treated. It is common for patients to be treated with an antiviral when there is a suspected viral infection or when being treated with corticosteroids. Patients with suspected adverse reactions to medication must be withdrawn from it. The use of plasmapheresis and hemodialysis to remove these agents is debated.[44] Macrolides are commonly used to treat MP infections, however there is an increase in resistance to this class of antibiotics. An estimated resistance rate of 27% was documented in the United States, and reaches up to 90% in China.[45] This is particularly challenging for children when there are not as many options for treatment because of potential toxicities.

Other treatments such as IVIg in patients with SJS, TEN, or EM are sometimes used to target Fas/FasL interactions, and are shown to have reduced mortality rates.[44] IVIg was used in only one case of atypical SJS which produced a good outcome (Table 2). Additional treatments include Tumor Necrosis Factor-alpha pathway antagonizers (TNF inhibitors, pentoxyfilline, thalidomide, infliximab) and immunomodulators (cyclophosphamide, cyclosporine, N-acetylcysteine, and pentoxyfilline) to reduce the amount of steroids.[44] Maintaining airway support and balancing nutritional and fluid intake is also crucial in improving the condition of these patients.

CONCLUSION

EM, atypical SJS, MPAM, SJS, and TEN are all disorders which change rapidly and may pose life threatening consequences. Despite all therapeutic efforts, the mortality rate is increased with the severity of the disease, age of the patient, and

with any underlying medical condition. Chronic ocular complications and mucosal scarring may persist after treatment. We recommend that all patients with ocular, buccal and genital mucosa erosions have ophthalmologic, ENT and dermatologic consultation. Patients should be admitted in the acute setting, particularly when there are issues of airway integrity. This allows for greater patient stabilization, improved diagnosis, and better multi-specialty team approach to the complex and often unusual patient presentation.

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The authors report no financial interests or conflicts of interest.

CONSENT STATEMENT

Consent was obtained by the patients father as patient was a minor.

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Review

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Debunking Medical Myths: The Eyebrow Shaving Myth

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ABSTRACT

The shaving of eyebrows has long been a clinical taboo. When a patient has a facial laceration or some other facial trauma involving or near the eyebrow, clinicians have classically been taught not to shave the eyebrow for fear that the hair will not grow back or will grow back abnormally. And, the fact that the eyebrow is so important for facial expressions and aesthetics further amplifies this concern. In this article, we briefly discuss the problem of perpetuated medical myths and discussed the outcomes of our review of the literature concerning the belief that eyebrows should never be shaved. We did not find a single article supporting this teaching in our review of the literature. Finally, we discuss other etiologies of eyebrow hair loss that may have contributed to this myth and review several more legitimate reasons for not shaving an eyebrow.

INTRODUCTION

In the practice of medicine, there are many precepts or beliefs commonly taught whose actual validity has never been seriously questioned. Consequently, there are many medical myths that will be taught into perpetuity unless they are exposed through a careful review of the literature. Unfortunately, just as with a "good lie" a persistent myth in medicine will contain a modicum of truth. For example, consider the myth that bullous myringitis is caused by mycoplasma pneumonia or the myth that testicles torsed for greater than 6 hours are rarely salvageable. It is true that a single case of *M. pneumoniae* was reported in 1967 as having been cultured from fluid directly aspirated from a bleb.[1] However, subsequently, many more articles have proven that bullous myringitis is simply a component of severe acute otitis media caused by the typical agents of that condition (*S. pneumoniae, H. influenzae, and Moraxella catarrhalis*).[2] Likewise, while there are cases of testicular torsion presenting with dead testicles at six hours or less from onset; there are scores of reports describing hundreds of patients whose torsed testicles survived unscathed far beyond that six hour time frame.[3] Unfortunately, the perpetuation of myths in medicine does have very real clinical consequences.

What about the widespread teaching that eyebrows should not be shaved because of the risk that they will not grow back? In this paper we carefully reviewed the literature to assess the evidence behind this well-known and commonly taught principle.

METHODS

The authors of this paper performed an extensive review of the literature by electronically searching the United States National Library of Medicine, National Institutes of Health literature archives using the search words, "eyebrows" and "eyebrow shaving". Each of the 2224 titles included under the "eyebrows" search along with titles under the "eyebrow shaving" and "eyebrow regeneration" search topics were carefully reviewed for possible relevance. When articles addressing these topics were found, those articles were carefully evaluated.

RESULTS

In our extensive and thorough review of the literature, we did not find a single article supporting the common teaching that eyebrow shaving was occasionally associated with failure of regeneration. While there are numerous conditions associated with failure of eyebrow growth, there was not a single reported case of eyebrow growth failure due to shaving. And, to the contrary, one small study with five study subjects demonstrated that shaven eyebrows will regenerate after being completely shaved off.[4] These patients consented to have their eyebrows shaved with follow up pictures periodically for 6 months. They had no facial trauma. The authors used two observers to analyze the final photographs, and the observers could not identify any differences between the brow which had been shaved and the control brow. This same study from 1999 also mentioned that in their literature review covering the years prior to their publication that there was no data to support abnormal eyebrow growth. Our literature review examined the same time period covered by these authors as well as the period of years since their publication.

DISCUSSION

Eyebrows are supraorbital arched eminences of hair bearing skin which give shape and character to an individual's face. The role of eyebrows includes protecting the eyes from sweat as well as their well-known contribution to individual identity, facial recognition and communication. Eyebrow hairs have some unique characteristics. For example, unlike hair on hormone-dependent body regions (i.e., scalp, beard, chest, axilla, and pubic region) these short and stiff eyebrow hairs that grow at an angle are not androgen dependent. There are three types of hair in the eyebrow. These are the fine vellus hair; the slightly larger and lightly pigmented hair; and the large terminal hair, also known as the supercilia. The terminal hairs are curved, 5 to 10 mm long, and have a punctuate tip. And, like all other hair types eyebrow hairs go through several cyclic stages of growth and regeneration. Hair growth has three phases, the anagen phase is the active hair growth phase. This phase is short in body hair (e.g. weeks to months for eyebrow hair) but longer in scalp hair (2 to 8 years). The longer the anagen phase the longer the hair length. Second is the catagen phase where the hair is dormant and last is the telogen phase, where the follicle grows new hair and sheds the old hair shaft. Overall, eyebrows grow slower than hair on other body locations. Eyebrows reportedly grow between 0.14 to 0.16 mm per day while for comparison scalp hair grows from 0.32 to 0.41 mm per day.[5] Furthermore, in contrast to scalp hairs that grow faster and have a shorter resting phase, the eyebrow hairs have a shorter active growth or anagen phase, have a much smaller percentage of hairs in the anagen phase at any one time, have a relatively long resting phase and have a significantly longer shedding or telogen phase.[6-8]

For many years physicians have been taught in the Emergency Department, on the wards, and in the operating rooms to not shave eyebrows. And, this prohibition is currently stated in textbooks such as Tintinalli's Emergency Medicine, "*Hair should never be removed from the eyebrows or at the hairline because potential for impaired or abnormal growth*" and in surgery texts like Current Diagnosis & Treatment: Surgery, "*... eyebrows should never be shaven...*".[9,10] But, after a searching the literature available on the topic there seems to be no evidence to support such a claim and, while limited, at least some evidence to support the contrary.[4]

On the other hand, there are many other reasons for eyebrow hair loss. Loss of eyebrow hair is associated with a long list of conditions including but not limited to leprosy, hypothyroidism, psychotropic medications, seborrheic dermatitis, dermatophyte infections, autoimmune conditions, syphilis, neoplasms, congenital etiologies, and others.[11,12] It is important to keep these etiologies in mind when dealing with alopecia confined to the eyebrow.

Finally, there may be appropriate reasons for not shaving the eyebrows other than the erroneous concern that they may not grow back. First, as detailed above, eyebrow hairs do grow slower than other body hairs. Consequently, the cosmetic and aesthetic issues associated with a prolonged period of eyebrow regeneration may be disconcerting to the patient. Second, removal of the hair prior to the surgical repair of a wound involving the eyebrow may remove important landmarks needed for proper alignment of the injured eyebrow.[13] Only after the eyebrow grows back will the visible cosmetic deformity be noted.

SUMMARY

This article helps debunk the long held belief that shaved eyebrows do not grow back. One more medical myth has been discredited; and hopefully, this will be good news for all of the interns who over the years have been painfully sanctioned for inadvertently shaving a patient's eyebrow.

CONFLICTS OF INTEREST

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Research Letter

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Colloid Supplementation during Induction of Anesthesia

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ABSTRACT

The present paper puts forward the hypothesis that infusion of colloid during induction will prevent the development of an oxygen debt. The reasoning behind this hypothesis depends on there being a drop in venous tone during induction, as a result of reduced sympathetic drive. The resulting venous relaxation leads to blood volume loss from the arterial side of the circulation into the venous side. The loss of arterial volume is responsible for the reduction in arterial blood pressure. The lowered value of Mean Arterial Pressure (MAP) results in a fall in Cardiac Output (CO) below normal, in the face of little if any change in Systemic Vascular Resistance (SVR). Most clinical assessments to date have emphasised changes in Stroke Volume (SV), whereas the fall in CO is the important variable since it determines Oxygen Delivery to the tissues (DO_2). When DO_2 is lower than normal it is responsible for the development of oxygen debt, and this is the main reason for development of the complications commonly found following anesthesia. The present hypothesis is that addition of carefully titrated colloid fluid during induction can be scaled to reduce or prevent the fall in MAP and CO. Although this means the presence of extra fluid in the circulation previous work suggests this will be eliminated readily during recovery. An alternative, giving phenylephrine over the induction period reduces the anesthetic induced venous wall relaxation. Phenylephrine is already being utilised successfully and is likely to be a useful adjunct to colloid supplementation. By maintaining normal or near normal pressure, as assessed prior to induction, and hence sustaining normal blood flow, normal DO_2 will be sustained. Avoidance of an oxygen debt should reduce or even eliminate the complications which result from tissue ischaemia during anesthesia. Vasopressor administration may raise arterial pressure but will worsen the cardiac output and hence increase oxygen debt.

KEYWORDS: Anesthesia; Colloid; Induction; Volume load; Arterial pressure; Cardiac output; Oxygen debt.

ABBREVIATIONS: SV: Stroke Volume; MAP: Mean Arterial Pressure; CO: Cardiac Output; SVR: Systemic Vascular Resistance; DO_2: Oxygen Delivery.

INTRODUCTION

It has been known for many years that most tissues exert auto-regulation of their blood flow. Green, Rapela, and Conrad[1] described auto-regulation in most tissues of the body, with evidence from earlier literature showing the extent to which haemodynamic dysfunction affected it. It was clear from many sources, already available, that auto-regulation (sustaining blood flow in the face of wide pressure changes) was most robust for cardiac and skeletal muscle vasculature. Auto-regulation was least robust for renal and splanchnic circulations. Cerebral auto-regulation was intermediate in its ability to withstand, for example, low arterial pressure. Guyton, et al.[2] also quote multiple sources showing that auto-regulation applies to these tissues. They also illustrate the precise increase in DO_2 as VO_2 increases with exercise. The determination of individual blood flow by the tissues is also illustrated by experimental work quoted in

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Guyton, et al.[2] where limb perfusion by either hypoxic blood or blood with normal oxygenation alter blood flow such that the rate of Oxygen Delivery to the limb is sustained. This precision adjustment of blood flow still occurred even when the limb innervation was cut, showing that the adjustment is made by the tissues in the limb, and is independent of the central nervous system. Determination of blood flow by the tissues has therefore been recognised as sub-serving delivery of oxygen to the tissues (DO_2). More recently DO_2 has been found to be maintained at a precisely controlled rate; for exercising skeletal muscle even with hypoxia and/or anaemia[3] and for brain.[4,5] An overview including auto-regulation of DO_2 by the heart and the whole body is given by Wolff.[6] The important feature here is that DO_2 specifically exceeds the rate of oxygen consumption (VO_2) such that each tissue has a preferred DO_2:VO_2 ratio (or the inverse, oxygen extraction, VO_2/DO_2). So, during routine behaviour in normal subjects, the adjustments of DO_2 are precisely regulated. Several situations can interfere with the precision adjustments of DO_2 matching with VO_2. For example, ascent to high altitude is accompanied by compensation for hypoxia with an increase in blood flow sustaining normal DO_2 in the face of lowered oxygen content. This compensation is adequate until the hypoxic insult is too great. Breakdown of the precise adjustment varies with the rate of ascent and from person to person. A second example, where the DO_2:VO_2 ratio falls off (oxygen extraction increases) is in severe exercise. Above a certain exercise intensity, probably the 'so called' anaerobic threshold, there is a progressive reduction in the DO_2:VO_2 ratio (i.e. an increase in oxygen extraction).

In anesthesia there is commonly a deficiency in the blood volume, either from relaxation of veins or from haemorrhage where under-filling of the circulation results from blood loss. Here, it is important to stress the fact that the dilatation of the veins in anesthesia is one form of vaso-dilation, the other being dilation of arterioles. It is important to recognise these two types of vaso-dilation have very different effects so, the present hypothesis specifies 'venous dilatation' in this discussion of the vascular problems of anesthesia.

CIRCULATORY PATHOPHYSIOLOGICAL CHANGES WITH INDUCTION

The relaxation of veins is a result of the anesthetic, or rather the patient's response to the anesthetic.[7] Since the veins relax but the total blood volume remains unchanged, at least in elective surgical anesthesia, the blood volume will be redistributed, with an increase in venous blood volume and a corresponding loss of blood volume from the arterial side of the circulation. Reduction of the arterial blood volume will, necessarily, reduce arterial blood pressure.

Shoemaker, et al.[8] were able to calculate the oxygen debt during and following surgery. Some oxygen debt occurred during anesthesia in most cases with progressive worsening post-operatively. Morbidity and mortality were strongly related to the extent of oxygen debt. Many studies have utilised a form of goal directed therapy during the postoperative stage attempting to reach a rate of Oxygen Delivery (DO_2) index at or above 500 ml min^{-1} with varied success. Shoemaker, et al.[9] were early contributors having found earlier that patients reaching this value spontaneously had least complications.[10,11] Many studies since then have also attempted bringing DO_2 to this level post-operatively, with varying success.[12]

The use of colloid for volume loading rather than crystalloid has been recommended because of its retention in the circulation. Over the short term crystalloid infusion can tide over a need for extra volume in the circulation. Ueyama, et al.[13] found considerably better results from colloid infusion than crystalloid infusion in parturient women undergoing spinal anaesthesia for elective caesarean section.

The realisation that intervention during anaesthesia rather than in the postoperative period might improve outcome occurred to Noblett, et al.[14] Their study included an intervention arm, assessing volume responsiveness throughout the period of anesthesia, and responding to evidence of volume responsiveness with the infusion of colloid. The control arm of the study relied on simple clinical impression to decide whether to give fluid and in this arm of the study colloid was also given. Both groups gave colloid fluid but the intervention group fluid was given in the early stages of the operative period whereas a very similar volume of colloid fluid was given much later in the control group patients. Cardiac output was significantly greater for the intervention patients throughout the operative period. Complications only occurred in 2% of the intervention group in contrast to 15% in the control group. Hospital stay was reduced from 9 to 7 days and food taken earlier (2 days *versus* 4 days) post-operatively.

Similarly, the findings of Green, et al.[15,16] that volume correction with colloid during anaesthesia reduced complications and avoided the need for postoperative intervention. Prior to this most studies introduced attempts at volume correction and augmentation of cardiac output postoperatively where an oxygen debt had already been incurred. A 'supranormal' cardiac output and DO_2 was aimed for and resulted in variable success.[12] The improved findings with volume loading during anesthesia[13-15] lend support to the present hypothesis.

The study of Wolff and Green[17] has outlined the main circulatory changes seen with the induction of anesthesia. The commonly observed pattern, of a falling arterial blood pressure with little if any change in Systemic Vascular Resistance (SVR), is illustrated in Figure 1.

Total blood volume will, of course, vary with body size, but the relative proportions of arterial and venous blood volumes will, usually, be much the same.

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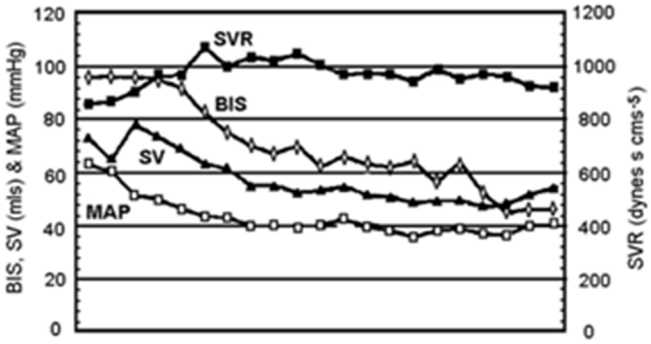

Figure 1: This shows how, with induction of anesthesia, SVR barely changes and yet Mean Arterial Pressure (MAP) falls. The better plot would include CO rather than SV but this will be falling similarly, in view of the fall in MAP (without SVR change). (From[17] open access. Figure originally a slide at a conference; Abstract[18]).

Mitigation of the fall in MAP during induction has been achieved by Green, et al. by concurrent infusion of low doses of phenylephrine.[16] An example is illustrated in the study of Wolff and Green[17] comparing the use of phenylephrine during the transition from pre- to post-anesthetic induction with the worse effect where phenylephrine was not given. It can be seen to be a useful alternative or adjunct to the proposed colloid titration during induction. The ability to counteract the sympathetic effects of anaesthesia with phenylephrine arose from the finding that venous wall relaxation was mediated by sympathetic block.[19]

The recommended procedure, to supplement blood volume with colloid during induction, requires awareness of the optimal values of arterial pressure and cardiac output. In order to know the pre-induction values one needs to start monitoring before induction. The pre-induction values can be used as reference optimum values, if the surgery is elective, and where there is no haemodynamic problem. CO may even be a little above optimum. Shoemaker, et al.[8] showed that with VO_2 values during anesthesia were typically 85% of pre-induction values. Hence, keeping CO (and DO_2) at or above 85% of pre-induction values should avoid development of an oxygen debt.

At this point (pre-induction) the normal circulatory volumes of the arterial, capillary and venous compartments can be envisaged, as shown in Figure 2 uppermost panel.

When the venous compartment expands during induction (say by 200 ml), there will be a shift of this volume of blood away from the arterial side of the circulation. A volume of 200 ml though small in terms of venous expansion constitutes a large proportion of the arterial volume. A loss of 200 ml from a total of 600 ml (12% of 5000 ml) constitutes a loss of 1/3rd of the arterial volume with a large fall in Mean Arterial Pressure (MAP). With little change in Systemic Vascular Resistance (SVR, see Figure 1) the reduced MAP will result in the, commonly observed, fall in cardiac output. Persistence of this low CO is the reason for development of an oxygen debt during anesthesia.[8]

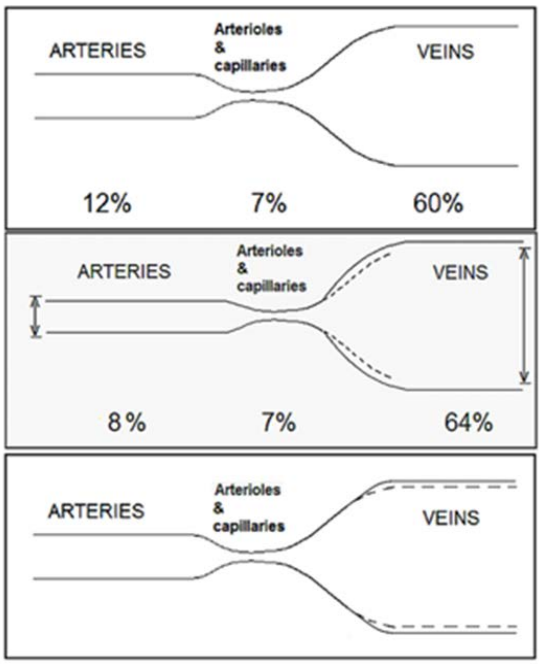

Figure 2: The upper panel shows the normal proportions of the blood volumes in arteries (12%) capillaries (7%) and veins (60%) clarifying the problem which will occur with venous relaxation (middle panel). The small proportional increase in venous volume causes a proportionally large fall in arterial volume. This causes the resulting fall in arterial pressure. Supplementation of the venous volume (lower panel) will re-expand the arteries with restoration of normal pressure.

DISCUSSION

Although infusion of colloid during induction will increase total blood volume the hypothesis is that this will, by filling the extra venous capacity, reduce the loss of blood from the arterial side of the circulation, thereby maintaining arterial blood pressure. The differences in body build will mean that differences will occur in the amount of colloid fluid required and this will mean observation of MAP and CO during induction, so that any fall can be prevented by careful infusion.

Giving volume expander (colloid) during induction

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should therefore enable the reference values of pressure and cardiac output to be sustained. The procedure is a logical extension of the idea that 'the earlier the intervention the better'; even earlier than the colloid administered during early anesthesia by the intervention group in the study by Noblett, et al.[14] The different nature of colloid and crystalloid discussed in Wolff and Green[17] also relates to their stress on avoidance of excessive crystalloid maintenance. Colloid infusion to counter volume dependency is simply adding a modest temporarily appropriate intra-vascular volume as distinct from the gross overfilling of total body water by excessive maintenance crystalloid.

An excessive depth of anesthesia will exacerbate the problems from venous volume relaxation. It is therefore important to be able to regulate the depth of anesthesia – not too deep and not too shallow. Although there are sceptics concerning the validity of BIS (electro-encephalographic assessment) its use has been associated with excellent results.[20]

Cerebral oxygenation monitoring also makes a valuable contribution. When a fall is detected, cerebral oxygen monitoring has been found to help with assessment of the adequacy of blood volume.[21] Furthermore, when therapeutic volume loading fails, it is an alert to haemorrhage sufficient to have significantly lowered blood volume.

The reduction or even elimination of complications, fundamentally due to ischaemia,[22] will both ease recovery and reduce the need for patient aftercare in high dependency units.

CONCLUSIONS

The hypothesis is that mean arterial pressure and cardiac output can be sustained at, or near, pre-induction values by means of slow supplementation of blood volume with colloidal fluid during anesthetic induction. This should, hypothetically, infuse the volume by which the venous system expands, thereby preventing the usual loss of volume from the arterial side of the circulation.

This titrated colloid infusion should, theoretically, prevent the commonly found fall in both arterial pressure and cardiac output. Since, this would sustain an adequate rate of Oxygen Delivery ($DO_{2)}$ it would prevent the development of an oxygen debt. Concurrent infusion of phenylephrine would also be helpful and could minimise the colloid requirement. These manoeuvres, in minimising oxygen debt should result in a considerable reduction in anesthetic complications. A clinical trial of titrated colloid infusion during induction would be of value.

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Recognition of Imported Tropical Infectious Disease in Returned Travelers in a University Hospital Emergency Department

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ABSTRACT

Objective: Healthcare workers practising in Ireland may encounter tropical illness in the returned traveler. This study aimed to establish the awareness of tropical diseases in front-line healthcare professionals working in an Irish hospital.
Methods: A questionnaire was administered to doctors and nurses working in an Irish university teaching hospital. The respondents' ability to obtain a travel history, to recognize tropical illness in returned travelers and to demonstrate awareness of the geographical distribution of tropical diseases was evaluated.
Results: Fifty clinicians completed the survey (29 doctors and 21 nurses), most of whom had not previously worked in the tropics and had not received formal training in tropical or travel medicine. The following items were not routinely included in their travel histories: illness in traveling companions, water and food consumption, insect and animal bites. Tropical illness was infrequently considered in patients presenting with a variety of common symptoms. There was a poor level of familiarity of several tropical infectious diseases. There was a tendency for doctors to underestimate the prevalence of dengue infection. A substantial proportion of doctors were not confident in their ability to manage a patient with malaria. The educational activities preferred by the majority of respondents were tropical disease manuals, workshops and wall charts.
Conclusion: This study highlights a low level of knowledge of tropical medicine among a sample of healthcare workers who may be called upon to assess the returned tropical traveler. Opportunities for training in tropical medicine should be provided to emergency department clinicians.

KEYWORDS: Recognition; Tropical; Infectious disease; Emergency department.

INTRODUCTION

With the marked increase in international travel,[1] and the growth of the migrant population living in Western European countries, multidisciplinary healthcare workers practising in Ireland are increasingly likely to encounter tropical illness in the returned traveler. Although most post-travel-related health problems in travelers to developing countries are mild, up to 8% of travelers seek care from a physician when they return to their home country.[2-5] Common diagnoses revealed by the GeoSentinel Surveillance Network Database in Europe include enteric fever, acute viral hepatitis, and influenza.[6] Life-threatening infectious diseases, such as *Plasmodium falciparum* malaria, melioidosis, and African trypanosomiasis, were reported in a study of GeoSentinel records of 53 tropical or travel disease units in 24 countries.[7] Lack of awareness of the possibility of tropical infectious disease in the differential diagnosis of an ill returned traveler could precipitate potentially complicated or fatal diagnostic delay.

Little is known about the preparedness of frontline emergency department clinical personnel in European healthcare institutions to promptly diagnose imported tropical infec-

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tious diseases in returning travelers. The current study aimed to establish the level of awareness of tropical diseases in a sample of healthcare professionals working in a major Irish teaching hospital; to evaluate their level of awareness of the geographical distribution of tropical diseases; and to characterise the ability of the healthcare team to record a detailed travel history, recognize tropical illness in returned travelers, identify the tropical disease risks associated with specific travel itineraries, and express their training needs in relation to clinical tropical medicine.

METHODS

The research protocol for this descriptive, cross-sectional survey was approved by the local clinical research ethics committee. A self-administered questionnaire was distributed to a convenience sample of Emergency Department (ED) doctors (16-item questionnaire) and triage nurses (13-item questionnaire) working at University Hospital Galway in Ireland. The questionnaire enquired about the previous training, if any, received by the healthcare team in tropical medicine, their awareness of the components of a comprehensive travel history, their ability to recognize tropical illness in returned travelers, their knowledge of the geographical distribution of tropical diseases, and of the infectious disease risks posed by specific travel itineraries. Survey respondents were also asked about their degree of confidence in managing a patient with imported malaria. The study also invited the ED clinicians to nominate their preferred educational activities in relation to clinical tropical medicine. Data were entered into a Microsoft Excel database, imported into IBM SPSS Statistics version 21.0, and analyzed using descriptive and inferential statistics. A two-sided chi-squared test was used to determine if there was a significant difference between expected and observed frequencies, with <0.05 representing statistical significance.

RESULTS

Fifty healthcare workers completed the survey (29 doctors and 21 nurses). The majority of medical respondents (76%, n=22) were non-consultant hospital doctors. Forty-five percent (n=9) of the nurses surveyed worked on a weekly basis as triage nurses in the Emergency Department. Most of the doctors (72%, n=21) and nurses (57%, n=12) in the survey had not previously worked in a tropical or sub-tropical region (Figure 1). The majority of doctors (66%, n=16) and nurses (67%, n=14) had not received formal training in tropical or travel medicine. The training received by doctors was considered to be less than satisfactory in 38% (n=5) of cases, and by nurses in 60% (n=3, Figure 2). The difference between the satisfaction rate of both professional groups was not statistically significant (p=.608)

The following items were not routinely included in the travel histories of the clinicians surveyed (Figure 3), and were more likely to be omitted by ED triage nurses than by ED doctors (NS=not significant): illness in a traveling companion (p=0.032), use of malaria chemoprophylaxis (p=0.009), water and food consumption practices (NS), insect bites (NS), and animal bites (NS). Tropical illness was unlikely to be considered in patients presenting to the ED with shortness of breath, skin rash, joint pain, headache, fatigue and confusion by both doctors and nurses (Figure 4). There was no statistically significant difference between professional groups in relation to the consideration of tropical illness based on these clinical presentations.

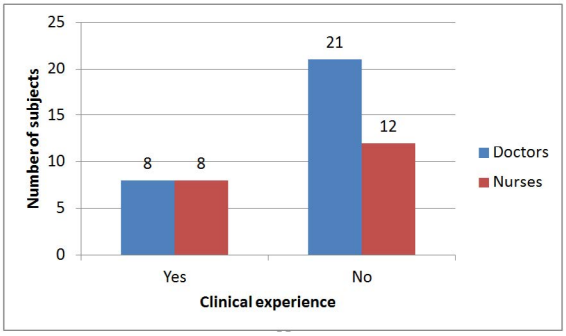

Figure 1: Previous clinical experience in tropical regions.

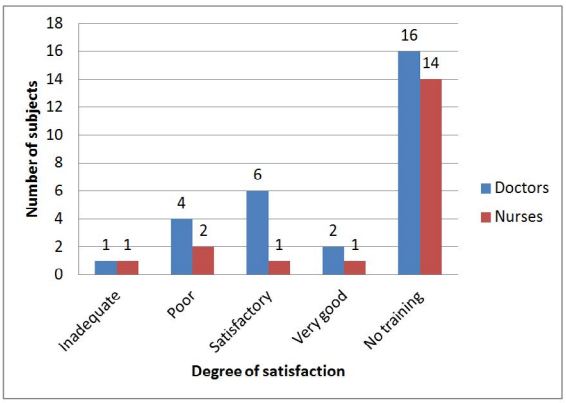

Figure 2: Satisfaction with previous tropical medicine training.

There was a poor level of diagnostic confidence in relation to a range of tropical infectious diseases with a significant proportion of both medical (Figure 5) and nursing (Figure 6) staff declaring unfamiliarity with important tropical diseases. Doctors were statistically more likely to declare confidence in diagnosing the following tropical infectious diseases compared to nurses: dengue (p=0.001), schistosomiasis (p<0.0001), hepatitis A (p=0.011), leishmaniasis (p=0.001), cutaneous larva migrans (p=0.001), trypanosomiasis (p=0.001), and filariasis (p=0.001). There was a tendency for doctors to overestimate the global distribution of malaria and yellow fever, while underestimating the prevalence of dengue infection (Table 1), upon considering specific travel itineraries. There was a reasonable level of awareness of the incidence of imported malaria in Ireland. Twenty-five percent (n=7) of medical respondents underestimated the annual incidence of imported malaria. A sizeable but non-statistically significant proportion of doctors (66%, n=19, p=0.79) were less than confident in their ability to manage a patient with malaria in an Irish hospital setting (Figure 7). The educational activities preferred by the majority of respondents were tropical disease manuals, designated workshops and wall charts (Figure 8). Nurses were more likely to express a preference for weekend courses (p=0.035).

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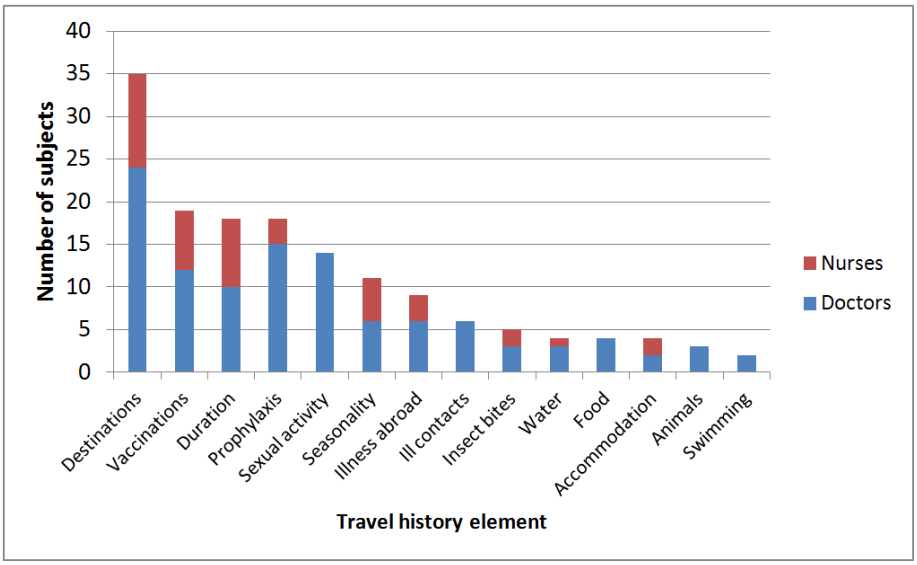

Figure 3: Elements of travel history routinely recorded.

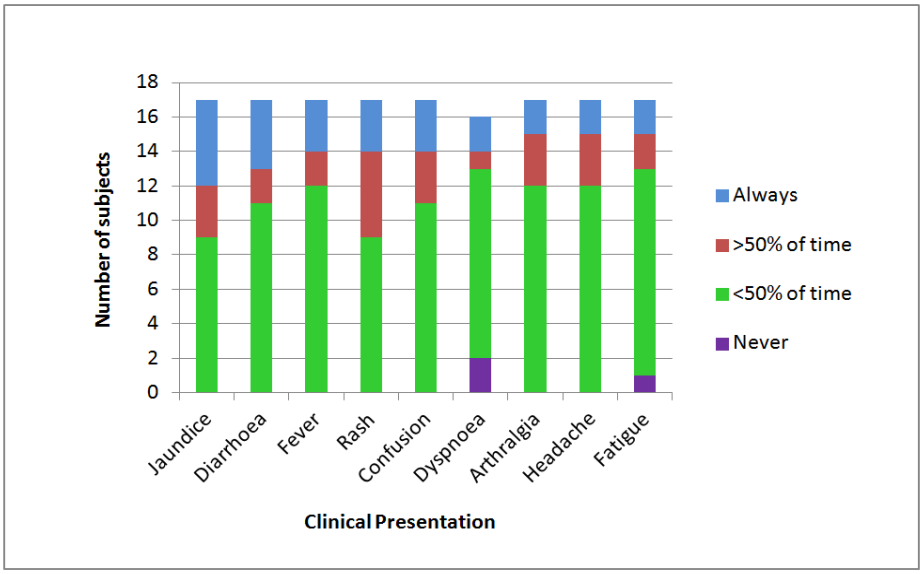

Figure 4: Physician likelihood of considering tropical disease in returned travellers.

The internal consistency of the Likert scale items on the questionnaire administered to doctors and nurses was high, with a Cronbach's alpha coefficient of 0.900 (n=43).

DISCUSSION

This study, though limited by its sample size, single centre location, and non-standardized instrument, provides useful insights into the familiarity of Emergency Department doctors and nurses with respect to the recognition and management of tropical infectious diseases presenting for emergency hospital care with a variety of symptoms. The lack of previous experience of working in a tropical healthcare setting was prominent in this group, and it is possible that many of those who had worked in a tropical country originated from such countries as the questionnaire did not record ethnicity or the country where basic nursing or medical education were undertaken.

Over two thirds of those surveyed had not completed any formal training in tropical medicine, reflecting the general lack of emphasis on this subject in undergraduate and postgraduate medical and nursing curricula. Currently there is no active taught postgraduate programme in tropical medicine in Ireland and the respected full-time courses available locally in the London School of Hygiene and Tropical Medicine[8] and the Liverpool School of Tropical Medicine[9] offer limited places and may be difficult to complete for full-time clinicians.

In a post-travel evaluation, it is recommended that the clinician considers several factors, including the severity of illness, travel itinerary, the timing of illness in relation to travel, underlying medical conditions which could affect susceptibility to infection, vaccines received, compliance with malaria chemoprophylaxis, and the individual's exposure history, which must include information on insect bites, contaminated food and water,

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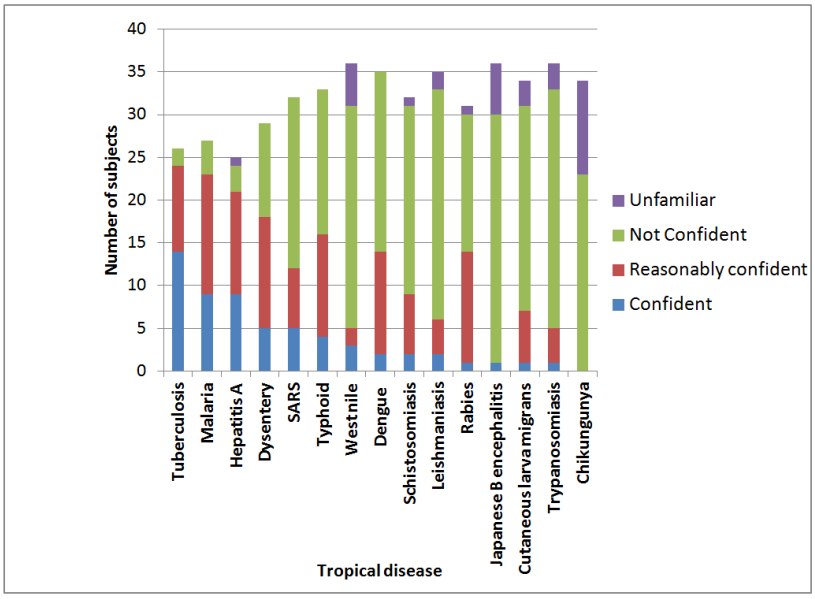

Figure 5: Recognition of specific tropical diseases by doctor.

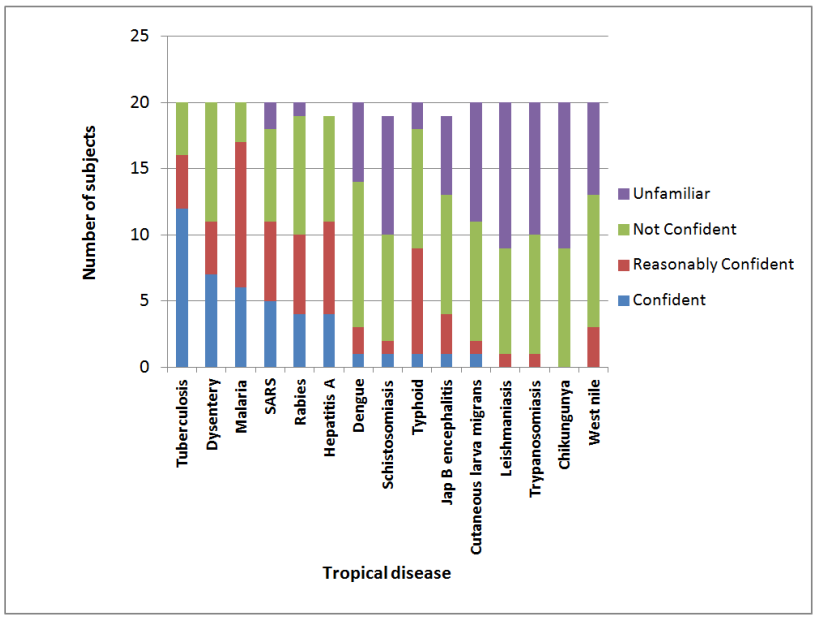

Figure 6: Recognition of specific tropical diseases by nurses.

freshwater swimming, purpose of trip, accommodation type, and any treatment accessed locally.[10] In a study of long-term travelers visiting GeoSentinel sites, Chen and co-workers[11] found that long-term travelers experienced greater levels of chronic diarrhoea, giardiasis, *Plasmodium falciparum* or *Plasmodium vivax* malaria, chronic fatigue, eosinophilia, cutaneous leishmaniasis, schistosomiasis, and amebiasis. In a study of a large, multicentre database of febrile returned travelers, Wilson and colleagues[12] found that over 17% of travelers with fever had a vaccine-preventable infection or falciparum malaria, and that malaria was responsible for 33% of the 21 deaths recorded in febrile returned travelers. Important clues may arise in the initial investigation of the ill returned traveler, including the possibility of helminthic infection in the returning traveler with eosinophilia.[13]

An interesting finding in the current study was the reluctance of healthcare staff to routinely record a detailed travel history and to consider tropical disease when faced with a patient who presents with a variety of common symptoms, such as fever, headache and arthralgia. The ill patient may not volunteer a history of travel, or may be too unwell to provide a reliable history, and the Emergency Department clinicians may not prioritise tropical illness in their differential diagnosis owing to lack of familiarity or case exposure. This failure to consider tropical infections was compounded by a stated lack of familiarity with a range of common tropical infectious diseases, all of which may be imported by an asymptomatic traveler returning from endemic parts of the world during the incubation period of the disease. While there was a tendency to overestimate the global

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Travel itinerary	Den n (%)	Mal n (%)	Sch n (%)	Hep n (%)	Typ n (%)	YF n (%)	JE n (%)
Business man spent 4 nights in a hotel in Southern India (n=25)	13 (52)	17 (68)	3 (12)	19 (76)	12 (48)	6 (24)	1 (4)
Medical student spent 2 months in rural Philippines (n=24)	16 (67)	16 (67)	8 (33)	16 (67)	12 (50)	11 (46)	11 (46)
Aid worker spent 4 months in Ethiopia (n=26)	9 (23)	21 (81)	13 (50)	13 (50)	13 (50)	10 (38)	1 (4)
Flew from Lima to Cuzco and trekked the Inca trail (n=25)	7 (28)	10 (40)	7 (28)	11 (44)	11 (44)	13 (52)	1 (4)
Spent 1 week in Istanbul, Turkey (n=23)	1 (4)	2 (9)	3 (13)	17 (74)	10 (43)	2 (9)	0 (0)
Flew to Buenos Aires and visited the Iguassu falls (n=23)	7 (30)	14 (61)	6 (26)	15 (65)	11 (48)	6 (26)	1 (4)
Trans-Siberian railway from Moscow to Beijing (n=22)	7 (32)	4 (18)	2 (9)	14 (64)	12 (55)	3 (14)	10 (45)
Flew from Rio de Janeiro to Manaus in the Amazon (n=24)	13 (54)	20 (83)	10 (42)	13 (54)	10 (42)	12 (50)	3 (13)
Honeymoon couple travelled on a 1-week Nile cruise (n=24)	7 (29)	12 (50)	10 (42)	17 (71)	16 (67)	4 (17)	2 (8)
Family spent 2 weeks in Cape Town, South Africa (n=20)	5 (25)	11 (55)	3 (15)	15 (75)	9 (45)	3 (15)	1 (5)
Flew from Bangkok to Hanoi visiting coastal Vietnam (n=23)	13 (57)	13 (57)	7 (30)	13 (57)	11 (48)	10 (43)	14 (61)
Flew to Bangkok and spent 2 weeks on Phuket (n=21)	6 (29)	10 (48)	6 (29)	16 (76)	9 (43)	6 (29)	6 (29)
Stopped over in Singapore for 2 nights en route to Perth (n=16)	3 (19)	6 (38)	3 (19)	9 (56)	5 (31)	3 (19)	6 (38)
Two-week trip to Cuba (n=18)	6 (33)	10 (56)	3 (17)	15 (83)	2 (11)	2 (11)	1 (6)

Key: Den = Dengue infection; Mal=Malaria; Sch=Schistosomiasis; Hep=Hepatitis A; Typ=Typhoid fever; YF=Yellow fever; JE=Japanese encephalitis.
Table 1: Physician knowledge of global distribution of tropical disease.

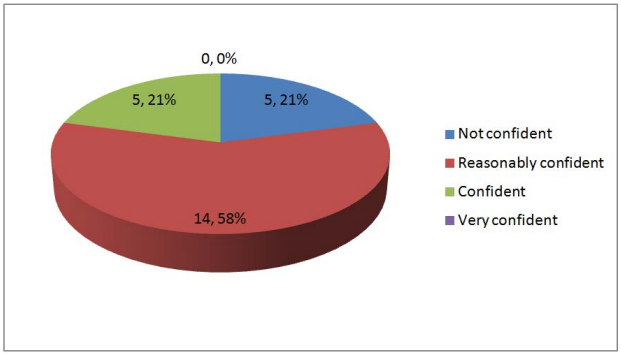

Figure 7: Confidence in management of malaria.

distribution of malaria, there were poor levels of confidence in managing malaria in an Irish hospital setting. This is especially significant given the increased burden of imported malaria in Ireland in recent years, predominantly among the visiting friends and relatives population.[14]

Most of the Emergency Department healthcare team members selected convenient educational activities from the list provided, with only 20% opting for a diploma course in tropical medicine. This may reflect their busy working lives with multiple competing responsibilities, the general nature of their typical diagnostic load, or the low priority given to tropical medicine in their careers to date.

Future studies should include larger random samples from hospitals throughout Ireland and other European countries, and should directly compare knowledge, attitudes and practices of indigenous and international graduates. A standardized curriculum in tropical medicine, delivered in common to nursing and medical students, should be designed as a first attempt to address the learning needs identified by this pilot study.

CONCLUSIONS

This study is the first of its kind in Ireland to examine the preparedness of frontline Emergency Department healthcare

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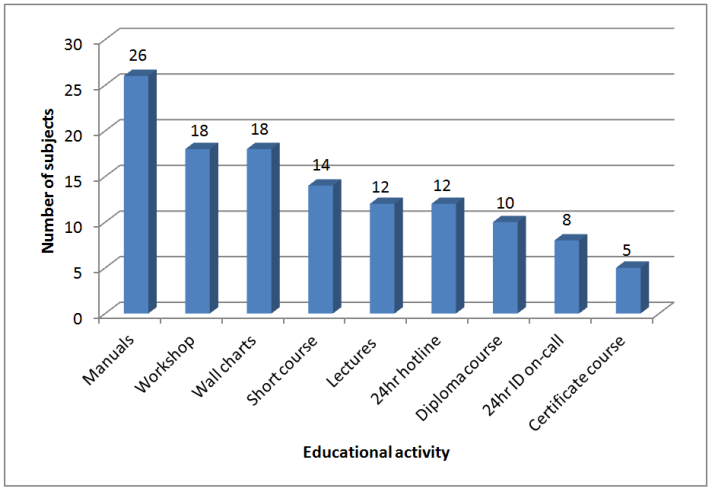

Figure 8: Preferred tropical medicine educational activities.

workers to diagnose and manage imported tropical infectious diseases in a hospital setting. Deficiencies were highlighted in the recording of a travel history, and there was a generally poor ability to recognize tropical illness in patients with a variety of presenting symptoms. Enhanced opportunities for training in tropical medicine should be provided to front-line healthcare professionals.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Review

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Primary Intra-Abdominal Hypertension and Abdominal Compartment Syndrome: Pathophysiology and Treatment

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ABSTRACT

Abdominal Compartment Syndrome (ACS) is a potentially lethal condition caused by various events that produce intra-abdominal hypertension. The most common cause is blunt abdominal trauma. Increasing intra-abdominal pressure causes progressive hypoperfusion and ischemia of the intestines and other peritoneal and retroperitoneal structures. Pathophysiological effects include release of cytokines, production of oxygen free radicals, and decreased cellular formation of adenosine triphosphate. These processes may lead to translocation of bacteria from the gut and intestinal edema, predisposing patients to multiorgan dysfunction syndrome. The consequences of abdominal compartment syndrome are profound and affect many vital body systems. Respiratory, hemodynamic, cardiovascular, renal, and neurological abnormalities are signs of abdominal compartment syndrome. Medical management of critically ill patients with raised intra-abdominal pressure should be instigated early to prevent further organ dysfunction and to avoid progression to ACS. Many treatment options are available and are often part of routine daily management in the ICU (nasogastric, rectal tube, prokinetics, enema, sedation, body position). Some of the newer treatments are very promising options in specific patient populations with raised IAP. Nursing care involves vigilant monitoring for early detection, including serial measurements of intra-abdominal pressure.

KEYWORDS: Intra-abdominal hypertension; Abdominal compartment syndrome; Damage control laparotomy; Laparostomy; Open abdomen.

ABBREVIATIONS: IAH: Intra-Abdominal Hypertension; IAP: Intra-Abdominal Pressure; APP: Abdominal Perfusion Pressure; WSACS: World Society of the Abdominal Compartment Syndrome; HOB: Head of Bed; ICU: Intensive Care Unit; CO: Cardiac Output; ICP: Intra-Cranial Pressure; CPP: Cerebral Perfusion Pressure; CVP: Central Venous Pressure; IVP: Intra-Vesical Pressure; PAOP: Pulmonary Arterial Occlusion Pressure; PCWP: Pulmonary Capillary Wedge Pressure; MABP: Mean Arterial Blood Pressure; GFR: Glomerular Filtration Rate; RBF: Renal Blood Flow; RPP: Renal Perfusion Pressure; PEEP: Positive End-Expiratory Pressure; RVEDV(I): Right Ventricular End-Diastolic Volume (index); MOFS: Multi-Organ Failure Syndrome; SOFA: Sepsis-Related Organ Failure Assessment; V/Q: Ventilation/Perfusion Ratio; SVR: Systemic Vas-cular Resistance; FRC: Functional Residual Capacity; TAC: Temporary Abdominal Closure; IBP: Intra-Bladder Pressure; IGP: Intra-Gasric Pressure; GRV: Gastric Residual Volume; VAP: Ventilator-Associated Pneumonia.

DEFINITIONS, INCIDENCE AND MEASUREMENT STRATEGIES IN INTRA-ABDOMINAL HYPERTENSION (IAH) AND ABDOMINAL COMPARTMENT SYNDROME (ACS)

The concept of the Abdominal Compartment Syndrome (ACS) has been rediscovered as a final common pathway of the physiologic sequelæ of increased Intra-Abdominal Pressure

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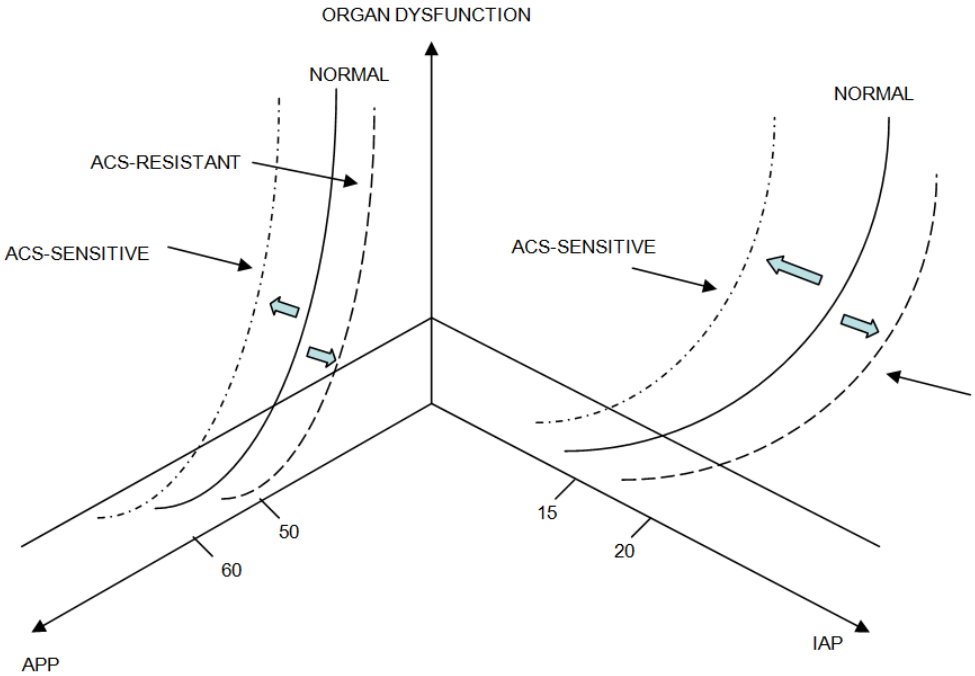
(IAP) and Intra-Abdominal Hypertension (IAH). The recent establishment of the World Society of the Abdominal Compartment Syndrome (WSACS: www.wsacs.org) in 2004 and its endorsement by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine has provided the imprimatur of international for a through the three World Congresses on ACS to emphasize the importance of this syndrome and its prodrome as distinct clinical entities in surgical and intensive care practice.[1] Part of this acceptance has been a rediscovery of these entities and of their complex pathophysiology and that of surgical decompression since they were originally highlighted in limb compartments by Richard von Volkmann[2] and since Abdominal Compartment Hypertension was suggested by Etienne-Jules Marey who was the first to measure intrathoracic pressures in 1863.[3] These original descriptions of the syndrome were supplemented by direct abdominal pressure measurements in dogs and the effects of IAP on major venous return and cardiac output by Haven Emerson in 1911,[4] and establishment of some of the factors which controlled IAP by Helen Coombs.[5] The coining of the term Abdominal Compartment Syndrome was probably used first by Robert Fietsam of Michigan in 1989 following abdominal aortic aneurysm repair.[6-8]

There is no strict definition of what represents abnormal IAP, but there is a general acceptance that measured pressures >12 mmHg when recorded 1-6 hours apart are considered to represent IAH, where Sugrue, et al. have shown that this represents up to 40% of cases admitted to a surgical Intensive Care Unit (ICU).[9] Although there are biases in the prospective assessment of a selective population admitted to an ICU who actually undergo IAP measurement, there is an inverse correlation between those patients deemed to have IAH who do not have surgical decompression and overall survival.[10] IAP behavior is similar to intra-cranial pressure (ICP) and there is an exponential correlation between organ dysfunction and IAP. The Monroe-Kellie doctrine would dictate an hyperbolic association between ICP and intracranial volume. This is illustrated in Figure 1 which shows that a distinction can be made between IAH, (a recording without organ dysfunction) and a state when the curve shifts to the left where with organ dysfunction the IAH value becomes clinically more critical. The further assumption that the abdomen behaves somewhat similarly to the cranium as a closed box is clearly not accurate. There are anisotropic variable compliances between the abdominal components, some rigidity in the relatively unyielding nature of the thoracic cage, costal margin, spine and pelvis, variability in the amount and type of soft-tissue intestinal and peritoneal distension and *in vivo* differences between the hydrostatic effects on abdominal contents and those dictated by Pascal's Law for *in vitro* systems.[11] The latter stating that there is equivalency of transmitted pressure of an incompressible fluid at all points within a connected system is largely true in the absence of significant intra-abdominal adhesions.

The effective definition of ACS would then represent



In each case if the graph shifts to the right, higher IAP and lower APP values may not be associated with significant end-organ dysfunction creating a degree of "ACS-resistance." Shifts to the left would create "ACS-sensitivity" where lower values of IAP (higher APP values) may still be associated with organ dysfunction which might not occur normally. This results in difficulty for broader acceptance of critical IAP and APP levels for individual cases. ACS-sensitivity may potentially occur in patients where there is pre-existing partial end-organ failure, morbid obesity or following fluid hyper-resuscitation in patients with severe burns, haemorrhagic pancreatitis, massive blood loss, widespread intra-peritoneal sepsis and high-output intestinal fistulae.
IAP= Intra-abdominal pressure
APP= Abdominal perfusion pressure[12]
where APP = Mean arterial BP- IAP

Figure 1: Relationship between organ dysfunction, IAP and APP.

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a pathophysiological effect as a consequence of raised IAP characterized by a tense abdomen with elevation in peak airway pressures, inadequate spontaneous ventilation and reduced urine output in combination with a documented improvement in these parameters following abdominal decompression.[13] This stated, that represents pathological IAH in some patients won't have deleterious effects, in others minor variations in IAP will have significant morbidity and mortality. Definitions will then be consequent upon associated organ failure in individual cases,[14] where other parameters such as falling arterial pH, decreased Cardiac Output (CO), rising serum lactate levels, rising peak airway pressures and falling oxygen delivery indices are secondary to the principal definition but not essential for its diagnosis.[15] The same process will be evident after surgery or secondary event rather than in the context of gradual increases in IAP as may occur in ascites or in morbid obesity.[16,17] This latter definition describes the syndrome secondary ACS which has been reported in patients without abdominal injury but who develop ACS after aggressive fluid resuscitation.[18-21] The concept of tertiary ACS is ACS redevelops after prophylactic or therapeutic management of primary or secondary ACS cases.[22] Such a situation may occur following the definitive closure of the abdominal wall after primary ACS or in the utilization of temporary abdominal closure as part of a damage-control laparotomy.[23]

IAH is only a prodrome to a potentially fatal syndrome.[24-31] Interest in direct IAP measurement has been refreshed during the rise of interventional laparoscopy[32] as well as part of the management of patients undergoing continuous ambulatory peritoneal dialysis[33] and in patients with intraperitoneal drains which may be readily connected to pressure transducers.[34] Most IAP measurements are made *via* a urinary catheter as transmitted IAP; a technique originally described by Kron and colleagues[35] showing validation with direct pressure measurements.[36] The original technique has the disadvantages of repeated needling and disconnection of the urinary flow tract with the risk of urosepsis, its intermittent measurement nature and debate concerning the optimal volume of bladder instillation for consistent Intra-Vesical Pressure (IVP) measurement without falsely high values being recorded due to detrusor contraction.[37,38] Modification of this system (where a multi-stopcock attachment is part of a closed system avoiding the use of repeated needling and urinary disconnection) has been made independently by Cheatham[39] and Sugrue, et al.[9] who used a T-piece to obviate violation of the catheter and commercially available devices such as the AbViser two-way valve mechanism for anuric patients[40] and the Holtech manometric meniscus biofilter system (Holtech Medical, Copenhagen DK) have recently provided an opportunity to use the urine as a pressure transmitting medium as first described for clinical use by Harrahill.[41] This latter system has recently been validated.[42,43] The recent introduction by Balogh, et al. of continuous IAP measurement *via* a 3-way Foley catheter shows wide agreement with intermittent methodology over a wide range of pressures in general surgical and trauma patients[44] where these authors recommend its routine use after major abdominal surgery, in severe pancreatitis, major burns and following damage control laparotomy.

Other validated methods of IAP measurement include the nasogastric route as originally suggested by Collee,[45] misurations can be made *via* a gastrostomy tube or gastric tonometry catheter,[46] through an oesophageal balloon catheter[47-51] or from a perfused rectal or trans-uterine catheter similar to that used for anorectal manometry.[52,53] These trans-intestinal methods are subject to all the disadvantages encountered in any form of gastrointestinal manometry where there may be extraneous migrating motor complexes and where extra-intestinal compliances and viscoelastic properties of the gut during perfusion and release will create alterations in recorded pressure that may not reflect intraperitoneal values.[11]

Other techniques have estimated IAP from caval catheters (both superior and inferior) which provides a continuous monitoring like a Central Venous Pressure (CVP) line with all its inherent problems, where there is a correlation with Intra-Vesical Pressures but not with gastric or rectal pressures in animal studies[54] and where superior vena cava pressures poorly correlate with IAP in a ventilated canine model using PEEP variations.[55] Most recently, a range of catheters for placement *via* the rectal, uterine, vesical or gastric routes have been fitted with microchip transducers for rapid calibration showing a high correlation with other methodologies although there are large variations with this new technique.[56] Another new technique is the Intra-Gasric Pressure (IGP) monitoring through a Gastro PV (Holtech Medical, Charlottenlund, Denmark). Advantages are potentially large: we can compare Intra-Abdominal Pressure (IAP) values from IGP and Intra-Bladder Pressure (IBP) to study the upper abdominal compartment in particular and to compare with the lower ab-dominal compartment. The Gastro PV technique reduces the nursing manipulations to measure the Gasric Residual Volume (GRV) and allows more frequent GRV measurements to anticipate possible GRV increases, with a potential to prevent Ventilator-Associated Pneumonia (VAP). An easier method to measure GRV reduces the nursing workload and allows more time to be spent on other activities. Measurement of IGP does not carry a potential risk for urinary tract infections. The cost analysis shows the Gastro PV to be cost-effective, in particular for those cases with large amounts of GRV.[12]

Somewhat akin to the parameter Cerebral Perfusion Pressure (CPP), Cheatham and colleagues have suggested utilization of the parameter Abdominal Perfusion Pressure (APP) where [APP=Mean arterial BP-IAP] as a more reliable guide for the diagnosis of ACS and as part of its management algorithm.[57] In utilization of the APP, Cheatham, et al. performed a retrospective analysis of patients admitted to a surgical ICU with IAH who underwent IAP monitoring using an intra-vesical method where there was a liberal unit policy towards abdominal decompression.[58] In this study, logistic regression analysis for a patient group with 53% overall mortality showed IAP, MABP,

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APP, arterial lactate, arterial pH, base deficit and urine output to all correlate with patient survival when IAH was present, with APP and arterial lactate being the most significant survival-related variables. Receiver-operating characateristic (ROC) curves generated for both IAP and APP show great similarity although the best APP threshold has proven to be about 50 mm Hg with moderate sensitivity (76%) and a lower specificity (57%) for APP as a predictor for patient survival under these conditions. These results have better ROC features for survival than the use of MABP alone and these findings have been confirmed initially in a small prospective analysis of 8 patients by Malbrain, et al.[59] designed to evaluate the clinical validity of APP as an end-point and then subsequently in a large mixed ICU cohort.[24] In this latter study[24] APP was significantly lower in non-survivors where an APP of 60 mmHg had a sensitivity of 55% and a specificity of 76% for predicting survival performing better than IAP in more commonly encountered pressure ranges. It is currently unknown whether APP may have some general value as a critical end-point as the total numbers of IAH patients in this large study were only 18% and ACS was defined in only 2% of cases. These findings have also been confirmed by both the Critically Ill and Abdominal Hypertension (CIAH) and the Critically Ill Renal Failure and Abdominal Hypertension (CIRFAH) multicentre study groups.[60] In the latter study, outcome did not vary in those patients with designated IAH although non-survivors had a higher overall IAP and a lower APP after day 3, suggesting that sustained increases in IAP of continuously monitored patients, where the overall period of time spent above a critical IAP threshold may be more important to outcome than individual IAP measurements. Clearly, both clinical standardization and validation of IAP measurement methodology (and parameter decision, namely IAP *vs.* APP) are essential in an effort to define the incidence and severity of IAH for use as a management-decision parameter.

PATHOPHYSIOLOGIC EFFECTS OF INTRA-ABDOMINAL HYPERTENSION

Raised IAP has a deleterious effect on respiratory mechanics, the cardiovascular system, liver and renal function and has an interrelationship with intracranial pressure and the splanchnic circulation.

RESPIRATORY SYSTEM DYNAMICS

Much of the understanding on pulmonary derangements during IAH have been studied in the pneumoperitoneum induced by laparoscopy where there is a diminution of functional residual capacity and pulmonary compliance and an increase in lung and chest wall impedance that mirrors the extent of the IAP rise.[61,62] Although most of these changes are eminently reversible,[63] diaphragmatic function can remain significantly impaired for some time after relief of the pneumoperitoneum.[64] In ICU patients, the pulmonary effects of IAH will be complicated by ventilation (and its mode), patient position, sedation or the use of neuromuscular blocking agents, atelectasis, ARDS, infection, massive volume infusion, traumatic lung injury and PEEP; some of which will contribute to a diminution in lung compliance, alveolar de-recruitment and poor gas exchange.[65]

These effects are all exaggerated in ACS, with diaphragmatic elevation compressing basal lung segments, reduction in alveolar dead space and Ventilation/Perfusion (V/Q) mismatch.[66] Pressures transmitted to the thoracic cage reduce total lung capacity with the principal reduction in compliance resulting from altered chest wall compliance without a definitive effect on the lungs.[67] Exact interpretations of these changes in compliance are dependent upon the techniques used to measure intra-thoracic pressure and the methodology of lung volume estimates.[68] The changes occurring in elevated IAP are exaggerations of those induced by general anaesthesia, where atelectasis is promoted but where there are no specific elastic or resistive changes in chest wall properties.[69] In ACS, there is actually an increase in chest wall elastance which for a given applied airway pressure results in a lower distending force of the lung, the transpulmonary pressure (i.e $P_{Alveolar}$- $P_{Pleural}$). This is accompanied by a higher pleural pressure with less lung distension,[70,71] a decreased respiratory system compliance and a rightward shift of the compliance (Pressure/Volume) curve.[72] In ventilated patients with IAH, the diaphragm moves upwards statically causing lower lobe compression; an effect which is exaggerated if the patient is obese.[73,74] This effect on Functional residual capacity of the lung (FRC) is offset by abdominal decompression and PEEP which both recruit lung volume and increase the PaO_2/FiO_2 ratio thereby reducing the alveolar/arterial O_2 pressure differential.[75,76]

This condition is associated, in animal models, with pulmonary oedema, depressed trans-thoracic lymphatic drainage, high-grade atelectasis and increases in both pulmonary neutrophil infiltrates and extra-vascular lung water content, correlating directly with the level of IAH.[77] These specific effects of IAH are all reversible with abdominal decompression. The clinical implications of these changes suggest that patients with IAH may develop a secondary ARDS pattern with a cytokine profile and bacterial translocation propensity which creates a ventilator-induced lung change resembling primary ARDS.[78,79] The ventilator strategy in these patients is specific and distinct from that of an ARDS case where the reduction in FRC and the trend towards pulmonary oedema suggests a role for a greater utilization of muscle relaxation and higher PEEP values despite its risk for barotrauma,[80] keeping alveoli recruited and open with permissive hypercapnia, a restricted tidal volume and peak inspiratory pressure that more readily permits weaning.[81,82] In summary the pulmonary effects of IAH are complex with diaphragmatic elevation increasing intra-thoracic and pleural pressure causing a reduction in FRC and all lung volumes commensurate with a restrictive lung deficit combined with basal compression atelectasis, with increases in mean, plateau and peak airway pressures and pulmonary vascular resistance. Static and dynamic chest wall (but not lung) compliance is reduced with hypoxia and hy-

percapnia, reduced oxygen transport, increased dead space ventilation and shunting, alveolar oedema and V/Q mismatch.

CARDIOVASCULAR SYSTEM EFFECTS

In patients with the IAH/ACS complex the causes of cardiac depression are multi-factorial where there is commonly an overlay of haemorrhagic shock, systemic inflammatory response syndrome and the cardiac effects of mechanical ventilation. The principal effect of IAH on the heart is a reduction of pre-load through venous compression and reduced venous return which acts in a pressure-dependent manner.[83] This effect is noted in humans during higher pressure laparoscopy where MABP reductions are fluid responsive.[84] This is exaggerated in hypovolaemic patients and those with limited myocardial reserve where further evidence of reduced pre-load is shown by an increase in femoral vein pressures through peripheral venous pooling with reduced femoral blood flow and pulsatility,[85] increasing the risk in these patients for deep venous thrombosis. This is reinforced in studies which have shown that a fluid challenge before the induction of pneumoperitoneum causes an increase intra-thoracic blood volume as part of an auto-transfusion so that unchanged values actually reflect relative hypovolaemia during IAH.[86]

Cardiac contractility is directly affected by increases of intra-thoracic pressure creating a combination of reduced right ventricular pre-load with increased pulmonary vascular resistance and after-load. These effects may be worsened by excessive fluid resuscitation increasing right ventricular myocardial work and leading to right ventricular infarction. The septal deviation and altered ventricular geometry induced by right ventricular overload will also impair left ventricular end-diastolic volume.[87-89] Systemic Vascular Resistance (SVR) generally rises in IAH consequent upon an increase in intra-thoracic pressure and through direct compressive effects on the aorta, the systemic vasculature and pulmonary radicals.[90] The initial reductions in stroke volume during the early phases of IAH are compensated by a concomitant rise in SVR which leaves the CO normalized, however, this state may be disabled by the utilization in the ventilated patient of high PEEP levels and consequent right heart failure.[91]

In this setting, the concerns about the complications of invasive monitoring methods have resurfaced particularly since in IAH the utilization of pressure monitoring to define volumetric analyses is suspect; an effect exaggerated by PEEP where the CVP and PAOP values are both falsely elevated.[92-94] This has the potential (along with catheter malplacement in a squeezed lung zone) to lead to under-resuscitation if these invasive values are relied upon in IAH cases. These difficulties in IAH and a lack of availability of RVEDVI catheters[95] has placed a greater reliance on semi-quantitative bedside echocardiographic estimations of left ventricular filling in these patients as well as a direct assessment of parameters predictive of fluid challenge responsiveness such as caval diameter,[96,97] peak aortic flow velocity[98] or the broad demonstration of right ventricular dilatation and dyskinesia[99] and increased left ventricular wall stress.[100,101]

RENAL FUNCTION IN INTRA-ABDOMINAL HYPERTENSION

Renal dysfunction is one of the definitional features of the IAH/ACS complex with an independently specific association between renal failure (and mortality with renal failure) and hypotension, age>60 years, sepsis and IAH when patients are admitted to ICU following abdominal surgery.[9,102] The aetiology of renal failure in IAH is unknown but probably multi-factorial including an overall decreased CO, reduced renal perfusion pressure and arterial flow, increased renal venous pressure and vascular resistance, enhanced cortico-medullary shunting (with consequent reduced GFR) and renal parenchymal and ureteric compression.[103-105] This is associated with an increase in ADH production[106,107] and stimulation of the renin-angiotensin-aldosterone mechanism[108] which is not ameliorated by fluid resuscitation except in the rat.[109,110] The concept of impaired Renal Perfusion Pressure (RPP) is akin to that of APP and CPP previously mentioned although there is no evidence that restoration of MABP (where RPP=MABP-IAP) prevents the development of renal failure in these patients.[111] Ulyatt has suggested that the more important parameter is the glomerular filtration gradient (i.e $P_{GLOMERULAR\ FILTRATION} - P_{PROXIMAL\ TUBULE}$) which reflects the force across the glomerulus, where in ACS proximal tubular pressure approaches the IAP value and where effectively the glomerular filtration pressure=MABP-IAP.[112] This would suggest that changes in IAP create a unique renal sensitivity over and above changes in the MABP. The renal structure implies a specific vulnerability to the effects of IAH where RPP also is significantly reduced when renal venous pressure is elevated in animal banding studies even in the face of a normal MABP and CO level.[113] There are no consistent studies which show that abdominal decompression will reverse these renal effects of IAH.[114,115] although there is a trend for post-decompressive diuresis in most studies.[116] The natural history of renal failure in this setting is ameliorated by the early institution of continuous veno-venous haemo-filtration with IAH[117] and with some evidence suggesting an advantage of continuous rather than intermittent renal replacement therapy.[118] This may on occasion not be an option in patients with hypotensive unstable ACS and associated Multi-organ failure syndrome (MOFS) plus coagulopathy.

SPLANCHNIC PERFUSION AND INTRA-ABDOMINAL HYPERTENSION

Intra-abdominal hypertension results in a steady reduction in mesenteric and mucosal blood flow with consequent metabolic acidosis that is disproportionate to the associated CO reduction.[119,120] These effects are combined with a commensurate reduction in hepatic arterial and microvascular blood flow;[121] an effect which is reversible after normalization of IAP.[122] These changes in mesenteric vascular resistance are in some studies

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reversible by low-dose Dobutamine[123] and are synergistically aggravated by concomitant hypovolaemia/resuscitation cycling in animal models of IAH.[124,125] These effects are followed by bacterial translocation[126,127] although this is not in animal studies exacerbated by concomitant IAH.[128] The importance of mucosal splanchnic ischaemia is in its integral role in the genesis of MOFS partly through enhanced bacterial translocation where the effect of IAH/ACS is a 'second-hit' after initial hypovolaemic shock in these patients.[129,130] This has been shown in animal models submitted to haemorrhagic shock with and without sustained increases in IAP where the combination resulted in greater acute phase pro-inflammatory cytokinaemic responses and lung neutrophil activation, provided that they were timed to stimulate neutrophil priming.[131] These changes are not, however, ameliorated by abdominal decompression.[132]

The effect of IAH on the liver is well documented but poorly understood. It is likely that part of the liver damage is the result of the impairment in mucosal barrier function[133,134] but there is also an alteration in hepatic arterial and venous blood flow which is locally pressure-dependent[135] as well as the global reduction of cardiac output. This has been supplemented by an observed alteration in hepatic mitochondrial function, unexplained unexplained liver enzyme changes and a pressure-related Budd-Chiari-like effect in IAH,[136-139] although others have been unable to demonstrate a clear association between hepatic function and IAP in mixed ICU populations.[140] Some of this data has been extrapolated from those patients experience liver trauma, intra-abdominal packing and sepsis[141] as well as some of the changes observed in IAP following liver transplantation; both of which are not strictly comparable to the changes observed as part of IAH/ACS syndromes alone.[142] What is evident, however, is that conventional pressure-related parameters for intravascular volume resuscitation assessment (such as CVP, PCWP, RVEDV) are inaccurate as estimates for management with the need for more sophisticated volumetric methodology not generally available at the bedside using modified pulmonary artery catheters equipped with fast-response thermistors or intra-thoracic blood volume indices designed to calculate stroke volume variation as more dynamic markers of pre-load assessment in these complicated cases.[85,143-146]

MISCELLANEOUS PATHOPHYSIOLOGY AND INTRA-ABDOMINAL HYPERTENSION

There is considerable evidence showing in both animal[147-151] and human[152] studies that there is a direct relationship between steadily increasing IAP and rising Intra-cranial pressure (ICP) as well as a coincident fall in Cerebral Perfusion Pressure (CPP); effects which are mechanical in nature in accordance with the Monroe-Kellie Doctrine through increases in jugular venous and sagittal sinus pressure. This is potentially relieved by abdominal decompression as well as by central volume expansion and PEEP ventilation.[153] The dynamics of the effect of IAP on ICP are different if there is a concomitant traumatic or non-traumatic brain injury,[154] although in patients with brain trauma and IAH, a more liberal approach towards decompressive laparotomy and a more judicious delay in closure of the open abdomen when it is employed is indicated.[155,156]

MANAGING IAH AND ACS

Part of the management of this syndrome is its early recognition and prevention. Those at risk include situations of shock with massive or supranormal volumes of fluid resuscitation on a background of abdominopelvic injury, widespread peritonitis and excessive abdominal wall tension occasioned by a tight abdominal closure. This may be exacerbated by difficulty in ventilation, coagulopathy and pre-existing disease such as hepatic cirrhosis. In multivariate analysis of ICU patients with ACS although there is a clustering of higher acute physiological scoring and MOFS, the 24-hour fluid balance and the peak airway pressures are most predictive of full-blown ACS.[157] Regular IAP assessment will alert the clinician to impending IAH, combined with a policy preventing overaggressive fluid resuscitation,[158,159] particularly in those with a prior cardiac or pulmonary history and in marked obesity.[160]

MEDICAL MANAGEMENT

The medical approach to assist with limiting IAP includes neuromuscular blockade, often used in combination with abdominal decompression.[161,162] The IAP may in some patients be diminished by abdominal paracentesis particularly in IAH associated with severe burns,[163] although in chronic ascites this can lead to a well recognized circulatory collapse.[164-166] This approach has been supported in one human study of the continuous negative extra-abdominal pressure (NEXAP) device[167] where previous animal studies have shown no reduction in IAP for IAH cases but where there has been an IAP reduction when its commencement value was normal.[168] The effects on respiratory dynamics of the NEXAP device are complicated and partially counterproductive. In their human study, Valenza and Gattinoni showed a slight NEXAP-induced reduction of CVP, shifting blood from the intra-thoracic compartment[169] similar to devices which have been used extra-thoracically. This has been coupled with an insignificant increase in functional lung volume in animal studies although this effect is counterbalanced by a slight reduction in chest wall compliance and a commensurate increase in pleural pressure imposed by the device. Octreotide,[170,171] melatonin[172] and high-dose diuretics in haemodynamically stable patients can reduce IAP with an unproven value of early dialysis and ultra-filtration, each of which is administered often with relatively high-dose inotropic support.[173] These approaches may be supplemented in the absence of prospective randomized data with gastric suctioning,[174] enemata, concentrated albumin,[175] gastric pro-kinetic therapy and colo-pro-kinetic administration but there are no proven advantages of these medical therapies.

Besides studies have shown that IAP in the semi-recumbent position increases in relation to Head of bed elevation (HOB).[176] Cheatham, et al.[177] demonstrated in a multicentre trial

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of 132 ventilated patients that IAP increased by 1.5 and 3.6 mm Hg when patients were placed in the semi-recumbent position at 15º and 30º HOB respectively. However, these differences were less obvious in patients with IAP>20 mm Hg. A more recent study by Yi, et al.[178] showed an increase in IAP by 4.1 mm Hg among 88 patients in the semi-recumbent position at 30º HOB. Pressure differences between the supine and HOB at 30º in other trials ranged between 0.41 and 5 mm Hg, with a higher range at HOB 45º (2.7-14.9 mm Hg). Clinicians should be aware of this pressure increase when changing body position, especially in patients with impending ACS, although other factors like body anthropomorphy may also play a role.[178]

SURGICAL DECOMPRESSION

The increasing use of 'damage-control' laparotomy provides some experience of the open abdomen as well as Temporary Abdominal Closure, (TAC) providing easier access for monitoring bowel viability, the possibility of repeat pancreatic necrosectomy and the ready potential for debridement in cases of necrotizing fasciitis.[179] This approach, however, provides a considerable risk for fistula formation and intra-abdominal sepsis as well as creating difficulties in fluid management and nursing. Generous midline releases are favoured as they do not result in denervation or devascularization permitting later local flap mobilizations if needed. The presence of the open abdomen does not, however, preclude the monitoring of IAP since a secondary ACS may still occur.[180] The physiological consequences of decompression have been little studied since there is less of a tendency to follow IAP after this surgery.[181] Many of the aberrant parameters return towards normal but do not normalize, such as the mean PaO_2/FiO_2 ratio,[114] however, there are no prospective studies assessing objective serial scoring of organ dysfunction through decompressive laparotomy despite reported improvements in peak inspiratory pressures, MABP and urine output which themselves may not be the best markers for individual organ function.[182]

Variations in the technique for TAC management are evolving and depend upon available materials and experience as well as an operative decision concerning the likelihood of early closure or re-exploration. The techniques of towel-clip closure[183] and the Bogota bag[184,185] are now fairly obsolete. Currently, a passive 'sandwich' pack dressing is more commonly recommended[186] or where available, a Wittman Dynamic Patch TM (Star Surgical Inc, Wisconsin USA) or Abra® dynamic closure system (Canica design, Ontario CA) may be used permitting patch advancement at the bedside.[187] The negative pressure vacuum-VAC closure device (KCI International, San Antonio TX) has had considerable recent success as a first-up method of open wound management[188] with selected alternatives including temporary absorbable and non-absorbable forms of mesh,[189,190] silos[191] and 'zipper-style' techniques.[192-194]

The sandwich suction dressing is the easiest and cheapest method to employ being a forerunner of the VAC technique with placement of large adhesive drapes into the paracolic gutter under suction drains.[195] This simple dressing is effective, containing the abdominal contents with minimal fluid leakage and is non-contributory either to worsening IAP or the early development of adhesions. It prevents skin maceration or blistering allowing some give with underlying peristalsis (as opposed to fascially fixed techniques) and permitting rapid access for repeat laparotomy. Moreover, if IAH is developing in its presence, the outer adhesive can be split and then reapplied without disturbing the internal arrangement. A range of meshes have been advocated for this circumstance although these have numerous disadvantages principally with sepsis, a lack of water-tightness and some degree of incorporation into the wound over time. Goretex (Polytetrafluoroethylene, Gore & Assoc, Flagstaff, AZ), Vicryl (Polyglactin, Ethicon), Dexon (Polyglycolic acid, Davis & Geck) and Polypropylene (Marlex, Bard, Prolene, Ethicon or Surgipro US Surgical, Norwalk, CT) are all alternatives which have been used. These may still be associated with ACS after placement and some cases may need mesh replacement or further decompression after deployment. The absorbable meshes have little tensile strength and can result in evisceration during patient turning with the non-absorbables being associated with a moderate rate of intestinal fistula.[196,197]

The further advantages of the VAC proprietary devices over temporary mesh usage include their versatility to the contour of large defects permitting the utilization of a laterally placed stoma in conjunction[198] and potential use even in the presence of a pre-existing intestinal fistula.[199] Where possible, stomas should be avoided as the geography of the abdominal wall may change in such a way that they retract significantly or where in a delayed setting they can compromise abdominal wall reconstruction and rectus advancements.[200] Where possible, enteral nutrition in patients with an open abdomen should be utilized and may be continued in the majority after abdominal wall closure.[201] A protocolized approach to the use of the VAC device in such patients has provided a high early secondary closure rate, with some 88% of patients being able to be closed between 9-21 days after initial decompression.[202] This compares with earlier reports with standard techniques of less than 50% secondary closure rates where open wounds were eventually skin grafted[203] and where there was a moderate incidence of delayed difficult hernia repair.[204,205] These modalities can be combined when there is excessive bowel wall oedema precluding early fascial closure so that decisions regarding either primary VAC closure (for example in the absence of a nearby intestinal anastomosis) or absorbable mesh can be selectively made.[206] The likelihood of early closure using this protocol is, however, affected by the presence of extra-abdominal sepsis, in particular ventilator-related pneumonia, blood stream infection and other surgical site sepsis in these patients.[207]

DELAYED ABDOMINAL WALL RECONSTRUCTION

There is no optimal management of the open abdomen which is capable of providing total protection of the abdomi-

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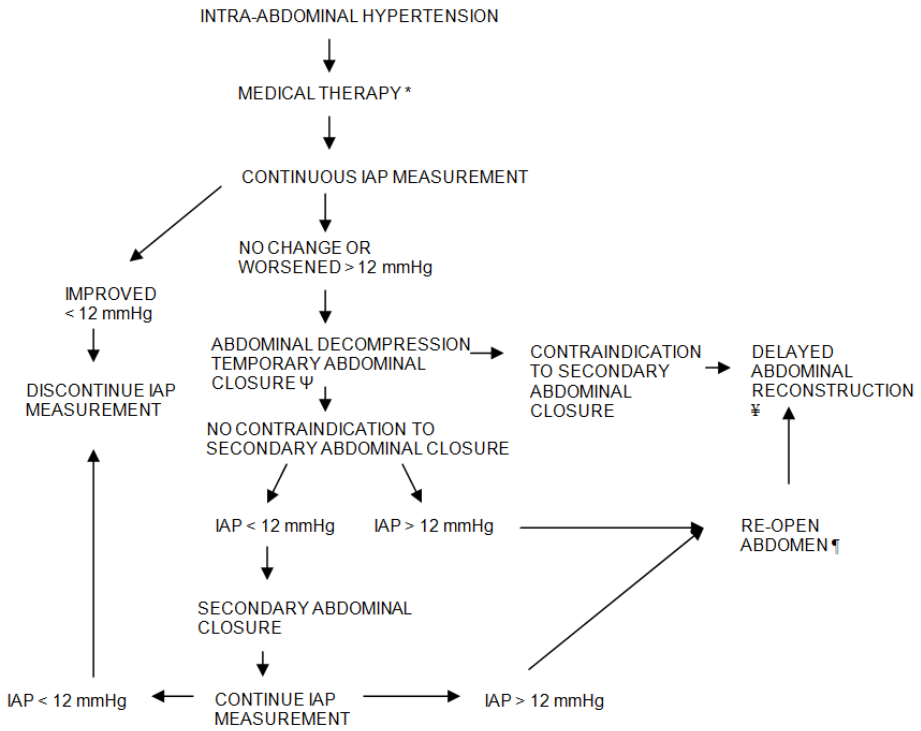
nal viscera from dessication and adhesions and which supports easy delayed fascial closure.[208] Significant delays in secondary closure which may occur for a range of complex extra-abdominal reasons may result in loss of abdominal domain for gut repositioning and have resulted in a variety of approaches including prosthetic mesh insertion, tissue expansion, local abdominal wall and free flap techniques and component separation methods.[209-213] Equally, local effects may preclude early direct approximation including ongoing haemorrhage, coagulopathy, intraperitoneal and retroperitoneal sepsis or bowel wall oedema. The simplest approach is delayed primary wound approximation although this is dependent upon feasibility issues to provide the best muscle function capable of supporting movement, coughing, defaecation and micturition as well as providing an acceptable cosmetic result and psychological outcome.[214,215]

This approach can be partial and equally assisted by mesh split skin grafting or with VAC assistance as part of a combination therapy[216,217] where further reconstructive surgery may leave the skin in place following initial de-Epithelialization. The insertion of mesh, acellular human dermis substitutes or composites can be supported by inter-muscular insertion of a temporary tissue expander although this usually requires repeated revision.[218-220] Advancement of the rectus muscles for approximation may be facilitated by components separation where the external oblique aponeurosis and the internal rectus fascia are incised and separated so that large defects above the umbilicus (up to 10 cm), at the umbilicus (up to 20 cm) and below the umbilicus (up to 6 cm) can effectively be closed.[221] This technique has been reported to suffer from considerable wound-related complications[222] which have been reduced by endoscopic-assisted[223] and periumbilical perforating vessel-preserving techniques.[224,225] Decisions regarding these techniques can be informed by intra-operative monitoring including intra-vesical pressure measurement.[226] The abdominal wall lends itself to random pattern flaps such as those used normally in abdominoplasty when the defect is infra-umbilical or axial pattern flaps including groin, rectus abdominis, tensor fasciae latæ, external oblique fascio- and myocutaneous flaps as well as free tissue transfers.[213,227,228] A suggested algorithm for the management of IAH/ACS and its aftermath are shown in Figure 2.

Medical management of critically ill patients with raised IAP should be instigated early to prevent further organ dysfunction and to avoid progression to ACS. Many treatment options are available and are often part of routine daily management in the ICU (nasogastric, rectal tube, prokinetics, enema, sedation, body position).[229,230] Some of the newer treatments such as tPA-assisted decompression of a haematoma, theophylline infusions to reduce circulating adenosine concentrations, octreotide as a reperfusion injury-limiting agent, and CNAP to reduce IAP, are all very promising treatment options in specific



*Medical therapy consists of selective use of sedation, neuromuscular blockade, nasogastric suction, gastro (colo) pro-kinetic therapy, enteral feeding, abdominal paracentesis and haemodialysis/ultrafiltration
ΨTemporary abdominal closure may consist of Bogota bag, sandwich-packing, VAC-assisted devices or dynamic commercial closure systems (*see text*)
¥Delayed definitive abdominal closure includes mesh utilization, abdominal components separation, tissue expansion, local axial pattern myo(fascio)cutaneous flaps or free flaps (*see text*)

Figure 2: A suggested algorithm for the management of IAH/ACS and its aftermath.

patient populations (ruptured triple A, pancreatitis) with raised IAP. Future studies are warranted to confirm some of these findings.[176]

CONCLUSIONS

The relatively recent recognition of the IAS/ACS complex has resulted in a profusion of animal and human work on its pathophysiology. Many of the features of the syndrome are still unknown and require a connection with the possibility of the diagnosis, with a routine IAP measurement, (most likely in high-risk cases by continuous technology) and a more liberal policy towards surgical decompression. This view would allow a less prolonged ventilatory, cardiac and renal support and is based on an improved management of the open abdomen and its consequences. Measurement techniques of the IAP and consensus concerning what levels are abnormal are needed, as well as prospective ICU-framed studies, to better assess circulatory filling status utilizing volumetric-modified pulmonary artery catheters and which more accurately define end-organ perfusion and dysfunction. This will be supported by better 'pathological' animal models which more directly address the capillary leakage syndrome as part of ACS, which separate the effects of decompression and volume restoration and which distinguish organ from global resuscitation.

CONFLICTS OF INTEREST

We declare that I have no conflict of interest in connection with this paper.

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