University of Western Ontario Medical Journal

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2008

UWOMJ Volume 78, Issue 2

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CONTENTS

It is our pleasure to bring you the "Infection and Immunity" issue of the UWOMJ. Today, infection remains an issue of great concern. While cancer is the leading cause of death in North America, infectious disease causes the greatest number of deaths globally.

To highlight this significant topic, this edition of the UWOMJ incorporates a wide range of fascinating articles. Furthermore, exciting structural developments have taken place within the journal itself, including the addition of a brand new departmental section: Interdisciplinary Collaboration. This focus reflects the growing multidisciplinary nature of health care today. In addition, original research and case reports make their debut in the following pages. More so than ever before, our departmental editors and writers have collaborated in producing this impressive edition.

We are proud that this unique edition brings attention to an extremely rare case of genitourinary tuberculosis, as well as the first reported case of ictal asystole secondary to an infection with herpes simplex virus. Our authors present an interesting perspective on the history of a well-established infection commonly known as fifth disease.

Not only are rare and curious cases and medical history included, but an up-to-date discussion of the world's major health concerns, including avian influenza, tuberculosis, rabies, and listeriosis round out our article collection. We now focus on prevention on a much larger scale, on an international rather than on a local basis. For instance, the possibility of an avian influenza pandemic has changed our worldwide perspective. Major strides in combating infections have been made with the advent of vaccines; a number of our articles look at the factors surrounding these breakthroughs.

Have you wondered what the environmental impact and infectious risk of your daily actions entail? Significant community health concerns are addressed in an intriguing article demystifying infection prevention.

Furthermore, infection is a social and anthropological concern. Poverty, poor access to health care, and lack of education are just a few of the many determinants of health. Such social factors are eloquently highlighted in a feature article focusing on the burden of respiratory infections in homeless populations.

For a far more personal viewpoint, an intimate career interview with Dr. Marina Salvadori, a pediatric infectious disease specialist, will inspire future doctors. Her career path demonstrates that a genuine passion for medicine can translate to advocacy work, global health and tangible effects on health policy.

Attractively binding this vast array of articles together, our cover art addresses the most pressing infectious health concern of our age – HIV – in both a stylistic and unique manner. The inside cover art is another testament to the genuine aesthetic talent and skill of medical students today. The creative geniuses of our artistic colleagues deliver the essence of infection and immunity, organized in a professional format designed by our new layout editor.

Overall, the cutting edge pieces included in this issue are a tribute to the hard work and research talent of our contributors, authors and editors. As always, the collective efforts of University of Western Ontario medical students are manifested in this impressive edition of the UWOMJ.

Special thanks go out to our managing editorial team for their drive and dedication in bringing this issue together. We would also like to express our appreciation for the many faculty reviewers who have contributed to the high quality of the articles published herein. Enjoy!

- Wendy Ng and Amber Menezes

Procedural approaches to drainage of prostatic abscesses

Paul Lau (Meds 2011) and Edward Weiss (Meds 2012)
Faculty Reviewer: Dr. Hassan Razvi, Department of Surgery, Division of Urology

Prostatic abscesses are a rare complication of acute prostatitis, and an uncommon clinical entity in the antibiotic era. Despite their rarity, untreated abscesses still remain potentially life-threatening, and require formal drainage to permit resolution. The transurethral approach to drainage used in the past has more recently given way to percutaneous interventions aided by trans-rectal ultrasonography. Although none of the currently-used strategies have proven ideal for complex cases, improved imaging techniques are expected to further increase the efficacy of percutaneous interventions and establish them as the standard of practice for treating prostatic abscesses.

Introduction

Prostatic abscesses (PAs) are defined by the accumulation of purulent material in one or more focal areas of the prostate. With the advent of antibiotic therapy in the twentieth century, PA has become a rare clinical entity. However, it can still present as a complication of acute bacterial prostatitis, which itself is thought to be caused by intraprostatic urinary reflux, ascending urethral infection, or hematogenous spread from an infection elsewhere in the body. Left untreated, PAs can rupture and progress to sepsis, as well as fistulization of the bladder, urethra, and rectum.[1] Thus, the need for expeditious diagnosis and treatment is not to be underestimated.

Symptoms of PA often mimic those of acute bacterial prostatitis (ABP) – fever, dysuria, low back and perineal discomfort, and pain upon palpation of the prostate. In the course of a digital rectal exam, the abscessed prostate is usually discovered to be enlarged, and sometimes fluctuant. The use of transrectal ultrasound or other imaging modalities such as computed tomography (CT) can provide radiological confirmation of the abscess even in the absence of prostatic fluctuation. On occasion the condition is suspected when the patient fails to respond to appropriately selected antimicrobial coverage.

Before the introduction of inexpensive and readily-available antibiotics, prostatic abscesses were often seen in sexually active young men as a result of infection with *Neisseria gonorrhoeae*. Because of the lack of diagnostic and interventional strategies, many patients presented with systemic infection due to spontaneous rupture of the abscess into nearby structures and cavities, and mortality has been estimated to have been as high as 30%.[2] More recently, the advent of antibiotic therapy has seen a marked decrease in the morbidity and mortality associated with PA, as well as concomitant changes in bacteriology and epidemiology. The most common organisms now encountered include *Escherichia coli* and *Staphylococcus aureus*,[1,3] and the disease is classically found in older men with predisposing factors such as diabetes, ongoing dialysis, or a history of urethral catheterization.[1]

The microbiological profile of PAs has also shifted in the wake of the increasing prevalence of immunodeficiency. Patients with AIDS have been known to present with abscesses caused by *Mycobacterium tuberculosis*,[4] and in other settings of immunodeficiency, such as immunosuppression following organ transplantation, organisms cultured from PAs have included *Cryptococcus*,[5] *Aspergillus*,[6] and *Candida*.[7] There is also preliminary evidence indicating that the increasing prevalence of

diabetes in some regions is associated with a higher incidence of PA in younger men,[3] which may reflect a significant ongoing epidemiological change that may be significant in the future.

Variable treatment modalities exist for the drainage of PAs. Transurethral unroofing, transrectal needle aspiration or transperineal needle aspiration are all options currently being used. This article will discuss the indications and methods for each therapeutic approach, as well as their respective risks and benefits.

Transurethral approach to drainage of prostatic abscess

Previously employed by urologists as the standard approach, the transurethral technique to drainage of a PA (otherwise known as unroofing) has recently been replaced by percutaneous measures.[7] However, transurethral unroofing of PAs is still employed for persistent abscesses that recur despite minimally-invasive treatment.
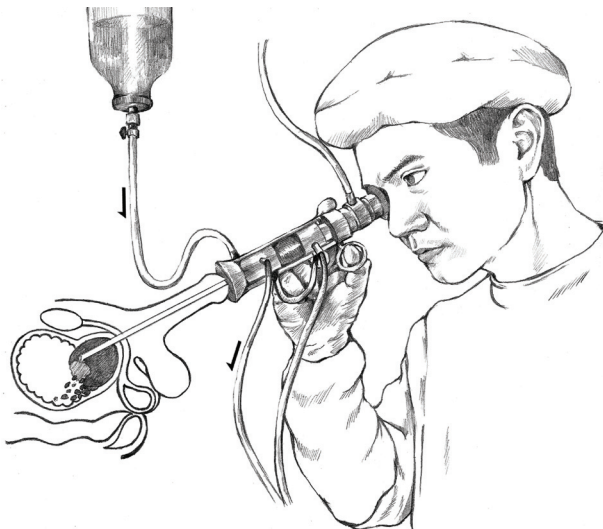
Figure 1. Transurethral radical prostatectomy is performed with a resectoscope equipped with a diathermy loop. The instrument is passed down the length of the urethra and the resection is performed with constant irrigation.

The procedure is typically performed under general anaesthesia with the patient in the lithotomy position (Figure 1). An electrosurgical resectoscope armed with either a Colling's knife or resectoscope loop is utilized to unroof the PAs which often are visibly apparent as a bulging

mass.[8] Transurethral approaches to drainage of PAs carry a risk of widespread bacteremia as well as all complications related to general anaesthesia.[7] Patients may also experience retrograde ejaculation and rarely urethral stricture and sphincter dysfunction following the procedure.[9] Additionally, transurethral unroofing is ineffective in patients presenting with peripherally located abscesses and multiloculated abscesses. The location and complexity of these abscesses leads to incomplete drainage through the transurethral approach,[10] a complication that can prove detrimental in immunocompromised patients. One case report has recommended the usage of sonographic guidance in conjunction with transurethral unroofing to treat complex abscesses; however, this has not been validated by further studies.

Transrectal approach to drainage of prostatic abscess

The first of two percutaneous methods to drain PAs, the transrectal approach utilizes a transrectal ultrasound (TRUS) to guide a needle through the rectal wall and into the PA for drainage (Figure 2). The procedure is performed under local anaesthesia with the patient in the left lateral decubitus position.[11] Lavage following drainage allows for antibiotics to be introduced directly into the post-drainage cavity.

In contrast to transurethral unroofing, the transrectal approach can be utilized for complex abscesses as TRUS enables direct visualization of the abscess and minimal tissue manipulation reducing the morbidity of the procedure. This technique requires no general anaesthetic and is less painful then the transperineal approach. Despite the advantages of TRUS guided drainage, Gan *et al* have demonstrated that repeat procedures for multiloculated abscesses are common using this method.[12] Formation of recto-urethral fistulae and potential prostatic contamination by rectal bacteria may also complicate recovery following drainage.
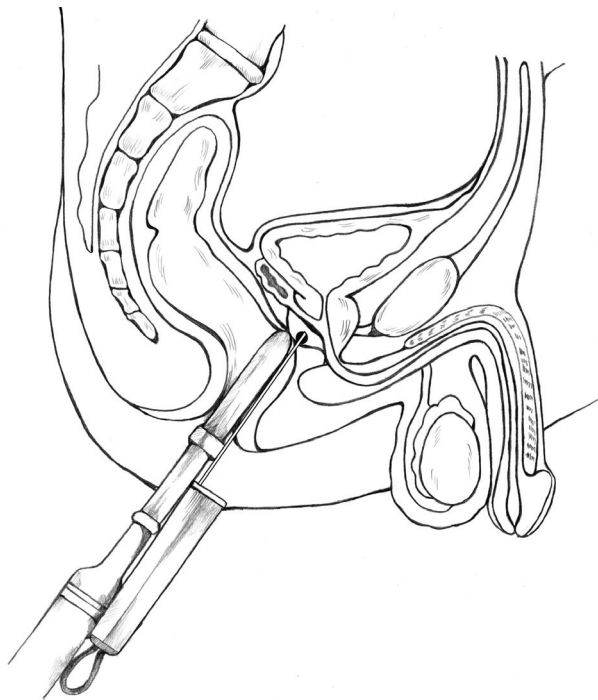
Figure 2. A transcrectal ultrasound probe with attached needle is used to puncture the prostate. NB: This image depicts a probe equipped with a biopsy gun. For drainage of prostatic abscesses, a fine needle or catheter is used, often introduced through an intra-probe needle canal.

Transperineal approach to drainage of prostatic abscess

Another percutaneous approach to drainage of PAs, the transperineal approach also employs the use of TRUS to guide a needle puncturing the perineum into the prostatic abscess.[13] The procedure is painful and may require the use of general anaesthesia although most procedures are tolerable under local anaesthesia. The patient is placed in the lithotomy position and a needle is advanced from the perineum into the prostate (Figure 3). Following complete drainage of the abscess, a guidewire is placed into the cavity and dilatation of the puncture tract is achieved via the Seldinger technique. A loop catheter is then placed for further drainage and is left in place for several days.

The transperineal approach is preferred over the transrectal approach by some clinicians due to the increased chances of complete drainage via the loop catheter. Disadvantages of the transperineal approach are also related to the

inability of the TRUS to adequately allow for complete drainage of multiloculated abscesses. However, the recent utility of 3D TRUS has shown promising results in the management of multiloculated abscesses by the transperineal approach.
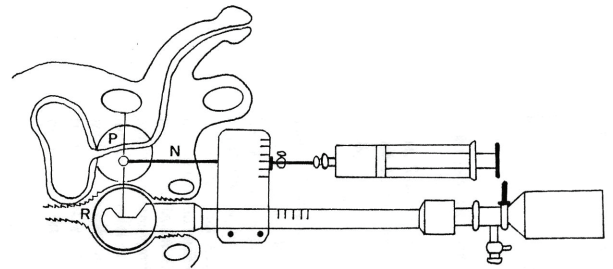
Figure 3. Transperineal needle aspiration of prostatic abscess. The transducer of the transrectal ultrasound is placed in the rectum (R), and the fine needle (N) has been guided ultasonographically into the prostate (P).

Discussion

In the post antibiotic era, PA is a rare manifestation of a urinary tract infection. Regardless, a failure to diagnose and promptly treat can cause significant morbidity. Current practices utilize imaging for diagnostic purposes. Existing data shows that the use of TRUS for the diagnosis of prostatic abscess is as sensitive as CT or magnetic resonance imaging.[14] With the ease of use and lack of ionizing radiation, TRUS is the gold standard for diagnosis and visualization of a prostatic abscess.[13] The diagnostic criteria include the presence of hypoechogeneic areas containing thick liquid in the transition and central zones of the prostate permeated with hyperechogeneic areas as well as enlargement or distortion of the anatomy of the gland. There is also a role for urinary culture for selection of pre-procedural antibiotics.

Although all three approaches to drainage of PAs are still being employed, the percutaneous measures (transrectal and transperineal) have come into favour due to their less invasive nature and association with lower morbidity.[7] Each procedure has been shown in literature to have potential for incomplete drainage although the recent evidence favouring 3D TRUS showed

complete drainage in all 7 patients studied.[13] Regardless of procedure, antibiotics are a key component in the management strategies of PAs. Antibiotics should be given orally or intravenously before any procedure to drain a PA.[8] Once drainage is complete, culture and sensitivity testing allows for a more targeted approach towards eradication of the infection.

Conclusion

With the incidence of prostatic abscess at a historic low, it is likely that many clinicians may go their entire careers without encountering what was once a fairly common presentation. However, the possibility of severe sequelae pursuant to an untreated PA and the suggestion that its incidence may rise in the future represent a strong impetus for becoming acquainted with the diagnostic and interventional strategies required to treat PA. Percutaneous transrectal or transperineal needle aspiration with ultrasonographic guidance have shown to be effective and minimally invasive treatment modalities, and future refinement of current ultrasound technology promises to extend successful treatment to more complex and resistant abscesses.

Acknowledgements

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Avian influenza: an emerging infectious disease with pandemic potential

Jason Essue (Meds 2011) and Rachel Bevan (Meds 2012)
Faculty Reviewer: Dr. John McCormick

There are numerous examples of infectious diseases that have wreaked havoc on the human population. Analysis of previous outbreaks has provided insight into the various ways that infectious diseases can be transmitted both between members of different species and among members of the same species. Furthermore, a thorough understanding of past outbreaks enables public health agencies to develop an informed approach to predict when new emerging or re-emerging infectious diseases will surface. Anticipating an infectious disease outbreak is essential to preparing an effective response strategy. The transfer of disease between species is of particular concern as a reservoir of emerging infectious diseases (EIDs) since approximately 75 percent of EIDs are estimated to have zoonotic origin. Bird-flu, or influenza strain H5N1, is an emerging disease of avian origin that is expected to cause the next influenza pandemic and has already begun to surface in humans from a wide geographic area. Frontline clinicians need to be aware of the signs and symptoms of H5N1 infection. Successful control of an H5N1 outbreak relies upon accurate identification by clinicians, reporting of an outbreak to public health authorities, and implementation of infection control procedures in a timely manner. The continued development of new technological advances that surpass traditional national boundaries, in order to track and report infectious diseases, is integral for rapid and efficient communication among public health agencies.

Introduction

Throughout history, numerous infectious diseases have had a large impact upon human health, through well-known epidemics such as the bubonic plague, (which most recently broke out in China in 1855 and is still ongoing) influenza (in 1918 and again in the 1950s), the current HIV pandemic, and also through the re-emergence of infectious agents such as Methicillin Resistant *Staphylococcus aureus* (MRSA).[2,3] Infectious diseases are estimated by the World Health Organization (WHO) to have caused approximately twenty-five percent of world-wide deaths in 2002 (15 million people, excluding complications due to infection as a cause of death).[1] Furthermore, the impact is greatest upon the disadvantaged and children.[1] Influenza epidemics in particular have demonstrated the ease with which infectious diseases can spread throughout the global population,[3] and remain a concern as a re-emerging infectious agent.[4]

Emerging Infectious Diseases (EIDs)

EIDs are infectious diseases that have either an increasing range or incidence. EIDs are discovered for various reasons: a previously unknown disease variant is discovered (e.g. *Helicobacter pylori* as a cause for ulcers); a new agent is created (e.g. Avian Flu is currently an emerging infectious disease); and the re-emergence of a disease after an initial period of decline (e.g. plague caused by *Yersinia pestis* is known to have caused at least 3 known pandemics which occurred hundreds of years apart).[2,3] Factors that precipitate or enhance the spread of EIDs can be categorized as either those that aid in the introduction into the host population of the infectious agent, or those that allow the infectious agent to become established and spread throughout the population (Table 1).

Table 1: Factors that promote the introduction and spread of emerging infectious diseases.

	Activity	Example
Factors that promote introduction of EIDs	Economic Development and Land Use	Exposure to living conditions that allows for zoonotic transfer (e.g. H5N1)
	Microbial Adaptation	Methicillin Resistant *S. aureus* (MRSA)
Factors that promote spread of EIDs	International travel & commerce	Severe Acute Respiratory Syndrome (SARS)
	Change/breakdown of public health measures	Measles and Rubella outbreaks
	Technology & Industry	Food poisoning outbreaks
	Human demographics/behaviour	Human Immunodeficiency Virus (HIV)

There are two categories of factors that promote EIDs: those that promote EID introduction, and those that promote EID spread. Note that the activities are taken directly from Institute of Medicine's factors for EID.[2,3]

One analysis of 335 EID events from 1940 to 2004 demonstrated that there has been a significant increase in EIDs over time, even when accounting for reporting bias.[5] Based upon this analysis, the majority of EIDs diseases came from zoonotic events (60.3%), and were caused by either *Rickettsia* (gram negative bacteria) and other bacteria (54.3%).[5] Globally, the distribution is non-random. Indeed, EIDs are most likely to occur in the lower latitudes, where the fewest global resources are focused, and reporting is least common.[5] Furthermore, despite the development of numerous antibiotics and vaccines, diseases caused by viruses, protozoa, helminths and fungi are still difficult to treat and eradicate.[2]

Zoonotic origins of EIDs

In general, one of the greatest causes for concern of newly EIDs is the reservoir found in animals.[3,6] Such diseases can transfer to humans either directly, or through a vector (such as arthropods), and have the potential to cause epidemics. The potential for epidemics is especially a cause for concern if the disease develops the ability to easily transmit between individuals within a population.[3] Diseases such as HIV and H5N1 (bird-flu) are examples of diseases of zoonotic origins. HIV, which is one of the most prominent examples of an infectious disease of zoonotic origins, is thought to have transferred from simians in Africa through the consumption of bush meat.[4]

Bird-flu, or influenza strain H5N1, is a newly emerging disease of particular public health concern.[3] Influenza is a rapidly mutating disease with two key surface proteins (hemagglutinin and neuraminidase) that have a large effect upon the successful spread and virulence of the disease. Hemagglutinin is an influenza surface protein that helps the virus to bind to cell surface receptors. Key mutations in hemagglutinin allow the influenza virus to bind host cells when host immunity has developed against other hemagglutinin antigens.[4] There are at least 16 known hemagglutinin subtypes. Neuraminidase is another influenza surface enzyme that confers virulence to influenza.[4] It is a glycosidic hydrolase enzyme with nine subtypes, many of which are present only in birds.[4] H5N1 represents an influenza strain that has not previously infected humans, and contains a combination of the H5 hemagglutinin and N1 neuraminidase subtypes.[3] Currently, H5N1 is highly virulent in chickens, and has begun to infect migratory birds.[3] It also has the ability to jump to humans and other mammals (including pigs), where it causes a high death toll.[3]

H5N1: the next pandemic?

Although H5N1 is largely expected to cause the next influenza pandemic, the following conditions must first be met for this to occur: 1) a new influenza virus subtype must emerge, 2) it must be capable of infecting humans and causing serious illness, and 3) it must spread easily from human to human.[7,8] H5N1 is of particular concern because it has already fulfilled the first two criteria and more recent reports from the World Health Organization (WHO) suggest that partial human-to-human transmission of H5N1 may have occurred in isolated cases in Thailand, Indonesia, and Vietnam.[7,8,9,10] However, at present, human-to-human transmission has occurred sporadically and with very low efficiency and therefore does not meet the third criteria.[7,8,11] Nonetheless, influenza-like viruses are highly mutagenic[11] and may become freely transmissible among humans at some point in the future, which means that the threat of an avian influenza pandemic remains very real.

Based upon past influenza epidemic outcomes, the United States Congressional Budget Office (CBO) has projected that a potential influenza pandemic could involve 200 million people infected, 90 million clinically ill, and 2 million dead. This would yield a case-fatality ratio of 2.5%. Furthermore, the economic cost could reach $675 billion.[12] As of September 2008, the WHO reported that H5N1 has already infected 387 humans and killed 245 patients worldwide, with a case-fatality rate of 63%.[12] Therefore, the CBO's projection likely underestimates the actual impact of an H5N1 pandemic given that the case-fatality ratio of H5N1 reported by the WHO is 25 times greater than the estimate put forth by the CBO (63% vs. 2.5%).

Signs of Symptoms of H5N1 Infection

Frontline clinicians need to be aware of the signs and symptoms of H5N1 infection because identifying the illness, reporting it to public health authorities, and implementing infection control procedures in a timely manner offers the best chance of controlling the spread of infection. Symptoms include typical influenza-like symptoms: fever greater than 38°C (100%), cough and sore throat (67%), myalgias (30%), pneumonia (58%), and diarrhea and vomiting (50%).[7] Symptom onset occurs within 2-14 days of exposure.[11,14] Complications include acute respiratory distress syndrome (ARDS), pulmonary hemorrhage, myocarditis, pericarditis, encephalitis, multi-organ failure with renal dysfunction, and sepsis.[7] Common radiographic findings include diffuse, multi-focal or patchy infiltrates and segmental or lobar consolidation with air bronchograms.[7] The majority of the deaths have been attributed to respiratory failure.[7]

Diagnosis and Treatment of H5N1

Diagnosing H5N1 infection poses a challenge because there are no pathognomonic signs and symptoms making it difficult to distinguish from other causes of influenza-like illness, severe community-acquired pneumonia, or ARDS.[7,11,14] The only findings that would raise suspicion of avian influenza (H5N1) is a history of presence in an endemic area and/or contact with poultry.[7,11,14,15] Therefore, obtaining a detailed history including travel and animal exposure is crucial. When H5N1 infection is suspected, the preferred test to confirm the diagnosis is real-time reverse transcriptase polymerase chain reaction (qRT-PCR) on a nasopharyngeal swab.[7,11,16]

Current opinion of the WHO states that patients presenting with the symptoms and historical features that are strongly suggestive of H5N1 infection should promptly be started on a course of Oseltamivir, pending the diagnostic results of PCR testing.[17] Oseltamivir is an antiviral agent that inhibits neuraminidase, which has been shown to reduce H5N1 infection-associated mortality in observational studies when it is administered in a timely manner.[17]

Mandatory Reporting of H5N1

Laboratory confirmation of a human case of H5N1 by qRT-PCR should trigger an immediate notification of local, sub-national, and national public health and agricultural authorities. However, the collection, shipment, and testing of specimens can often take several days or longer. Therefore, it is often necessary to notify the appropriate public health officials and initiate an

investigation before laboratory test results are available for persons suspected of having H5N1 infection.[18,19] National health authorities must then notify the WHO and readily share information and biological specimens.[19,20]

New methods of surveillance and reporting EIDs

Although this reporting structure provides a solid basis in order to approach outbreaks in a globally concerted manner, the hierarchical nature of the system could cause unwanted delays in communication from the local governmental level to the WHO. Furthermore, some parties may be less willing to report potential new H5N1 infections for fear of local or national economic repercussions, leading to further delay.[20] For these reasons, new structures of communication are being created by public health scientists to share information more rapidly. ProMED-mail is an e-mail based group dedicated to infectious diseases with a membership exceeding 30,000, giving the group global reach and influence.[21] ProMED is known to report outbreaks before local authorities. During the 2003 SARS epidemic, that spread from the Guangzhou province in China to nearly 37 countries[22], the first public report of the epidemic was posted on ProMED more than a month before the Chinese government's official announcement.[21] ProMED's membership is volunteer-based and not affiliated with a governmental organization. Therefore, they have greater freedom to report what they observe than official organizations, which may have political constraints on what they can publicly report. This on-the-ground reporting is thought to push governments to disclose more information than they might normally.[21]

HealthMap (http://www.healthmap.org/) is a newer surveillance system that continuously monitors the internet, aggregating real-time information on infectious disease outbreaks from news media sources, blogs, and discussion groups.[23] HealthMap illustrates the distribution of reported infectious diseases by superimposing these incidents on a map of the world. The WHO is one of its top users.[23] This is significant because it allows WHO to learn of emerging infectious disease without having to exclusively rely on local public health agencies.

Conclusion

In summary, there are a variety of infectious agents capable of causing disease in humans. H5N1, a virus of avian origin capable of crossing the species boundary to infect humans, has the potential to cause the next influenza pandemic and is thus of particular concern. In order to adequately respond to the next outbreak, frontline clinicians need to be eternally vigilant at the community level. Furthermore, clinicians must be aware of the need to act in a concerted manner with other nations at the global level. New technological advances should be fully exploited to facilitate such globally coordinated responses. The next pandemic will not observe national boundaries, and our approach to the control of EIDs should reflect an awareness of this. The global community cannot afford to let state boundaries prevent a necessary response to the emerging pandemic threat posed by avian influenza, or any other emerging pandemic threat.

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Drug-resistant tuberculosis and the ethics of tuberculosis control

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Despite the declaration of tuberculosis (TB) as a global health emergency by the World Health Organization in 1994, many in North America were unaware of the rapidly increasing health burden of TB until the highly-publicized Andrew Speaker incident. Speaker, an American lawyer, knowingly left the United States while infected with extremely drug-resistant TB and prompted an international health scare which led to the first federal quarantine order since 1963. This incident highlights the growing concern of emerging drug-resistant strains of tuberculosis, regarding which the WHO issued a global alert in 1996. It also raises many issues meriting ethical examination, including public health measures to control TB, individual obligation to avoid infecting others, and the role of the physician in infectious disease control.

The global health burden of tuberculosis

Historically a leading cause of human mortality, tuberculosis was thought to be on its way to being eradicated in North America as early as the 1950s. This decline was interrupted by a highly publicized resurgence in New York City during the 1980s and 1990s, primarily among homeless and HIV positive individuals. The epidemic was eventually brought under control in the 1990s following enormous health care expenditure and coercive public health measures, including mandatory directly observed therapy (DOT) and detention of patients who were noncompliant with their prescribed treatment regimen.[4] However, TB has remained a significant issue all along in developing nations; with one-third of the global population infected with a latent form, TB is currently the second leading infectious cause of mortality worldwide.[5]

Prior to the Speaker incident, awareness of the increasing global health burden of TB had been largely overshadowed in Western society by media focus on the HIV/AIDS epidemic. The episode also highlighted the threat of emerging drug-resistant strains of tuberculosis. Approximately 20 percent of worldwide TB cases are identified as multi drug-resistant (MDR-TB), and 10 percent of these are extremely drug-resistant (XDR-TB).[6] MDR-TB is defined as TB resistant to at least two of the four first-line medications, namely isoniazid and rifampicin. XDR-TB refers to MDR-TB, in addition to resistance to fluoroquinolones and any one of the second-line anti-TB drugs.[6]

The Speaker incident

Despite acknowledgement from the US Centers for Disease Control (CDC) and the WHO of the emergence and spread of extremely drug-resistant TB (XDR-TB),[7] the issue did not receive extensive attention until Andrew Speaker became a household name in May 2007. Speaker tested positive for tuberculosis in January 2007, following a pulmonary abnormality detected on chest x-ray and CT scan, and a subsequent diagnostic bronchoscopy, for which he was prescribed a standard regimen of first-line medications.[2] He underwent susceptibility testing at the Fulton County TB Clinic in Georgia following the disclosure that he planned to travel overseas for his honeymoon in May 2007. This susceptibility, or sensitivity, testing was done to determine the likelihood that his drug treatment regimen would be effective in eliminating or inhibiting the growth of the infection. The results indicated that Speaker was infected with multi drug-resistant tuberculosis.

Despite being advised by his primary care physician and the Fulton County Health Department that he should not embark on his planned international travel, Speaker flew to Europe without informing any public health official. The discovery through further sample analysis that he had XDR-TB prompted a nation-wide border alert, and the Center for Disease Control located Speaker in Rome and instructed him not to travel on a commercial aircraft because of the significant threat he posed to other passengers. Despite this warning, Speaker flew to the Czech Republic and then to Canada, having correctly assumed that there was an order preventing him from boarding any US-bound flight. He reentered the US by automobile and was promptly discovered by the CDC and served the first provisional federal quarantine order since 1963.[2]

Public health versus individual liberty

One of the main ethical challenges highlighted by the Speaker case is how to balance public health concerns, which encompass the utilitarian aim to promote the greater good, against the libertarian aim of protecting individual rights and liberties. Most would agree that neither public nor individual interest should always be given absolute priority over the other. The challenge, therefore, lies in striking an ethically acceptable balance between these two interests. Speaker's actions raise questions concerning the ethical obligation of individuals to avoid infecting others, which follows from the accepted 'duty to do no harm.'[8] However, there must be limits to these duties, as it would be excessive and virtually impossible for all potentially infected individuals to take all possible precautions to avoid infecting others. There is no disputing that Speaker behaved in an ethically inappropriate manner in ignoring the health authorities' traveling advisory. One must also realize, however, that an ethical obligation to avoid infecting others must involve full understanding of the risk of infection. One of the points of controversy in this case involves Speaker's allegations that he was initially simply cautioned against, and not explicitly prohibited from, traveling.[8] Regardless of the truth of this claim, we may learn from it that we, as health

care providers, can strengthen this ethical obligation to avoid infecting others by making certain the patient has full knowledge and understanding of the risks involved in undertaking a particular action. Relevant to this case, these include knowledge of the transmission of tuberculosis through airborne spread, the nature of drug-resistant TB, and the dangers of air travel and the risks posed to others.

It might also be possible that Speaker was not adequately reassured that he would receive acceptable care in Italy, or be returned to the US in a timely manner for treatment. While he might have been aware of the risk he posed to his fellow travelers in returning to Canada, his sense of ethical obligation might have been distorted through a lens of fear following a frightening diagnosis of extremely drug-resistant TB. Although it is also entirely possible that his actions were driven by selfishness and self-interest rather than fear, the health authorities could have endeavored to alleviate this fear by assuring him of the quality of TB-related care in Italy and providing him with a plan and timeline for returning him to the US.

Another ethical challenge regarding TB control, along with other infectious diseases, follows from the concept that an individual is both a victim of disease and a vector by which the disease may be transmitted to the greater population.[9] How may we determine to what extent isolation measures, namely the coercive restriction of movement, are justified for the purpose of TB prevention, and who should be confined? Factors to consider in making these decisions include whether or not the patient is infectious and the risk the free movement of the patient poses to the general population. There is an obvious difference between confining someone with active illness and refuses to take their medication from someone with latent illness or a very low risk of contagion. One of the ethical failings in the control of the New York City TB epidemic involved the confinement of noninfectious patients who, although labeled as 'recalcitrant' for failing to take their medications properly and to report for scheduled medical appointments, posed no immediate infectious

danger to others.[4] One of the interesting aspects of the Speaker case is that, although he was infected with an XDR-TB strain, his level of contagion was actually quite low, yet he was still placed and kept under federal quarantine for several months.[2] It would not be unreasonable to infer that the isolation measures were therefore influenced by his noncompliant behavior and the threatening nature of his diagnosis, as opposed to strictly his level of infectious risk. As physicians, we should advocate for appropriate diagnostic tests to assess the patient's level of infectivity and for evidenced-based isolation measures that are appropriate to the risk posed by the patient.

Fear-Driven Public Health Measures

Smith, Battin et al. discuss the ethics of public health decision-making regarding infectious diseases in context of their overwhelming ability to provoke fear and panic in populations.[9] They argue that this fear can lead to emotionally-driven decision making that challenges basic medical ethics principles such as autonomy and social justice. In certain instances, the results of these decisions may be positive. For example, during the New York TB outbreak, the decision to institute mandatory directly observed therapy was motivated by the recognition of drug-resistant strains of the disease that were more difficult to eradicate, and this eventually helped to stem the outbreak. However, in other instances, fear-driven public health procedures may come into conflict with bioethical principles or even basic human rights. South Africa's current policy involves enforced quarantine of patients with drug-resistant TB in prison-like hospitals with high fences patrolled by guards to prevent escape.[10] Although the country is battling the highest global TB prevalence with a concurrent HIV/AIDS epidemic, some patients are required to spend several years in hospital, long past the point of infectiousness. Several recent studies have ascertained that these hospitals can, in fact, serve as breeding grounds for drug-resistant TB, such that patients with MDR-TB are contracting XDR-TB strains at an alarming rate.[11] Thus, not only is this enforced quarantine a challenge to patient autonomy and human rights, but it is posing additional risk to the patients and is a huge financial burden on an already weak health care infrastructure.

The enormity of the media attention the Speaker case received, as well as the issue of the first federal quarantine in over 40 years, highlights the panic and fear that the emergence of drug-resistant tuberculosis has engendered in Western society. Given that his actual contagion was low, one must wonder whether the nature of his diagnosis with XDR-TB and the fearful response provoked by his actions influenced the health authorities' decision to take extended isolation measures. This highlights our role as physicians in an era of mass media coverage to put infectious diseases and epidemics into context for the general public, and to assuage community hysteria when it is disproportionate. We have an ethical obligation to help our patients understand the severity of a situation, such as the danger posed by travel with infectious disease, but must also help public health authorities to minimize fear-driven decision making that is non-evidence-based or ethically suspect.

Social Justice in Tuberculosis Control

Another interesting aspect of the Speaker incident involves the fact that the case of one infected individual traveling through the developed world could generate so much media attention and bring the issue of drug-resistant TB to the global stage, when it has been a serious problem all along in developing nations. Speaker does not resemble the typical TB patient in that he is a wealthy, white, educated male from a developed country. Infectious diseases affect primarily the poor and developing world due to lack of sanitation and weak healthcare infrastructure, among other factors. When making public health decisions that may pose ethical challenges and infringe upon individual rights and freedoms, it is important to consider the nature of the population these decisions will affect. As developing nations are oppressed by virtue of their economic position, and will shoulder the burden of public health measures for the control of tuberculosis, it is important to give consideration to individual rights where possible, as the "blame, stigma, and ostracism associated with isolation and quarantine

are especially real for diseases linked to the poor… or the disenfranchised."[2]

Conclusions

Though by no means exhaustive, the ethical issues highlighted with respect to the Speaker incident illustrate the need for ethical reflection in developing public health policies for tuberculosis control. Drug-resistant tuberculosis, which has now become a global threat, is largely propagated in poor countries where poverty and a weak health care infrastructure often preclude finishing a full course of TB treatment. Improved health care provision in endemic areas would therefore reduce the frequency by which we would have to make public health decisions that challenge individual rights and freedoms. The role of the physician must involve providing the patient and the public with appropriate and adequate information in order to strengthen individual obligation to do no harm, as well as to prevent community panic and emotionally-driven decision making which can lead to public health policies that infringe upon the rights of the individual.

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Infection prevention myths demystified

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In the mid-20th century, industrialized countries underwent the 'epidemiological transition' whereby the leading cause of death evolved from infectious and parasitic to chronic and degenerative diseases.[11] This transition, however, has not yet occurred in many developing countries.[11] In 2002, infectious and parasitic diseases caused the greatest burden in disability-adjusted-life years (DALYs) to human beings worldwide.[16] Although the threat of infectious and parasitic diseases in developed countries such as Canada has decreased since the middle of the last century, protecting ourselves against such diseases should remain a priority since we reside in a global community. We take this opportunity to explore three "urban legends" of day-to-day infection prevention and determine whether there is truth to these myths.

Hand towels vs. air dryers

The Myth

The Centres for Disease Control and Prevention (CDC) has a list of recommendations regarding hand-washing, which includes drying hands using a paper towel or air dryer.[23] This step in the procedure has sparked considerable debate in the infectious disease realm. Are paper towels or air dryers more effective? Proponents of towels argue that you may as well not wash your hands if you insist on using air dryers as they just blow the germs back on. Proponents of air dryers lament the environmental impact of towels. Unfortunately, the literature is similarly divided on the issue.

The Evidence

Early studies on this topic were strongly in favour of hand towels. In 1984, one of the first comparisons of the two drying methods found that paper towels could reduce bacteria on hands by 55% while air dryers achieved a dismal 9% reduction.[4] Subsequent studies found towels to be safer and more hygienic than air dryers,[6,7] while one study even found that not only were air dryers less effective, but they actually *increased* the number of microorganisms left on hands.[4]

Uncertainty began to mount in 1991 when a study in the American Journal of Infection Control reported that air dryers were more effective in reducing the numbers of *Escherichia coli* and rotavirus from hands.[3] The argument was levelled when a randomized control trial conducted in 2000 failed to find a significant difference in bacterial numbers when the use of rotary dispenser towels, stacked paper towels, air dryers, and spontaneous evaporation were compared.[2] It is interesting to note that in a separate study, it was found that hands that were held stationary under the dryer retained fewer bacteria than rubbed hands.[4] This difference was explained by the fact that rubbing allows bacteria to migrate from the hair follicle to the skin surface, thus the finding may simply be a measurement bias. Nonetheless, they concluded that stationary hands under an air dryer was the best method, followed by a tie between paper towels and rubbed hands.[4]

When investigations were broadened from microbes remaining on hands to microorganisms in the washroom environment, the equivocality remained.[4] Taylor *et al* concluded that in bathrooms equipped with paper towels, the germs were transferred from the hands to the towels, which were then disposed of in open receptacles where they acted as reservoirs of bacteria. In contrast, while the air dryers killed a sizable proportion of microorganisms by virtue of the heater, the splattering of water droplets onto the wall behind the dryer made this one area of the

bathroom to avoid. This dispels the myth put forth by towel proponents: air dryers do not just concentrate microorganisms from the air onto the users' hands, as evidenced by the fact that dryer outflow contained significantly fewer organisms than inflow.[4]

The Verdict

Despite the controversy, all studies were in agreement about the importance of hand washing. Proponents of towels can argue using evidence from early literature, the finding that paper towels were more effective in removing bacteria from the fingertips in particular[1] and the CDC recommendation that one use a paper towel to turn off the tap.[23] They may also argue that air dryers are not recommended in critical care environments due to the possibility of air dispersal of bacteria-laden droplets.[8] Air dryer enthusiasts can cite findings from more recent studies, environmental considerations, and the capacity to remove bacteria from the air. However, there is no clear victor in this debate. The important takeaway points are to wash your hands well; if you choose a towel, dispose of it in a closed receptacle; if you choose an air dryer, try to use an automatic model and don't rub your hands.

Antiseptic hand sanitizers vs. soap and water
The Myth

Since Semmelweis' groundbreaking observations in 1847 that proper hand sanitization measures can reduce infection rates, health professionals have been provided with procedures and guidelines aimed to perfect the hand washing process.[4] These guidelines are applicable both in the hospital and the community since hands serve as the main vector for micro-organism transfer.[6] However, poor compliance with hand hygiene has been attributed to a variety of factors including lack of time and skin irritation.[22] Antiseptic sprays and rubs have been introduced as a means to confront these problems, however the question remains: do the new methods work as well as traditional hand-washing?

The Evidence

Hand-washing involves the use of plain soap and water to clean hands, whereas antiseptic hand-washing employs a soap containing an antiseptic agent, which differs from an antiseptic hand rub in that the latter does not require water.[25]

Plain (non-antimicrobial) soaps are an effective means by which to reduce both the transient bacteria colonizing the superficial layers of skin and the transmission of these pathogens.[24] These soaps do not, however, remove the resident flora found in the deeper layers of skin.[24] Prior to surgery, antiseptic hand-washing scrubs are typically employed, as these are more effective in eliminating bacteria.[25] Some centres have introduced pre-surgical rubs, further highlighting the inconclusive nature of the literature.

With respect to hand rubs, chlorhexidine- and alcohol-based products are two common varieties. Chorhexidine rubs are efficient in eliminating gram positive bacteria, but are not as effective for gram negative bacteria and nonenveloped viruses.[25] Further, certain bacteria have been demonstrated, *in vitro*, to adapt and develop resistance against chlorhexidine, leading to resistance to other anti-infective agents.[24] The epidemiological implications of these findings in humans are not yet fully understood and require further study.[25]

Conversely, while alcohol-based rubs have minimal residual activity[25] and do not effectively eliminate bacterial spores, protozoan oocytes or certain nonenveloped viruses[25], there have been no reported cases of acquired resistance to these rubs. Furthermore, alcohol does prevent the transfer of certain nosocomial pathogens and effectively reduces bacterial load on hands.[25]

The Verdict

Conflicting evidence exists in the literature as to the effectiveness of the various antiseptic agents used for handwashing, which is due in part to the fact that not all studies assess effectiveness in the same manner.[26,27] However, a review by the CDC found agreement among studies that alcohol-based handwashes and rubs are more effective in eliminating bacteria on hands than plain soap, and often more so than antimicrobial soaps.[25] Their effectiveness,

however, is dependent on a variety of factors including the type, concentration, and volume of alcohol used.

Plastic water bottles

The Myth

Plastic water bottles have recently been the subject of much debate in the media. The litany of offences attributed to the vessels include: acting as a reservoir for germs, leaching toxic chemicals, and posing unnecessary stresses on the environment.[10,13,18] Waterloo has banned the sale of plastic water bottles in schools and Toronto appears poised to follow suit in 2009.[18] Despite these controversies, bottled water continues to be a $35 billion industry, with 1.7 billion gallons consumed last year (nearly 3000 Olympic swimming pools' worth).[17] This exorbitant consumption also means that 150 million water bottles are disposed of each day.[9] A seemingly probable solution would be to reuse the water bottle, but the literature suggests that this environmentally friendly solution could wreak havoc on our health.

The Evidence

Researchers in Calgary selected an elementary school as their source of water bottles for analysis in 2002.[10] They found that total coliforms exceeded Canadian Drinking Water Quality guidelines in 13.3% of water bottles examined; 8.9% contained fecal coliforms, and 64.4% contained heterotrophic bacteria. While heterotrophic bacteria are not necessarily pathogenic, they are a marker of overall water quality.[20] Some of the students had left water bottles for months without a proper cleaning- significantly longer than the eight hours that the literature suggests it takes for bacterial regrowth.[10] When combined with the finding of no significant microbial content of water sources (taps and fountains), the researchers determined that the germs were coming from the bottles.

Several studies have suggested that plastic water bottles provide a better breeding ground for bacteria than glass or metal.[12] Plastic bottles tend to contain fast-growing bacteria (pseudomonads, Flexibacter, and Acinetobacter), numbering in the realm of 10^5 cfu/mL after one week of growth.[12]

In contrast, glass bottles contained slow-growing bacteria (mainly Acinetobacter) and were an order of magnitude less in quantity. Not only is the type of material important, but the quality. Jones *et al.* isolated mainly coccoid bacterial cells from the caps of plastic water bottles, while rod-shaped cells were found adherent to the walls of PET bottles.[15] Rougher surfaces were associated with a significant increase in bacterial numbers.

The issue in the Calgary study was not the *use* of plastic water bottles, but the subsequent *reuse*. Both nonpartisan researchers and the Canadian Bottled Water Association have established that bottled water does not contain *E.coli*, coliforms, *Giardia*, or cryptosporidium at the time of bottling.[13,19] The real problem lies in the fact that water at room temperature is an ideal environment for microbial growth. A simple solution would seem to be meticulous washing of the water bottles. However, this solution was discredited by a 2001 presentation by a University of Idaho student who found that realistic reuse simulation (sunlight, heat, physical degradation) released a number of chemicals from the plastic water bottles into the drinking water.[13] The longer water bottles were reused, the more organic chemicals were leached from the material.

The environment vs. health debate has thus seemingly reached an impasse- reusing water bottles is good for the environment but sets up a bacterial breeding environment, necessitating vigorous cleansing, which in turn liberates toxic chemicals. One appears to have the choice between infection, intoxication, or pollution.

The Verdict

The evidence is fairly clear that water bottles pose a threat both to human health and to the environment. However, a little common sense may go a long way in settling the clash of values. Soft-plastic water bottles such as those sold in vending machines should not be reused as their ability to stand up to the vigorous washing needed in order to prevent colonization has not been established. Hard-plastic, glass and metal water bottles may be more well suited to the challenge of multiple uses and their use is condoned by the Minister of Health Canada.[21] Water bottles

should be thoroughly washed in hot soapy water after each day of use.

It is very difficult to come to generalized conclusions as to the safety of water from municipal taps and from rural wells as compared to bottled water. The importance of the presence of trace amounts of chemicals in tap water as compared to bottled water is not known. Moreover, the entire picture needs to be examined – the energy required in making, bottling, and distributing bottled water is immense and this may impact not only the individual consumers, but also the health of human populations. The safety of the individual must be weighed with the potential harm the use of water bottles has on the environment. For water bottles, whether single use or washed multi-use, the evidence is inconclusive.

Three common societal beliefs have been discussed that may impact our lives as individuals or as a population. This paper attempted to use an evidence-based approach to make recommendations. It is also important to review the evidence as a whole to consider the threats to the individual, to the people in the immediate environment, and to the broader global community. Given the human health importance of hand-drying techniques, hand sterilizers and water bottles, it is suggested that the apparent simplicity of these issues not deter future research.

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Erythema infectiosum, fifth disease, and parvovirus B19: how did they get together in the first place?

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The purpose of this paper is to provide a detailed overview of how and when the associations between erythema infectiosum, fifth disease, and parvovirus B19 were established. Attention will be paid to the discovery of a "milder form of rubella" in 1889; the naming of erythema infectiosum in 1899; the emergence of the name "fifth disease" in 1905; the discovery of parvovirus B19 in 1975; and the eventual linking of erythema infectiosum and parvovirus B19 between 1983 and 1985.

Introduction

Erythema infectiosum is a common rash-like illness that often occurs during childhood and is caused by parvovirus B19.[1] It is also known as "fifth disease" and "slapped cheek disease," the latter of which refers to the condition's characteristic, red rash. While most medical students will cover these details at some point in their medical training, they may never know how the connections between erythema infectiosum, fifth disease, and parvovirus B19 were established, and where these terms come from.

Why is erythema infectiosum called the "fifth" disease anyway? A Wikipedia article on the topic states that "The name… derives from its historical classification as the fifth of the classical childhood skin rashes or exanthems."[2] In typical Wikipedia style, however, no explanation is provided.

Even more legitimate resources do little else to clarify this issue. Up-to-Date, the bastion of evidence-based medicine, notes that "Erythema infectiosum is… referred to as 'fifth disease' since it represents one of six common childhood exanthems, each named in order of the dates they were first described."[3] But just like its unreliable counterpart, Wikipedia, no other details are given.

The purpose of this paper is to: (1) clearly describe how and when erythema infectiosum was first discovered; (2) explain how and when it became known as fifth disease and why this name is perhaps inappropriate; (3) describe the coincidental discovery of parvovirus B19; and (4) explain how the connection between parvovirus B19 and erythema infectiosum was finally made.

The discovery of erythema infectiosum

Erythema infectiosum was first described in 1889 by Tschamer, who thought it represented a milder form of rubella (German measles).[4] Additional cases were described by Gumplowicz in 1891[5] and by Tobeitz in 1898.[6] According to a review of cases presented by Shaw in 1905, the first person to suggest that this infection was a separate clinical entity was Escherich in 1896.[7]

This condition didn't actually become known as erythema infectiosum, however, until 1899, when it was given that name by Georg Sticker, a Professor of Medicine at Giessen University, Germany.[8] Sticker's description included the lack of perceptible fever at the time of presentation and emergence of red patches on the cheeks, consisting of large symmetrical blisters with red halos. The following day, the rash spread to the lower arms and thighs, as well as over the trunk, forehand, temples. This secondary rash consisted of round red spots or

larger, irregular, red patches (see Figure 1). Sticker noted that these eruptions tended to be slightly raised and that they were better felt than seen. These symptoms were most apparent on the third or fourth day of the infection and then rapidly resolved.
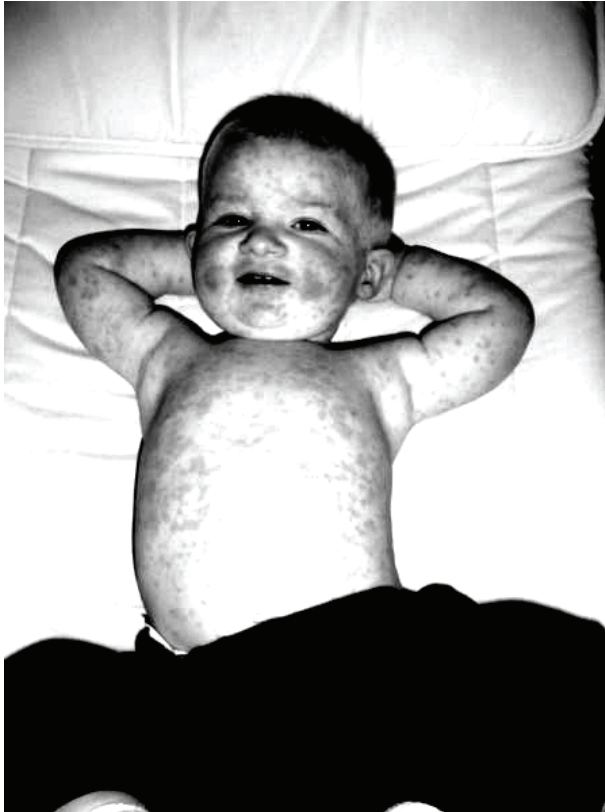
Figure 1: Classic presentation of erythema infectiosum (fifth disease) in a child aged 16 months. Note the smooth rash on the cheeks and lace-like pattern (secondary rash) on the rest of the body.

Sticker observed how erythema infectiosum spread through families and was consequently able to confirm its contagious nature. He also suggested that it belongs to the group of so-called "acute exanthems," but that its particular course and skin symptoms excluded any confusion with scarlet fever, measles, or rubella (German measles). Sticker's description of erythema infectiosum ends with an interesting acknowledgement: "In trying to find the specific cause we have been just as unsuccessful as other researchers have been with other kinds of kinds of infectious exanthems." Indeed, the medical community would have to wait almost a century before the causative agent would finally be found.

Sticker's description of erythema infectiosum had such an impact that for many years it was known simply as "Sticker's disease." Even as the term "fifth disease" became more common in some parts of the world, the reference to the Professor's name persisted in Germany for years to come.

It began with the fourth

The origins of the name "fifth disease" go back to 1885, when a Russian physician named Nil Filatow was working on another childhood exanthem. His work was read at the Moscow Medical Society meeting on November 20, 1885, and later in published in German.[9] As with Sticker, the list of childhood exanthems established up until this time included measles, scarlet fever, and rubella (German measles). Filatow argued for the existence of a fourth exanthem, which he called rubeola scarlatinosa. He reasoned that if patients could get this disease after having already had scarlet fever, or if contracting this disease did not protect them against getting scarlet fever in the future, then scarlet fever and rubeola scarlatinosa must be two different things. Filatow had seen evidence of this happening in one set of patients and appealed to doctors working in larger institutions to provide further evidence for the existence of this clinical entity.

One such doctor came along several years later named Clement Dukes. Dukes was a physician at a Rugby school in London, England, where he believed he had seen many patients similar to those described by Filatow. In 1894, he published an article in the Lancet in which he referred to rubeola scarlatinosa as epidemic roseola or rose rash.[10] (This is not to be confused

with roseola infantilitis, which was described in 1910 and later became known as sixth disease.[11])

Dukes went into great detail describing what he believed were clear differences between scarlet fever, rose rash, and measles. He conceded that "In their elucidation they have entangled many of the ablest physicians, to our professional discredit and to the detriment of the welfare of our schools," but insisted that "… They are as separable as typhus and typhoid fever."

Dukes published a second article on this topic in 1900.[12] In this paper, he noted that he "… would not venture to suggest an appropriate name for this disease," and referred the question of nomenclature to the Royal College of Physicians of London. "Pending this authoritative decision," Dukes "… tentatively employ[ed] the general expression of the 'fourth disease.'" Ironically, this name not only became permanently associated with rubeola scarlatinosa, but it also initiated a numbering system for the classic childhood exanthems that remains to this day.

The naming of fifth disease

Today, the fourth disease is regarded by most as a non-entity.[13] In spite of the detailed reasoning presented by Filatow and Dukes, other studies could not establish that the fourth disease exists independently of scarlet fever, measles, or rubella, nor could a causative agent be determined. The most obvious flaw in the Filatow-Dukes logic is the fact that it is possible to get scarlet fever more than once.[14] Thus, the idea that an infection confers immunity, and that any future infection that looks like scarlet fever must be something else, is incorrect.

Still, the idea of the fourth disease lasted long enough for the naming of fifth disease several years later. In 1905, a French physician named Cheinisse described erythema infectiosum in a weekly periodical called *La Semaine Medical*. He made reference to the three classic diseases of childhood: scarlet fever, rubella, and measles, and mentioned the so-called fourth disease, rubeola scarlatinosa, in his introduction. His subsequent description of erythema

infectiosum was entitled "Une cinquème maladie éruptive: le mègalérythéme épidémique" (i.e., *a fifth eruptive disease*: the infectious erythema). It is unclear when exactly this name was changed to simply *fifth disease*, but the basis of its numbering can be traced back to Dukes "general expression of the fourth disease" in 1900.

The fact that fourth disease is now considered a non-entity suggests that the name fifth disease is perhaps inappropriate. While it is true that it was discovered after fourth disease, this numbering system makes the false assumption that Filatow-Dukes' disease actually exists.

The discovery of parvovirus B19

Early attempts to connect erythema infectiosum with its causative agent included the inoculation of supposedly infected human sera in monkey renal cells.[15] In another attempt, researchers obtained blood samples, throat swabs, and stool or rectal swabs from 27 infected patients and looked for pathological changes in various tissue cultures.[16] Neither of these studies were conclusive. Another researcher went so far as to suggest that the causative agent of erythema infectiosum wasn't infectious at all, but that correlation with the use of a margarine emulsifier indicated that it was based on nutritional and personal factors.[17]

Given the clinical course of erythema infectiosum (see Figure 2), it is easy to see why it was so difficult to identify its causative agent, parvovirus B19. While it is true that the lifetime prevalence of this virus approaches 90%, the viremia occurs before the emergence of the characteristic, red rash, and then rapidly resolves. Furthermore, the symptoms during the prodromal period are mild and non-specific. Many other cases are asymptomatic throughout the entire infection. It should be no surprise then that the discovery of parvovirus in human blood occurred coincidentally.

The human parvovirus was discovered by someone who had no interest in erythema infectiosum whatsoever. While working in

Together at last
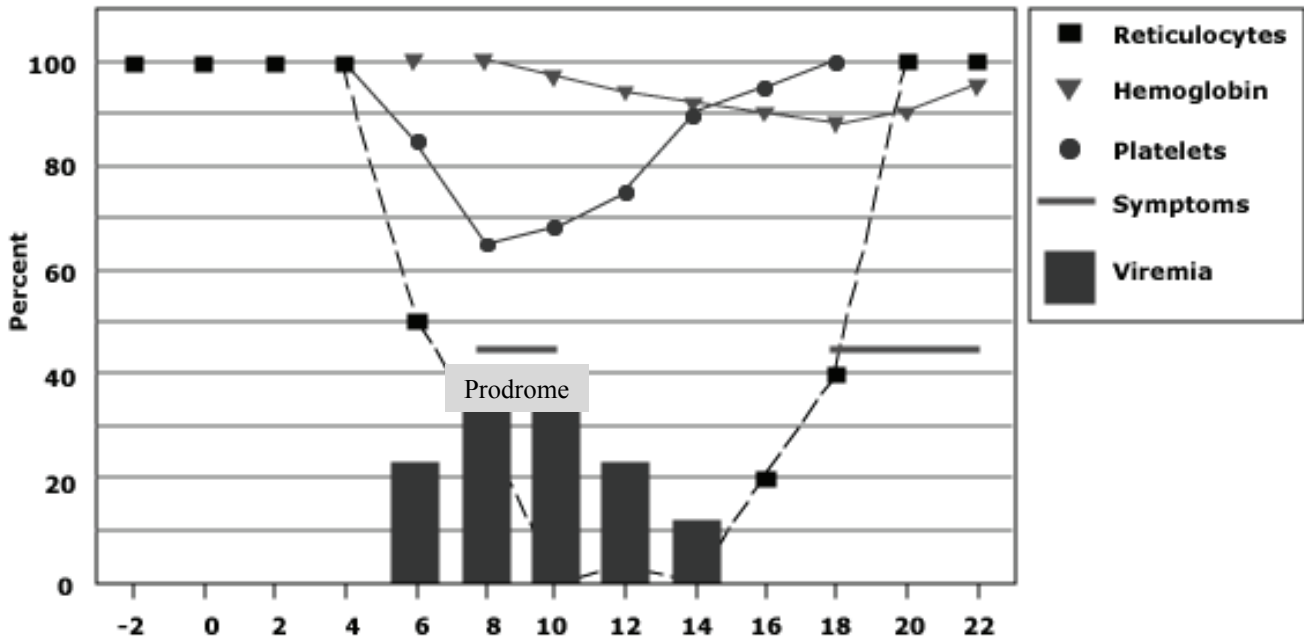
Figure 2: Schematic representation of the clinical course and laboratory abnormalities in normal hosts with parvovirus B19 infection. Note the biphasic timing of symptoms, during the peak viremia and again after the viremia has cleared. Rash, arthritis, and other symptoms typically associated with parvovirus B19 occur during the second period.[2]

virologist named Yvonne Cossart came across a collection of parvovirus-like particles while screening blood samples for hepatitis B.[*] The sample containing these particles happened to occupy position 19 on plate B, which eventually led to the name B19.

Parvoviruses had long been known to infect cats, rats, mice, minks, dogs, pigs, rabbits, geese, and cattle.[18] But up until Cossart's discovery, there was no evidence for parvovirus infection in humans. As a result, researchers were initially reluctant to refer to B19 as a true parvovirus, opting for terms like human parvovirus-like agent (PVLA)[19] and human serum parvovirus-like virus (SPLV)[20] instead.

The search for the causative agent of erythema infectiosum was so elusive that it actually ended up taking place the other way around. Following Cossart's discovery in 1975, a microbiologist named Anderson was busy studying parvovirus B19 at King's College Medical School in London. In 1982, he noted that "Infection with PVLA [parvovirus B19] is an apparently common event, occurring most often in childhood. Studies… show that that peak of antibody acquisition occurs between the ages of 4 and 6 years, and by the age of 16 one-third of subjects have PVLA antibody…"[19] He also noted that "… three of the four blood donors from Dr Cossart's group of nine who were followed up became ill shortly after giving blood; two complained of fatigue which was in one individual accompanied by leucopenia, while the third developed a rash."[19] As seen in Figure 2, these symptoms and sequelae are classic to erythema infectiosum.

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[*] Cossart later discovered the presence of parvovirus in the serum of a patient diagnosed with acute hepatitis. This coincidence raised the possibility of parvovirus being the elusive non-A, non-B virus. This, of course, turned out to be not the case, with hepatitis C being discovered several years later.

In 1983, this same researcher, obviously aware of what a parvovirus B19 infection might entail, provided epidemiological evidence of a parvovirus being the cause of erythema infectiosum.[21] This connection was aided by a coincidental outbreak in north London and the use of parvovirus-specific IgM radioimmunoassay to confirm true cases.[20,22] Further evidence on this outbreak was provided in 1984.[23]

The final confirmation of parvovirus B19 being the cause of erythema infectiosum occurred when seronegative volunteers were inoculated with parvovirus from an asymptomatic donor.[24] One week after inoculation, symptoms included mild illness, malaise, and other non-specific complaints, as well as viremia, excretion of the virus from the respiratory tract, and decreased levels of hemoglobin, reticulocytes, lymphocytes, neutrophils, and platelets. 17 to 18 days later, a second-phase of the illness with rash and sore joints lasting three days occurred in three of the four infected volunteers. (Refer to Figure 2 for an overview.) This constellation of symptoms was consistent with erythema infectiosum and explained why parvovirus infection could cause aplastic crisis in patients with chronic hemolytic anemia (such as sickle cell disease).

Conclusion

The associations between erythema infectiosum, fifth disease, and parvovirus B19 evolved gradually over almost 100 years. The turning points in this history include: (1) the recognition of a "different form of Rubella" by Tschamer in 1889; (2) the naming of erythema infectiosum by Sticker 1899 (and the evidence for its independence from scarlet fever, measles, and rubella); (3) the influence of Dukes and his general expression of fourth disease in 1900; (4) the reference to a fifth disease by Cheinisse in 1905; (5) the discovery of parvovirus by Cossart in 1975; and (6) the evidence of parvovirus as the causative agent by Anderson from 1983 to 1985.

It is true that some of these details amount to little more than historical trivia. But it is the authors' hope that this overview will give students a greater appreciation of erythema infectiosum, fifth disease, and its elusive causative agent, parvovirus B19.

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Lessons from the listeriosis outbreak

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Introduction

The recent outbreak of listeriosis has been called the worst epidemic of this illness that the world has ever seen.[1] To date, there have been 53 confirmed cases across Canada and 20 confirmed deaths in which listeriosis has been the underlying or contributing cause of death.[2] Despite the August 24, 2008 recall of over 220 different products, concerns of continued spread persist in the wake of a November 22 warning from the acting chief medical officer of health regarding the discovery of *Listeria monocytogenes* in seven provincial correctional facilities.[3, 4] Given the magnitude of this outbreak, criticisms of the responses of all parties involved have been inexorable. The Public Health Agency of Canada (PHAC), the Canadian Food Inspection Agency (CFIA) as well as Maple Leaf Foods and other corporations have all been faulted as the toll of this outbreak continues to rise.[5] Although opinions differ where, if at all, blame should be laid, most would agree that the listeriosis outbreak has given Canadians cause to examine one of the most vital areas of collaboration in our health care system – the interaction between the various organizations which safeguard our food.

Overview of the outbreak

As early as June 2008, Toronto Public Health Units noticed a minor increase in the number of reported listeriosis cases. By mid-July Toronto Public Health increased their investigations after a listeriosis case was discovered in a Toronto nursing home. Food samples from the nursing home were sent to Health Canada labs and on August 5, 2008, a sandwich was found to be contaminated with *Listeria*. Toronto Public Health then notified the CFIA of the positive food

samples and on August 12 Maple Leaf Foods was informed by the CFIA that a formal investigation of their products was underway. CFIA officials met with public health officials two days later and the decision was made to stop serving certain meat products in hospitals and long-term care facilities. On August 16 the CFIA and Health Canada met and recommended a recall on certain Maple Leaf products. The following day Maple Leaf announced a voluntary recall of some products from their Toronto plant; over the period of August 17 – 24 the list of recalled products grew to 220 as the number of listeriosis cases and associated deaths continued to rise. The recalled products also included prepared sandwiches by other corporations including Lucerne Meats, Atlantic Foods Ltd. and Metro Ontario Inc. During this time Maple Leaf Foods' Toronto plant was shut down to undergo cleaning and re-evaluation of safety practices. The Public Health Agency of Canada announced on August 23 that tests confirmed the link between the listeriosis outbreak to Maple Leaf Foods and the following day television ads begin airing featuring Maple Leaf CEO Michael McCain's apologies on behalf of the corporation.[6, 7]

Since then, the Public Health Agency of Canada has been continually issuing updates on the number of confirmed and suspected cases. However, critics of the Ministry of Health and Long-Term Care (MOHLTC) and PHAC would argue that Michael McCain, rather than acting Chief Medical Officer of Health, Dr. David Williams or Chief Public Health Officer, Dr. David Butler-Jones, has been the major public figure informing Canadians about the outbreak.[5] Similarly, critics of the CFIA have lambasted 2007 reforms that allowed the food industry itself a much greater degree of self-monitoring.

Considering both the controversy about the management of the outbreak and the extent of its spread Prime Minister Stephen Harper announced an investigation into the outbreak. This investigation includes an evaluation of the "efficiency and effectiveness of the response by federal agencies in terms of prevention, the recall of contaminated products, and collaboration and communication among partners in the food safety system and the public".[1]

The following discussion will examine the major agencies involved and review some of the criticisms elicited by the epidemic.

The Public Health Agency of Canada and the chief public health officer

The Public Health Agency of Canada (PHAC) was created in the aftermath of the SARS outbreak of 2003. It was initially its own ministry, with a cabinet seat reporting directly to the Prime Minister. However, in 2006 the government eliminated the ministry and cabinet position and relegated the Chief Public Health Officer to a civil service position under the Minister of Health.[5]

The tasks of the agency include preventing both chronic disease and outbreaks of infections. The latter task falls primarily under the Infectious Disease and Emergency Preparedness (IDEP) branch. This branch contains the subdivision known as the Centre for Infectious Disease Prevention and Control (CIDPC), which is responsible for public health surveillance and epidemiological studies during foodborne epidemics. The National Microbial Laboratory (NML) and the Laboratory for Foodborne Zoonoses (LFZ) are also involved in outbreak surveillance and provide pathogen strain differentiation and other analytical services.[8]

As per the current Canada Foodborne Outbreak Response Protocol, the PHAC and specifically the CIDPC has the responsibility of "communication with the public as it relates to the public health implications of the epidemiological investigation", until a food source has been identified, at which point the CFIA "will have the lead for public communications as it relates to the food safety investigation and any necessary food safety recall activities".[9] Despite the specificity of this protocol, critics have suggested that the Chief Public Health Officer failed to act as "the leading national voice for public health, [particularly] in outbreaks and other health emergencies".[5] Some have noted the greater relative prominence of the Minister of Agriculture and Agri-Food Canada and Michael McCain of Maple Leaf Foods during the outbreak. Such criticism has led to concerns about the independence of the Chief Public Health Officer, who may be constrained by prevailing political considerations. As he or she serves under the Minister of Health and has less protection from dismissal than similar positions in the United States and United Kingdom, some have questioned this officer's ability to raise public health concerns without fear of political repercussions. The independent investigation initiated by the Prime Minister will be able to assess the efficacy of the PHAC and the Chief Public Health Officer given their current apparatus and whether the agency acted with due diligence. However, new concerns are being raised that "the investigator will not have any power to subpoena witnesses or documents; the investigation will be closed to public participation; and there is no commitment to publish the investigator's findings or report to parliament".[1]

The Canadian Food Inspection Agency and the role of industry

The Canadian Food Inspection Agency (CFIA) reports to the Minister of Agriculture and Agri-Food and is responsible for protecting the safety of Canada's food supply. The CFIA implements surveillance and inspection programs intended to provide an early warning for problems within the food supply. In the event of a food safety emergency, the CFIA works in partnership with Health Canada, provincial agencies, and the food industry to operate an emergency response system, including food recalls.[10]

Inspection of ready-to-eat meat products, such as the contaminated cold cuts at the centre of the listeriosis outbreak, was formerly done by

CFIA inspectors. However, a Canadian government review of the CFIA in November 2007 resulted in various reforms to inspection policy. Of particular importance was a decision that effectively transferred inspection duties to the meat industry, with government inspectors taking on more of an oversight role.[1] This decision meant that inspectors spent less time on plant floors conducting visible inspections and more time analyzing data collected by industry.[11] Maple Leaf Foods was an early supporter of these inspection reforms.[1]

The push towards greater industry self-regulation has not received universal support. Those who argue in favour of self-inspection say that industry has greater incentives to ensure safe products for their customers and are more likely to develop new scientific testing technologies and protocols.[11] Those who argue against self-inspection say that industry is more concerned with profits than product safety. They are concerned that tests may not be performed adequately, results may be altered, or government inspectors may be denied full access to the data.[11]

The listeriosis outbreak has affected the operations of both the CFIA and Maple Leaf Foods. Dr. Brian Evans, CFIA Executive Vice-President and Chief Veterinary Officer of Canada, has conceded that the agency should have done a better job communicating with the public during the outbreak.[12] The CFIA is also revising its *Listeria* surveillance protocols to ensure greater transparency and more protection for consumers, including reinstating a rule compelling companies to inform inspectors of positive *Listeria* tests.[13] For its part, Maple Leaf Foods estimated the outbreak and following recall cost the company over $25 million directly and another $14 million in lost sales.[14] Moreover, the results of a class-action lawsuit filed against the company are yet to be determined. Following the outbreak, Maple Leaf Foods toughened its own policies regarding *Listeria*, to a level more rigorous than the proposed CFIA protocols.[13]

Conclusion

Despite the many criticisms of all parties involved in the listeriosis outbreak, it remains unclear as to where the prevention and response systems failed. In fact, it can be argued that all parties responded adequately given the circumstances. Further investigations by the government may yield valuable recommendations to improve the response to foodborne illness and the safety of the food supply, provided that such investigations are thorough, objective, and transparent. However, the listeriosis outbreak has already demonstrated the importance of rapid communication and collaboration between private industry and all levels of government to ensure the health and safety of the public.

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Pushing the envelope on organ donation

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In June 2007 a Dutch television station broadcasted a program in which a terminally ill patient interviewed three potential candidates in order to select one of them to receive her kidneys.[1] The choice of recipient was to be made on the basis of the contestant's history and profile, as well as based on conversations with their family and friends; viewers were also able to add their input via text messages. As expected, medical professionals and politicians were outraged when the program was aired. Soon after, it was revealed that the show was a hoax intended to raise awareness about the shortage of organ donors; the donor was in fact an actress, while the three potential recipients were genuine. Even though the impact of the program on the public and on government policy is difficult to assess, it does bring to our attention the fact that there is a significant worldwide shortage in the supply of donated organs for those in need.[1] In fact, just like most other developed nations, Canada has been unable to keep pace with the demand for organs. This issue of organ shortage is worth exploring in order to be able to make conclusions about the causes and possible solutions.

The Situation in Canada

In order to assess the extent of the problem in Canada it is important to review some of the available statistics. For instance, 4,195 Canadians were on wait-lists for organ transplants on December 31, 2007[2] compared with 3974 people on Jan 1, 2006 and 2592 people in 1995.[3] Only 2188 transplants were performed in 2007[4] and 193 Canadians died waiting for an organ transplant in the same year.[2] Moreover, according to the Canadian Organ Replacement Registry, Canada's cadaveric donation rate for deceased donors in 2005 was 12.8 per million inhabitants,

which falls well below the rates in countries like Spain (35.1), Estonia (26.5), Belgium (22.8), Italy (20.9) and the United States (21.5) as projected by the International Registry maintained at the University of Barcelona, Spain.[3] On the bright side, living donation rates in Canada are rising and currently stand at 15.6 per million inhabitants. Nevertheless, there are significant regional variations in deceased and living organ donation rates. Deceased donations range from 5.1 in Manitoba to 17.9 in Quebec. Living donations range from 7.0 in Quebec to 19.9 in Alberta.[3] There are also significant provincial variations in wait times for transplants. In fact, a recent study of 7034 dialysis patients found people under 40 waited a median 8 years in Ontario for a new kidney, compared with 3 years for those in Alberta.[5] Hence, not only does Canada have a shortage in organs, the nation also possesses a very fragmented system that has led to regional variations in organ donation rates as well as provincial variations in wait times for transplants.

One of the problems of the Canadian system is that less than half of the organs that could potentially be transplanted are actually harvested. There are a number of reasons for the inefficiency including the fact that in many cases the family members of an individual are simply not approached for consent. In addition, there is no concerted effort and little resources allocated to educate Canadians about the benefits of organ donation.[4] However, the main problem with the Canadian system lies in the presence of many fragmented organ donation programs that are so varied that it is difficult if not impossible to characterize national practice in Canada as a whole.[3] The existence of many organizations and programs that vary from province to province is a

"reflection of the fractured jurisdiction over health care".[3] In fact, it has been suggested that Canada's low organ donation rates maybe be partly due to a lack of a coordinated and centralized approach to dealing with the issue.[3]

New Developments

In recent months there have been attempts by both federal and provincial governments in Canada to make policy changes that will reduce the shortage of organs available for transplantation by attempting to decrease the fragmentation and improve the coordination and communication amongst the provinces. In fact, one very recent positive development with regards to organ donation in Canada was an agreement reached in August 2008 between the federal, provincial (except Quebec) and territorial governments to develop an "integrated national organ donation system" [6], including national oversight and allocation mechanisms for all donated organs and tissues. Prior to this initiative, Canada was the only developed country without a national transplant system, which has resulted in a significant variation in organ donation rates across the country and a lack of equal access to life-saving transplants.[4] Under the new funding arrangement, the Canadian Council for Donation and Transplantation (CCDT) has merged with Canadian Blood Services, which has expanded its mandate and operations to include organ and tissue donation and transplantation.[2] While the fragmented provincial transplantation agencies will continue to run independently, more effort will be put into improving the co-ordination amongst the different agencies.

The initiative is further aimed at creating and managing three electronic registries: the Urgent Status Registry to ensure patients most desperately in need of organs are treated first, regardless of where they live; the Living Paired Exchange Registry to facilitate the donation of organs such as kidneys and lungs by living donors; and the Intent to Donate Registry to co-ordinate the various provincial programs that allow potential donors to give their consent to donate organs when they die.[4] The creation of these registries will not only reduce the

fragmentation in our approach to organ donation, it will also provide us with much needed data and evidence to allow us to better evaluate our progress. In addition to the national organ-sharing network that will be created, there will also be efforts directed at standardizing consent policies and creating nationwide wait lists for all available organs. Mandatory organ sharing and other requisite elements of a national organ donation and transplantation program will be phased-in over a number of years.[6]

Alternative options

At the present time, Canada utilizes an "opt-in" approach to organ donation. An individual needs to give consent by signing an organ donation card, or explicit consent needs to be obtained from surviving family members before a person's organs can be used after their death.[3] This approach to organ donation has proven to be suboptimal when it comes to harvesting organs to give to those in need. In fact, Canada possesses a legal framework that does not promote organ donation.

An alternate strategy would be a "presumed consent" (opt-out) approach, whereby everyone is presumed to be a donor unless they have specified otherwise in advance.[3] There are two main variations of this policy that have been utilized in some European countries. For instance, Spain, a world leader in organ donations, has managed to achieve the highest organ donation rate in the world by implementing a policy of "soft" presumed consent whereby relatives may opt-out for a dying patient.[7] In addition, the Spanish government invested heavily in educational campaigns and "transplant support teams"[7] who provide emotional support to bereaving families, helping decrease refusal rates. Since the implementation of the "soft" presumed consent approach in Spain in 1990, donation rates have doubled to their current level of 35 per million. Another variation of this policy is the "hard" presumed consent policy seen in Austria where relatives may not opt-out for a dying patient. This approach began in Austria in 1982, and since then, their donation rate has quadrupled to 25 donors per million.[7] Ontario

rejected the presumed consent approach on the grounds that Canadian society "is not ready"[3]; however, it is difficult to say whether or not the government has the right to judge if the people are or are not ready for a new approach to organ donation. Still the Ontario government is not sitting idle and is considering the idea of "first person consent", whereby an organ is automatically harvested when a donor card has been signed, with no consideration for the opinion of the donor's family.[3]

As effective as presumed consent appears to be, however, simply changing organ donations laws and regulations will not solve Canada's shortage of organs. What is needed in addition to changing the laws is a significant shift in attitudes toward organ donation. In Spain for instance, considerable emphasis is placed on organ donation awareness. There is special funding and training provided for transplant teams, who are responsible for working with grieving family members to explain the situation and explain to them the value of organ donation. Furthermore, the general public needs to be educated about the importance of signing their organ donation cards, and about the many lives they can save if they choose to do so. Without such a system of education and counseling for grieving families, a presumed consent law will not live up to its potential.[7]

In addition to presumed consent, there are a number of other strategies that can possibly be implemented to address the shortfall in donated organs. These include monetary incentives for those who signup to be a donor. For instance, making an offer to the family to reimburse the donor's funeral expenses. Other incentives could include providing priority access for previous donors in the event they need an organ.[3]

Conclusion and Future Outlook

All in all, Canada has had a dismal record when it comes to organ donation and that must change sooner rather than later because the demand for organs has been growing over the years. The federal and provincial governments have taken some positive steps in recent years to try to improve the situation; the most significant step has been the plan to develop an integrated national organ donation system, including national oversight and allocation mechanisms for all donated organs and tissues. However, more needs to be done to correct the current state of affairs. This could involve amending the current laws and regulations pertaining to organ donation, educating the public and raising awareness about the importance of organ donation, as well as providing incentives for those who agree to donate their organs. Until such time we can only look with admiration towards countries such as Spain, which has become a world leader when it comes to organ donation.

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Applications of Nanotechnology in Infectious Disease

Pencilla Lang (Meds 2011) and *Jenny Shu (Meds 2012)*
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Nanotechnology is a major recent technological development affecting medical approaches to disease treatment and immunity induction. For example, nanoparticles can be used to create anti-microbial agents and vaccine adjuvants to target difficult microbes such as HIV, Salmonella, Tuberculosis and Listeria. While this new technology makes lofty promises, it is important to keep in mind the possible biological and environmental hazards of nanoparticles. In the coming decade, physicians will be called upon to make both treatment and policy decisions regarding the use of nanoparticle technology.

Introduction

For those who are not "nanotechnology" scientists, the word appears to be much of an enigma, conjuring up science fiction style images of micromachines, computer chips and lithography. Richard Feynman may not have been thinking about battling infectious diseases when he coined the famous quote "There's plenty of room at the bottom", but there is certainly plenty of room for nanotechnology in our campaign against microbes.

Despite the fact that nanotechnology is rapidly changing the face of medicine, many physicians are still unable to define it. The US National Nanotechnology Initiative defines "nanotechnology" as "understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications".[1] In the past, engineers were confined to using naturally occurring materials and forming them through industrial processes. Material properties frequently constrained device designs. Nanotechnology allows materials to be custom-designed on a molecular scale and enables the design of new and different devices.

Like much of medicine, our battle with infectious disease has been one of broad sweeps because it is difficult to target microbes and components of the immune system with high specificity. Treatment has been caught in a perpetual tug of war attempting to balance the dangers of illness against the damage incurred by therapy. The immune system is a perfect example of molecular machinery at its most complex. Nanotechnology provides the opportunity to meet microbes and our immune systems at a molecular level. While there are many potential applications for nanotechnology in the area of infection and immunity, some of the earliest and most promising developments have been in the development of antimicrobial agents and new vaccines.

Antimicrobial Agents

Nanoemulsions are oil-in-water droplets ranging from 200-600 nm^2. These are high energy droplets thermodynamically driven to fuse with lipid-containing organisms. The electrostatic attraction between the cationic charge of the emulsion and the anionic charge on the pathogen enhances the fusion. When fusion occurs, the active ingredients inside the particle and the energy released in the fusion process destabilize the lipid membrane, resulting in cell lysis and death. These antimicrobial agents can be used in wound irrigation and decontamination of high-risk surfaces (for example in hospitals). Studies have shown these agents to be effective against bacteria (E. coli, Salmonella, S. aureus), viruses (HIV, Herpes), and fungi (Candida).[2]

Nanoparticles are also used to deliver antimicrobial agents. A microscopic carrier hides and protects molecules from degradation in the body, and allows it to be delivered to specific target cells in a controlled manner.[3] Alternatively, special "carriers" can be designed to carry therapeutic agents across membranes into specific intracellular compartments and through the blood-brain barrier. These areas have traditionally been difficult to reach.[4] Research in this area began in the early 1990s, and has since expanded to encompass treatment of many intracellular infections, including fungal and parasitic infections, Listeria, Salmonella and Tuberculosis.[5,6] Nanoparticle carriers can be metallic, lipid-based, polymer-based or biologic (resembling a virus).[6]

Silver particles have long been known to be bactericidal. Recent research on silver nanoparticles have demonstrated them to be quite promising against new strains of bacteria resistant to current antibiotics, and gram negative bacteria, including E coli, V cholera, P aeruginosa, and S typhus. The bactericidal properties of nanoparticles are size dependent, with particles 1-10nm having the best direct interaction with bacteria. Silver nanoparticles act primarily in three different ways. Nanoparticles attach to the surface of the cell membrane and disturb its function, rhey penetrate the bacteria and interact with DNA, and they release silver ions which have a separate bactericidal effects.[7]

Vaccine Development

The effectiveness of a vaccine is measured by its ability to interact with, and stimulate, the immune system. The nano-engineering of vaccines allows the creation of better adjuvants and vaccine delivery systems. Currently, nanoparticles are being used in the design of nasal and transcutaneous vaccines. A nasal vaccine attempts to generate an immune response by exposing the nasal mucosa to antigens. Similarly, transcutaneous vaccines target the immature dendritic cells (professional antigen-presenting cells) found in high density in the epidermis and dermis of the skin.

Traditionally, nasal vaccines have had limited effectiveness because free antigens are readily cleared from the nasal cavity, poorly absorbed by nasal epithelial cells, and generally have low intrinsic immunogenicity. Encapsulation of the antigen into bioadhesive nanoparticles will allow these particles to be tailor-made with specific ligands, adjuvants and endosomal escape mediators. Some of the promising nasal vaccines underdevelopment include vaccines for: Parainfluenza, Hepatitis B, Measles, Yersinia pestis, and HIV.[8, 9, 10, 11]

Particular attention is being paid to the HIV vaccine. Since HIV targets immune cells in an unusual way, standard approaches to an HIV vaccine have been met with limited success. Vaccines administered in the nose to induce mucosal immunity are also able to induce immunity in the genital mucosa. Development of mucosal immunity may play an important role for protection against HIV, as it allows the body to mount an immune response early on in the disease process.[8] The production of IgA antibodies on mucosal surfaces is unique to mucosal immunization. Mucosal immunization will stimulate both the mucosal and systemic immune responses (systemic immunization will only induce the systemic response), improving vaccine efficacy.[12]

Current transcutaneous particle-based vaccines are made of naturally occurring "particles" and can vary in quality from batch to batch and induce adverse events. Manufactured nanoparticles can be topically applied to hair follicles.[13] In a similar fashion to the nasal vaccine, this technique uses nano-sized inert solid carrier beads to covalently bond antigen.[14]

In both the nasal and transcutaneous vaccines, particle characteristics are important determinants of the effectiveness of the vaccine. Nanoparticles allow particle characteristics to be designed to specification. It also allows for a systematic study of the effects of parameters such as particle size, shape, and charge.[15] Nanoparticles approximately $10\mu m$ in diameter are selectively uptaken by cells in Peyer's patches in the gut. It is postulated that particles

resembling the size of viruses will trigger a viral-type immune response (cellular), whereas particles the size of a bacterium are more likely to trigger a humoral response. Smaller nanoparticles are also more rapidly absorbed by nasal mucosal cells. Since epithelial cells carry a negative charge, a positively charged nanoparticle should be more effective than a negatively charged particle.[16]

With all the hype surrounding nanotechnology, physicians need to be prepared to address patient concerns regarding the new vaccine designs. Some questions they should be prepared to answer include: Are these vaccines fundamentally different from those used in the past? What potential problems may arise from their use? How do they differ, in terms of risks, effectiveness and adverse events from other vaccines?

Other applications

With clinical applications of nanoemulsions and nanoparticle vaccines already in use, it is not difficult to imagine other potential applications of nanotechnology in immunology. Drug delivery systems designed to interact with tissue in specific locations and times are currently being used in engineering. These systems should allow for more accurate targeting of therapeutic agents – allowing greater therapeutic effects through increased activity, and decreased adverse effects. These medications take advantage of the ability to control molecular structure to allow for enhanced activity.[16] Perhaps most fantastic of all is the idea that scientists may eventually be able to create special pieces of machinery that imitate the immune system to destroy specific targets, in essence manufacturing artificial "antibodies" that can be administered to patients as anti-microbial agents.[17] While these prospects may appear to still be speculations of the future, it is not too early for physicians to be preparing for their eventual integration into mainstream medicine. Pharmaceutical companies are already actively pursuing and preparing for this major change in how therapeutic agents will be delivered and work. Published patent applications in this area have increased at a near exponential rate in the

past 10 years, and this is expected to continue well into the future.[18] Most significantly, the Nanomedicine Initiative of the National Institutes of Health Roadmap for Medical Research initiative predicts that nanomaterials will begin yielding significant medical benefits within the next 10 years.[19] Diagnostic application of nanoparticles are also important for rapid treatment to some infections.

Nanotechnology – Friend or Foe?

While nanotechnology holds a lot of promise, it is important not to overlook the potential problems and hazards that this technology may pose. The creation of new materials may impart unintended novel chemical properties that may be harmful to human health. These may be difficult to identify in short-term clinical trials.[20] In recent years, the significance of nanotoxicology has started to become recognized and studied. Nanotoxicology has developed into its own emerging discipline, including its own international conference, NanoTox, which emerged in 2007 to study the potential problems arising from the use of nano-sized particles, materials and machines, and potential solutions.[21] Another recent study from the Woodrow Wilson Centre's Project on Emerging Technologies concluded that there is limited understanding of the effects of nanotechnology on human health.[22] Physicians will have a significant role in the management of these problems.

There are also major political, economical, environmental and social ramifications associated with this technology. For example, the small size of particles, combined with potentially novel chemical properties, poses a question of how ingested but non-metabolized particles may be collected and properly disposed of. In addition, the effects of such particles on the environment, and the environmental impacts of production processes have not been adequately studied.[23] As a major stakeholder in nanovaccines and nanoemulsions, physicians will be looked upon by governmental and regulatory agencies to comment on the balance of benefit and hazards posed by these materials.

Developments in nanotechnology have opened up many new approaches to treating and preventing infectious disease. Nanoparticle anti-microbials and vaccines are examples of how this new technology is likely to be used in the coming decade. Physicians will have a major role in policy-setting, technology implemention and answering the questions of a concerned and curious public.

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An Interview with Dr. Marina Salvadori

Julie Hughes (Meds 2012) and Emma Love (Meds 2011)
Faculty Reviewer: Dr. Marina Salvadori

"Part of what drives people in infectious diseases is that we find some international and tropical diseases just fascinating… We're often people who like details, we're good at trivial pursuit – that's just the nature of who we are. Part of what drives us is that there really are no borders in the world, and disease does not stop at a border. There is a famous quote that says, 'There is nowhere anymore from where we are distant, there is no place that is remote.' Infectious diseases affect all of us."

Dr. Marina Salvadori is passionate about fighting infectious diseases, and with good reason. Infections have been a driving force of history in fields as diverse as politics, economics, and art. Alexander the Great died prematurely of a lung infection, the bubonic plague contributed to the shift away from European feudalism, and tuberculosis helped to shape the Romanticist movement. Part of the tried-and-true fabric of medicine, in Dr. Salvadori's words, Infectious Disease is "about advocacy, about global health, about "stamping out disease and pestilence."

Dr. Salvadori is a pediatric infectious diseases specialist active in advocacy work, with a particular focus on the promotion of vaccinations. Her medical career started in the Queen's University medical class of 1991, which she followed with a pediatrics residency in Winnipeg:

"I decided when I was about 12 that I wanted to be a doctor, probably because I absolutely loved my family doctor. I thought he was the most wonderful person in the world and I just thought it would be such a fun thing to do. I also was raised in a family that had a tremendous sense of social justice and social responsibility, so I knew my final career choice had to have an aspect like that…

At first I did pediatrics, and I think that was because I grew up in an immigrant family

and had no cousins or grandparents or anything, so the oldest people I knew were my parents, who were 46 when I went to medical school… When I did pediatrics I felt a sweeping sense of relief."

It may reassure current medical students and residents that, while she is happy in her current work, her choice of careers was not without a few bumps along the road:

"Once I was in pediatrics I realized that I had very poor technical skills and I'm not good with my hands, which I did know beforehand, but it was emphasized in pediatrics! I'm what I call a cognitive kind of doctor. … If I had known about community medicine and public health, I may well have done that."

When asked about a typical day, she responds that answering such a question is impossible:

"That's what I like about being a pediatric infectious diseases specialist – the fact is there actually is no such thing as a typical day! By the nature of infectious diseases, most things are very acute, so when I get up in the morning I have no idea what I'm going to have to deal with that day… On a given day I can't predict my patient load, I can't predict what kinds of problems I'm going to see, and that is partly why I do

academic medicine and why I do infectious diseases.

I do various things… teaching medical students and residents, teaching other health care professionals, interfacing with public health on policy development, working on national advisory committees for immunizations, traveling… What's most rewarding is when I'm part of national and provincial decision-making that comes out with a policy that actually has a huge health impact that nobody sees or knows about."

Such contributions include advocating for the infant pneumococcal vaccine for Ontario–a relatively low-profile health policy change that has nonetheless had a significant impact on health for all. Dr. Salvadori's work consists of a remarkably diverse collection of endeavours, including some international health initiatives:

"I've had some fabulous opportunities. I joined a group from UBC and did some teaching of pediatric infectious diseases doctors in China, because they don't have infectious diseases as a specialty, and after SARS thought they should. A large Hong Kong donor asked that Canada be part of a training program for these people. I went there to teach and some of them have come here, and that was a wonderful experience. I've also been asked to do policy development for a pediatric oncology hospital in Egypt, because they're trying to get a pediatric oncology care for the Arab world. They needed someone to help adapt policies to their situation, and that was really interesting."

Dr. Salvadori continually emphasizes the need for "big picture" thinking in medicine. When asked about challenges she faces on an individual basis, she comments not on obstacles associated with patient care, but on policy issues. In particular, she highlights the importance of developing nationally driven policies rather than fragmented provincial guidelines, and alternative financing models that encourage physicians to be involved

in advocacy and preventative medicine. She also comments more broadly on the challenges facing the world of infectious diseases:

"There are so many. There's the HIV epidemic, which is changing the political and economic landscape of Africa. There's tuberculosis coming out as multi-drug resistant. There's global warming, which is dramatically affecting the habitats of animals and then changing how the microbes they carry interface with humans, so we're getting all kinds of new infectious diseases emerging…. If you look at a global picture, infectious diseases are still the number one killer of people and the number one health care issue. If you look at our very privileged North American society, infection control is becoming more and more paramount in hospitals, as are infection-related illnesses from drug resistance."

I also have to say that the implementation of vaccination programs with growing groups of vaccine naysayers, who could actually lose all the ground we as a society have gained in the fight against infectious diseases, is a huge challenge…. There are a lot of challenges, and certainly a lot of work to be done."

Nonetheless, she has high hopes for the future, and a firm belief that there will be world changing scientific advances within this generation:

"Another rewarding aspect [of my work] is vaccine evaluation and development that has the potential—and I know this sounds grand—to change the face of disease in the whole world. The Human Papilloma Virus vaccine and cervical cancer is one such vaccine. Rotavirus vaccine is another. We lose 600,000 children in the world a year and now that vaccine has been developed. To be part of guidelines for its use really makes me feel that we can have a local, provincial, national, and global impact….

We're doing very well. AIDS in Africa is really difficult, but there will be an effective vaccine. It will happen. We all want it tomorrow, but if it's in 20 or 30 years, that's a very small timeframe in the history of the world. I think it will be before that, and then we can really make a difference. When you look at it, vaccination is the only thing that we as a global community endeavour to at least offer to every global citizen. There is nothing else."

Many infectious disease specialists see global health as an essential obligation as well as a way to re-ignite their initial passion for their field. Dr. Salvadori sees new possibilities in this area as a result of increased funding:

"I look to some of my colleagues, who in the latter part of their careers, do fantastic projects with the World Health Organization. They've done immunization implementation that's rational and that you can apply to the local culture and situation. I'm really inspired and driven by that kind of work. I tell people that before the internet and computers—before any kind of mass communication—we as a global community eradicated smallpox. We can do that for other diseases, like polio, and we actually can conquer these as humankind.

The Bill and Melinda Gates Foundation has the largest impact in the infectious diseases world, particularly in developing nations and immunization initiatives, of anyone else. They have given $800 million a year, which is the exact same budget as the World Health Organization. Some of my colleagues who have toiled away in unknown parts of Africa on obscure diseases with $20,000 grants have now been able to make huge steps forward. For these people, it wasn't intellect, drive, or ability, but money that stopped them from reaching their potential."

In sum, both abroad and at home, Dr. Salvadori seeks to fulfill the dual roles of the physician as health care provider and patient advocate:

"For me, being an infectious diseases doctor, advocacy and patient care are so intertwined, and so much a part of what I do. Advocating for appropriate immunization schedules for infants actually takes care of my patients as a whole because then they don't get infectious diseases. I cannot separate my professional roles of advocacy, teaching, and immediate patient care on an individual level because they're so intertwined in who I am and how I practice medicine."

Pediatric Pneumonia

Kalpa Shah (Meds 2012) and Aiman Alak (Meds 2011)
Faculty Reviewer: Dr. Michael Rieder

Case

Accompanied by his mother, seven-year-old John presents with worsening non-productive cough and fever. Two days ago, he was diagnosed with an upper respiratory tract infection at a walk-in clinic and prescribed amoxicillin; however, his condition did not improve. His past history is negative for allergies, asthma, cardiovascular disease, and cancer. However, his mother recalls about 5 similar episodes over the years. John was born at term, and his immunization is up-to-date.

On physical exam, his oral temperature is 38.2°C, his heart rate is 95 beats per minute, his respiratory rate is 35 breaths per minute, and his blood pressure was 100 over 60 mmHg. The child is occasionally coughing, but does not appear toxic.

A chest radiograph revealed left lower lobe consolidation consistent with a diagnosis of pneumonia. John was treated with clarithromycin and improved over the next two days.

Etiology/Causative Agents

Pediatric pneumonia is a significant cause of morbidity and mortality worldwide causing two million deaths yearly.[1-5] In North America, the annual incidence of pneumonia ranges from 15 to 45 per 1000 children, depending on the particular age group. Although not a major cause of mortality in North America, pneumonia in children is a major source of morbidity.

In planning therapy knowing the responsible pathogen is a key element in designing the therapeutic plan. The best predictor of the causative agent is age (Table 1).[6-8] However, even in prospective research studies, the pathogen could not be identified in half of the cases, and in the clinical setting blood cultures of children with pneumonia are commonly negative. As the determination of the causative pathogen is difficult, empirical therapy is the common treatment course for children with pneumonia.

Table 1: Causative agents based on age group.

Age	Causative agents (in descending order of frequency)
Birth to 20 days	Group B streptococci, gram-negative enteric bacteria, cytomegalovirus, *Listeria monocytogenes*
3 weeks to 3 months	*Chlamydia trachomatis,* respiratory syncytial virus, parainfluenza virus 3, *Streptococcus pneumoniae, Bordetella pertussis, Staphylococcus aureus*
4 months to 4 years	Respiratory syncytial virus, parainfluenza viruses, influenzavirus, adenovirus, rhinovirus, *Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Mycobacterium tuberculosis*
5 to 15 years	*Mycoplasma pneumoniae, Chlamydia pneumoniae, Streptococcus pneumoniae, Mycobacterium tuberculosis, influenza A or B, adenovirus, other respiratory viruses*

Risk factors

Risk factors that increase the incidence or severity of pneumonia in children include: prematurity, malnutrition, low socioeconomic status, attendance at day-care centers, passive exposure to smoke, pollution or toxic fumes.[9] Inhalation of harmful substances contributes to lung inflammation and damages cilia function, thereby reducing the ability of the lungs to clear themselves, thus making them more prone to infection. Also, children whose immune systems are compromised by illness, immunosuppressant drugs or chemotherapy have a higher risk of contracting infections.[10]

Clinical Assessment

Pneumonia should be suspected when a child presents with fever and one or more signs of respiratory distress including grunting, nasal flaring, rales, retractions, wheezing or tachypnea.[11] It has been suggested that tachypnea is the best indicator a child has pneumonia rather than an uncomplicated upper respiratory tract infection.[12] The most commonly used guidelines for assessing tachypnea are that of the World Health Organization's and are as follows: for children one to five years of age a respiratory rate of more than 40 breaths per minute and in children older than five years more than 30 breaths per minute signifies tachypnea.[13] Measurement of tachypnea requires a one full minute count while the child is quiet. Pneumonia is unlikely in patients without fever and more than one respiratory sign.[14] In patients with respiratory distress but no fever, a reactive airway disease, aspiration of a foreign body, or underlying pulmonary or cardiac disorder should be considered.

It should be mentioned that classically two presentations have been described for pneumonia:
- Typical pneumonia: fever, chills, pleuritic chest pain and a productive cough.
- Atypical pneumonia: gradual onset over several days to weeks, dominated by symptoms of headache and malaise, nonproductive cough and low-grade fever.

However, clinically it is often difficult to distinguish between these two presentations. Also, it is not possible to distinguish whether the cause of pneumonia is viral or bacterial based on clinical signs alone.[15]

Diagnosis and Testing

The main support for a diagnosis of pneumonia comes from the patient history and physical examination. A chest radiograph is considered by many to be the gold standard for confirming a diagnosis of pneumonia.[16] However, there is some controversy regarding the utility of using chest x-rays to distinguish between causative organisms. Classically lobar infiltrates were associated with bacterial infections and interstitial filtrates are thought to be indicative of viral infections. However, both lobar and interstitial filtrates have been found in viral, bacterial and viral-bacterial infections. Some studies flatly state there is no relation between the appearance of the chest x-ray and the causative agent.[17] Whereas, others claim there is some value in using radiological features to distinguish between bacterial and viral etiologies.[18]

When additional information is required to help decide whether antibiotics are necessary a WBC and differential count may be useful.[19] The pneumonia is likely of bacterial origin if the WBC count is elevated (typically greater than 15 000) with predominance of polymorphonuclear cells.[20] If the child is more than 10 years of age and is able to produce sputum a Gram stain test and culture of the sputum can be used to help identify the cause.[21] For Mycoplasma and Chlamydia species serologic testing for IgM or increase in IgG titres may be useful.[22] However, serologic testing is often of little use in the immediate treatment a patient, and usually provides only a retrospective diagnosis to determine the cause of an outbreak.

Table 2. Empirical antimicrobial therapy for pediatric pneumonia depending on age and severity.*

Age group	Outpatients	Hospitalized patients	Patients in intensive care unit
3 months to 5 years	Amoxicillin, erythromycin, or clarithromycin	Cefuroxime	Cefuroxime plus erythromycin or clarithromycin
5 years to 18 years	Erythromycin or clarithromycin	Erythromycin or clarithromycin with or without cefuroxime	Cefuroxime plus erythromycin or clarithromycin

*Adapted from Jadaviji T, et al (1997)[10]

In most children with community acquired pneumonia identification of the causative organism is not critical. However, in cases where the patient has severe symptoms, is not responding to treatment or if there appears to a community outbreak, the responsible organism should be determined.

Management

As mentioned above, identifying the causative agent is difficult. Thus, the current Canadian guidelines for the treatment of Paediatric pneumonia, established in 1997, approach the problem from an age based, etiologic perspective.[23]

The consensus group suggest therapy based on age and the most common causative agents. They favoured antibiotics with the cheapest price, narrowest spectral range, minimum side effects, and ease of compliance. These guidelines allow for flexibility based on the overall clinical presentation, and the local resistance patterns of predominant bacterial pathogens. The consensus groups add that the scarcity of well-conducted randomized controlled trials make their recommendations weak.

Most moderate forms of pneumonia could be treated with oral agents, while intravenous administration is reserved for patients with severe pneumonia requiring hospitalization. Children age less than 6 months, children with toxic appearance, children requiring supportive therapy, or children not responding to oral antimicrobial therapy should probably be admitted to the hospital. The recommended therapy based on age

group and pneumonia severity is summarized in Table 2.

An important part of treatment is supportive care, including hydration, antipyretic therapy and oxygen as necessary. As well, the child should be monitored and follow-up arranged to determine if therapy has been successful or if therapy needs to be re-evaluated.

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Genitourinary tuberculosis: a rare but potentially devastating disease

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Extrapulmonary manifestations of tuberculosis (TB) are an uncommon but important disease entity. Genitourinary (GU)-associated infections in particular occur mostly secondary to those of the lungs, but can also occur as primary infections through infected clothing or even via sexual transmission. Two case reports, one of a man with a cutaneous penile tuberculous ulcer, and the other of his wife who later contracted endometrial TB, illustrate the latter route of transmission. While penile ulcers in men and infertility in women have long differential diagnoses, it is important to keep in mind that extrapulmonary TB is a possibility, especially in patients from TB endemic areas. Investigations of these disorders should therefore include a full TB workup in patients in whom TB is a possibility, including Mantoux testing, histopathology looking for caseating granulomas, and chest radiography to differentiate between primary and secondary genitourinary TB. Given the serious complications of genitourinary TB, including sexual dysfunction in men and infertility in women, it is extremely important to effectively recognize and treat GU manifestations of TB.

Introduction

Although the majority of primary tuberculosis (TB) occurs in the lungs, approximately 20% of infected patients will develop an extrapulmonary manifestation over time. The genitourinary (GU) tract is the most common site for extrapulmonary TB, with the most frequently affected sites within the GU tract being the epididymis (42%), seminal vesicles (23%), prostate (21%), testes (15%) and vas deferens (12%) in males, and the fallopian tubes in females.[1,8] The first cases of genitourinary TB were described in the 19th century, in which they occurred as a complication of routine infantile circumcision, after which TB-infected surgeons sucked the bleeding penis, thus transmitting the disease to the infant. Now however, other methods of transmission to the GU tract are being described.

Amongst all GU-associated TB infections, penile cutaneous TB is extremely rare, comprising less than 1% of all cases in males.[2] It may manifest as primary, secondary, or papulonecrotic tuberculide type. Primary infection may be acquired by direct inoculation of the mucosa through contaminated skin or clothing. Secondary infection, on the other hand, refers to disseminated TB occurring after infection of other organs in the genitourinary system or arising from haematogenous spread from the lungs. Lastly, papulonecrotic tuberculide type is a subset of secondary infection, representing an allergic reaction to bursts of TB antigen reaching highly immune-sensitive skin following haematogenous spread from an internal nidus (such as the lungs).[4] Of the three types of transmission, primary is thought to be the most rare. Sexual transmission has been recognized as a legitimate mode of primary spread with important implications for reproductive health, as demonstrated by the following case reports.[3]

Case 1

A 50-year-old Indian man living in the United Kingdom presented with a painless, indurated ulcer near the penile corona after a recent trip to India. The lesion had been present for two months and had increased in size to measure 1 cm in diameter and 1 cm in depth at the time of examination. Left inguinal lymph nodes were palpable and non-tender, but no additional local or systemic symptoms were present.

Investigations began with a punch biopsy that was negative for penile carcinoma, however granulomas of an unknown cause were revealed. Urine tests, chest radiograph, and abdominal ultrasound were unremarkable. The patient did not consent to HIV testing, but stated that his wife had been his only partner for the past 25 years. An excisional biopsy demonstrated the presence of caseating granulomas which produced *Mycobacterium tuberculosis* on culture.

The initial treatment regimen was combination therapy of isoniazid, rifampicin, pyrazinamide, and pyridoxine for two months. Isoniazid and rifampicin were then to be continued for an additional four months. The ulcer regressed and did not recur. Although screening conducted by the Public Health Department in Oxfordshire could not uncover other cases of TB in the patient's family, the patient's wife did not consent to genitourinary screening.

Case 2

The 49-year-old wife of the patient in Case 1 presented with menorrhagia, fever, sweats, and weight loss one year after her husband's diagnosis of penile TB. An endometrial biopsy was obtained and revealed multiple caseating granulomas of an unknown cause. She had no known previous infection with TB, but had been having unprotected sexual intercourse with her husband prior to his diagnosis. Urine and abdominal ultrasound results were unremarkable, but an inactive calcified granuloma in the left apex of the lung was discovered. A second biopsy of the endometrium was performed and culture produced *M. tuberculosis*. Following this discovery, restriction fragment length polymorphism analysis was performed and confirmed that both husband and wife had been infected by identical organism, thus making this the first confirmed case of sexually transmitted TB.

Presentation

Clinically, TB of the penis generally presents either as superficial ulcers of the skin or glans of the penis, or as tuberculous cavernositis (inflammation of the cavernous bodies).[4,] In most cases, the lesion appears as a superficial ulcer on the glans or around the corona, as this is the most common part abraded during sexual contact or with infected clothing.[2,7] The normal penile mucosa is highly resistant to tuberculosis, but in the case of sexual transmission, the bacilli are inoculated into abrasions caused by vigorous sexual activity.[7] Although the glans and corona are most commonly affected, the lesions can also be extensive, with involvement of the urethra and corpus cavernosum, and rarely may even present as hardened nodules.[2] Male patients with penile tuberculosis can present with impotence, and advanced cases may also present with erectile failure due to tuberculous caveronositis.[3,7]

Female genitourinary tuberculosis is associated with infertility, although diagnosis is difficult since patients are usually asymptomatic. Some women (such as the one in the preceding case reports) do however present with symptoms such as menorrhagia, fever, sweats, weight loss, and malaise.

Making the diagnosis

The differential diagnosis of chronic penile ulcer with histological features of granulomas is extensive, and thus diagnosis of penile disease can often be difficult.[3] Consideration needs to be given to bacterial and fungal infections (such as syphilis and herpes simplex), parasitic infections, vasculitides, inflammatory bowel disease, sarcoidosis, penile carcinoma, foreign body reactions, and other rare causes.[3,5]

In general, the basic process used to diagnose TB of the penis includes physical examination revealing typical clinical features, positive Mantoux test, raised ESR, and the typical histopathological findings. More specifically, the presence of acid-fast bacilli in the smear examination, and typical granuloma with giant cells and caseous foci on histopathology with no

evidence of malignancy can help to clinch the diagnosis. Furthermore, chest X-ray, intravenous pyelography (IVP), urine culture and culture for *Mycobacteria* should be done to differentiate primary from secondary manifestations.[9] Intravenous urography should also be carried out to exclude upper renal tract TB.[2] Clinical cure is possible through the treatment regimen described in the preceding case study, but relapses have been known to occur, making follow-up a necessity. Patients diagnosed with penile TB should be counseled to abstain from sexual contact or at least use a condom for 4 to 6 weeks following treatment.[8]

As with penile TB, the finding of caseating granulomas and Langerhans giant cells in association with chronic inflammation is diagnostic of endometrial TB. Though the tuberculin skin test does have some utility, it is not the most sensitive test available. Hysterosalpingograms (HSG's) are very useful for visualizing the internal anatomy of the uterus, which may reveal features such as calcifications, occlusions, 'beaded' Fallopian tubes (if infected), and irregular uterine outlines if the patient does indeed have genitourinary TB. However, even if a female patient is correctly diagnosed and effectively treated with antitubercular medications, the prognosis for future pregnancies remains poor.[8] Thus, it is important to prevent the transmission of endometrial TB by all possible routes, including sexual transmission.

Conclusions

Although TB of the penis is rare, physicians need to be aware of this infectious disease when undiagnosed ulcers on the penis are observed. In particular, suspicion of cutaneous TB should be raised in countries which still show a high prevalence of tuberculosis, such as India where one third of the population is infected.[2] Given that endometrial TB is associated with infertility, it should also be considered in female patients from TB endemic regions that have difficulty conceiving. Since sexual transmission of TB is possible, as evidenced by the case reports in this article, it is also important to consider the implications for partners of infected patients engaging in unprotected sex. Thus, awareness of the extrapulmonary manifestations of TB and proper counselling of patients with GU manifestations in particular is crucial in preventing the serious sexual and reproductive consequences of this disease.

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Rabies vaccine meets the laws of supply and demand

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Rabies is a viral neuroinvasive disease that causes encephalopathy in mammals. Vaccination is the primary method of rabies prevention, given as both pre- and post-exposure prophylaxis. North America is currently experiencing a heightened rabies threat due to recent problems in vaccine production. Since 2007, the pharmaceutical industry has been struggling to meet North American demand for the rabies vaccine. The Food and Drug Administration (FDA) and the two vaccine-producing pharmaceutical companies, Sanofi-Pasteur and Novartis, are jointly responsible for the current supply shortage. This shortage of rabies vaccine has resulted in a rationed approach to delivering prophylaxis. Conservative measures such as avoidance behavior and vaccination of animals are to be used in place of pre-exposure prophylaxis. Public health officials must review all cases in which post-exposure prophylaxis is requested to ensure the limited supply of vaccine is appropriately distributed.

Introduction

Rabies is a viral neuroinvasive disease that causes encephalopathy in mammals. The most common vector for human infection is animal bites, and if untreated, rabies is almost always fatal. While rabies has been well controlled or eradicated in some areas of the world, death from rabies is not uncommon in Asia and Africa. Prevention of rabies by vaccination has been a mainstay of prophylaxis since the late 19th-century and is largely responsible for declining incidence in both animals and humans in North America.[1]

North America is currently experiencing a heightened rabies threat due to recent problems in vaccine production. Since 2007, the pharmaceutical industry has been experiencing problems in meeting North American demand for the rabies vaccine. This has affected the front lines of medicine by causing a disturbance in the practice of rabies prophylaxis.[2] Here we will discuss rabies and the rabies vaccine, the events that precipitated the current shortage in supply and how this production-related strain on resources has caused a reactionary change in the practice of medicine.

Background and epidemiology

Rabies is considered a zoonotic infectious disease. This implies transmission to humans and animals occurs via other animals. It is an RNA virus belonging to the family *Rhabdoviridae* and genus *Lyssavirus* and is contained in the saliva of infected mammals.[1] After a bite occurs, the virus enters the central nervous system of the next host and causes non-specific prodromal symptoms followed by progressive encephalitis that is almost always fatal. Early symptoms include paresthesias, pruritis and pain at the site of viral entry. In humans the incubation period usually varies from several weeks to months. Diagnosing rabies is difficult due to the long and variable incubation time, as well as the lack of symptom specificity.[2]

Historically, the most common vectors for rabies transmission have been domestic and stray dogs and cats. In the United States in 1946 over 8300 rabies cases were reported among dogs. By 2006, aggressive canine vaccination programs and improved stray animal control have resulted in a greater than ten-fold reduction in canine rabies cases. This has translated into a roughly ten-fold drop in human rabies cases in the United States.[3] There has been an increasing rate of rabies in

traditionally forest-dwelling wildlife such as skunks, bats and raccoons. This is concerning as urbanization and suburbanization increases in North America and these animals are in greater contact with humans. Between 2000 and 2005, 40% of Canada's 2238 confirmed animal rabies cases were skunks, 26% were bats, and 8% were raccoons. Only two rabies deaths have been reported in Canada since 1985 and both were caused by bat exposure.[4] Responding to changes in the pattern of rabies transmission requires adequate supply and effective use of preventive measures.

The rabies vaccine and prophylaxis

Prior to the development of the first rabies vaccine by Louis Pasteur and Emile Roux in 1885, almost all rabies infections resulted in death. This early vaccine was developed by harvesting cells from nerve tissue of infected rabbits.[5] Research into an attenuated strain of the virus led to the development of new vaccines including the human diploid cell rabies vaccine in 1967 and a newer, less expensive purified chick embryo vaccine. These are available as Imovax® by Sanofi-Pasteur and RabAvert® by Novartis, respectively. They are the only two rabies vaccines currently approved for use in Canada and the United States.

In humans, rabies vaccines are intended for pre- and post-exposure prophylaxis. Pre-exposure prophylaxis is indicated for those at high risk of contacting the virus, such as veterinarians, animal trappers, and travelers to certain regions in Asia and Africa. Post-exposure prophylaxis is given to those who have experienced open skin wounds as a result of an animal encounter. Individuals that have never received the vaccine and are in need of post-exposure prophylaxis also require rabies immunoglobulin to provide intermittent immunity. Post-exposure prophylaxis with rabies vaccine in humans has been validated as an effective and safe method of preventing infection, particularly when administered within 6 days of exposure.[1] Thus, the recent shortage in rabies vaccine supply to North America has been of great concern, particularly to those in immediate need of prophylactic treatment.

Cause and implications of the vaccine shortage

A current shortage of rabies vaccine has resulted in a rationed approach to delivering prophylaxis in North America. Much like other elements of preventive medicine such as colonoscopies, the indications for receiving the rabies vaccine have become more stringent in response to strained resources. Unique to the shortage of rabies vaccine is that the origin of the resource constraint is not intrinsic to the healthcare system; there are no infrastructure, human resource or financial constraints limiting the use of rabies vaccine. The Food and Drug Administration (FDA) and the two vaccine-producing pharmaceutical companies, Sanofi-Pasteur and Novartis, are jointly responsible for the current supply shortage.

In June 2007, Sanofi-Pasteur began renovating its Imovax® production facility in France in order to comply with new requirements from the FDA and a French regulatory body. Prior to these renovations the company stockpiled a finite amount of vaccine that was expected to meet demand until the facility re-opened. Shortly after renovations began it became evident that the estimation of demand was incorrect and the stockpiled supply would be inadequate.[6] Also at this time Novartis, which controls 50% of the North American rabies vaccine market, experienced FDA scrutiny and was asked to temporarily halt production of RabAvert®. Public health and industry officials have since declared that the rabies vaccine should be used for post-exposure prophylaxis only. Conservative measures such as avoidance behavior and vaccination of animals are to be used in place of pre-exposure prophylaxis. Public health officials must review all cases in which post-exposure prophylaxis is requested to ensure the limited supply of vaccine is appropriately distributed. RabAvert® was recently cleared by the FDA, and Novartis has been attempting to meet vaccine demand. However, as of October 2008, the Center for Disease Control (CDC) has not changed recommendations for prophylaxis and

has informed travelers to certain regions in Asia and Africa that pre-travel vaccination is not available.[6] Current projections estimate the supply of vaccine to restore to normal in mid-2009 upon the re-opening of the Imovax® production facility.[6]

Discussion

For many years the international pharmaceutical industry has acted alone and in conjunction with governments around the world to change the landscape of modern medicine. Positive economic pressure, such as the encouragement of research and development by government incentives, has translated into economic growth for nations and an intended improvement of quality of life of the masses. Stringent regulatory forces on the pharmaceutical industry have also had a trickle-down effect in which government bodies or other stressors temporarily shock the business of drug production, which in turn changes the way medicine is practiced. This is evident in the recent shortage of rabies vaccine in North America.

The practice of medicine in Canada has attempted to demonstrate flexibility and poise amidst a storm of stressors. Elements of healthcare delivery have crumbled in the face of limited resources while other areas have thrived on the heels of innovation. For example, some Canadians have had to seek more timely care in the United States or overseas. However, others have benefited from new models of primary care, allowing them to attain both timely and high quality care. While these examples are considered to be largely intrinsic to our method of healthcare delivery, it is important to note that external forces may also drastically change the practice of medicine.

The current philosophy of medicine in the Western World requires the efficient production of pharmaceutical agents as well as regulatory bodies to ensure the safety of the population. The nature of the pharmaceutical industry makes it necessary for the practice of medicine is agile and prepared to deal with sudden change.

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Infective Endocarditis: Diagnosis and Treatment

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Introduction

When one thinks of infectious disease, endocarditis – infection of the heart- does not always leap to mind. However endocarditis is a serious life-threatening condition if not diagnosed and treated promptly. Infective endocarditis is inflammation of the inner surface of the heart following microorganism colonization. This creates the prototypical lesion of infective endocarditis called the vegetation, a mass of platelets, fibrin and microorganisms. Infective endocarditis results in damage and destruction of heart valves, specifically the aortic valve. The purpose of this article is to provide a synopsis for medical students about the prevalence of infective endocarditis, the pathogenesis and microbes responsible for the disease and the signs and symptoms of infective endocarditis, with particular emphasis on diagnosis and treatment.

Epidemiology and Pathogenesis

Infective endocarditis is a relatively uncommon infectious disease, but failure to recognize it in predisposed patients can have disastrous consequences resulting in heart failure, embolism and even death. It occurs with an incidence of 1.7 to 7.0 episodes per 100 000 people in North America, and occurs in 1.4% of patients within the first year following aortic valve replacement.[2,3,4,5] Patients on dialysis infrequently develop endocarditis, but have high mortality. For a patient to develop endocarditis of the aortic valve, they typically have a cardiac abnormality leading to jet injury across the valve and they must have blood borne microbial colonization of the valve surface.[1] Patients at particular risk for developing infective endocarditis may have a congenital heart abnormality, such as congenital bicuspid aortic valve, degenerative aortic stenosis, aortic calcification, rheumatic aortic valve disease or prosthetic heart valves. Highly virulent microorganisms, such as *Staphylococcus aureus*, can cause endocarditis in people with normal aortic valves.

The pathogenesis of aortic valve endocarditis occurs from a sequence of events which allow microorganisms to gain access to the valve and destroy it. An initial insult to the valve occurs, independent of infection, damages the valve and allows microbes to colonize. Microorganism colonization may spread to the adjacent structures such as aortic annulus, mitral valve and aortic root and form an abscess. It is possible for the abscess to rupture and spread into the pericardial cavity. Infective endocarditis destroys the cusps of the aortic valve and can also lead to cardiac fistulas and paravalvular abscesses. Thrombosis of microbial vegetations from the aortic valve can lead to coronary and systemic embolic events such as acute myocardial infarction, cerebral aneurysms, strokes, or ischemic arterial occlusions.[6] Organs at particular risk of infracting from vegetative embolisms are the spleen, the liver, the kidneys and limbs.[29] The mitral valve can become secondarily involved if large vegetations from the aortic valve prolapse into the left ventricle and contact the leaflets of the mitral valve.[7,8]

The infective organisms involved in aortic valve endocarditis depend on whether the valve is native or prosthetic. *Staphyloccous aureus* and *streptococcus viridans* are the two most common bacteria responsible for infecting native heart valves. *S. aureus* is very virulent and can cause infective endocarditis in people with no predisposing cardiac lesions. *S. viridans* is not as

virulent and infects people with predisposing lesions, such as calcified aortic valves or congenital bicuspid valves. *Streptococcus epidermidis* and other streptococci are also able to infect native heart valves.

Endocarditis due to Gram negative bacteria is uncommon, but is very serious as these microbes tend to be antibiotic resistant. These microbes include *Hemophilus*, *Actinovacillus*, *Cardiobacterium*, *Eikenella* and *Kingella* – the HACEK group of bacteria. Endocarditis due to fungal infection predominantly involves *Candida albicans* and *Aspergillus fumigatus* and tends to be rare but extremely serious.

Prosthetic valve endocarditis is defined as early onset if it occurs within two months after valve replacement and is considered late if it is more than two months after surgery.[10] Prosthetic valve endocarditis can be due to colonization of the valve after the surgery or due to a contaminated valve being implanted, which may lead to endocarditis up to one year after surgery.[10] Early prosthetic valve endocarditis is due to contamination of the valve at the time of surgery. The microbes responsible are *S. aureus, S. epidermidis* and *Enterococcus faecalis*.[5,11] The etiology of late prosthetic valve endocarditis is more difficult to determine, but it is most likely due to bacteremia and colonization of the prosthetic valve, usually by *S. aureus* or, *S. epidermidis* but can be caused by many other microbes.[12,13,14] It is important to obtain blood cultures in endocarditis patients, so as the correct antibiotic can be used, however, there are cases of culture negative endocarditis where no microorganism is cultured from the valve tissue or from blood.[11]

Diagnosis

Clinically, endocarditis is classified as acute or subacute. Subacute endocarditis is caused by less virulent organisms, such as *S. viridans*, and occurs in patients with a preexisting diseased or prosthetic aortic valve. Patients present with low grade fever, malaise and symptoms suggestive of the flu. Physicians tend to treat these patients with antibiotics which will improve symptoms within 10 days; however discontinuing the antibiotics may cause symptoms to return. On physical exam, the patient's only abnormal heart findings may be an aortic murmur. Other physical findings include splenomegaly and petechia, a rash caused by hemorrhage of capillaries that can occur anywhere on the body. Patients with long standing congenital valve disease may also have evidence of clubbing. Patients can present with congestive heart failure (CHF) due to aortic insufficiency. Vegetation thromboemoblism can also occur causing myocardial infarction, stoke, splenic or hepatic infarcts. Blood cultures should be obtained, as well as complete blood cell count looking for leukocytosis or anemia which may indicate infection.

Acute endocarditis is generally caused by more virulent organisms like *S. aureus*, and can affect people with normal aortic valves. Antibiotics alone will not be able to eradicate the infection. Patients present with all the signs and symptoms of subacute endocarditis but have more severe symptoms and overwhelming sepsis. Signs unique to acute endocarditis include the Janeway lesion, a painless red-blue lesion found on the soles of feet and the palms of the hands, and the Roth spot, an oval pale area surrounded by hemorrhage in the optic disc. Acute endocarditis patients may not necessarily have a history of pre-existing valve disease. If the patients have a paravalvular abscess, they likely have abnormal EKG findings including prolonged PR interval or evidence of heart block.

Doppler echocardiography is an extremely useful tool in diagnosing infective endocarditis. It is able to detect vegetations as small as 1-2 mm in size and is very sensitive in detecting paravalvular abscess and cardiac fistulas. In general, transesophgeal echocardiography (TEE) with multiplane views is much more sensitive than transthoracic echocardiography (TTE)[14,15]

Physicians from Duke University recommended criteria for the diagnosis of infective endocarditis, which has been modified over the years in attempts to improve its limitations.[16] In general, there are major and

minor criteria which are suggestive of endocarditis. A patient is said to definitively have endocarditis if they have two of the major criteria, or 1 major criterion and 3 minor criteria, or 5 minor criteria. A patient is said to possibly have endocarditis if they have 1 major criterion and one minor criterion or if they have 3 minor criteria (Table 1).

Treatment

The first line treatment of infective endocarditis is use of antibiotics. The choice of antibiotic depends on the clinical circumstances and should begin after obtaining blood cultures. Patients with recent dental work should be given antibiotics against bacteria of the oral cavity. Patients with a recent urinary or colonic procedure should be given antibiotics against Gram negative bacteria. IV drug users are at risk of *S. aureus* and *S. epidermidis*, and antibiotic therapy should be directed against these bugs. The use of 2 or 3 antibiotics that will increase the effect of each other is the best treatment for endocarditis caused by virulent organisms, and should be administered intravenously for 6 weeks. It often proves difficult to treat endocarditis with just antibiotics, especially when dealing with virulent organisms, like *S. aureus, Pseudomonas aeruginosa, Serratia marescens* or fungus

endocarditis. These organisms destroy the native aortic valve leading to aortic insufficiency and congestive heart failure (CHF).

Once antibiotic therapy has been started, surveillance blood cultures should be taken within 48 hours to monitor the efficacy of the treatment. The patient should be monitored for signs of CHF, thromboembolism and infection. In the two weeks following diagnosis, the patient should have daily electrocardiogram (EKG) and frequent echocardiogram. Abnormal findings of aortic abscesses or large vegetative growths should prompt immediate surgical intervention to prevent heart failure, shock or embolism.[14,17,18] Anticoagulation therapy isn't recommended in patients with endocarditis. It does not prevent embolization of vegetations and it is associated with an increased risk of neurological complications.[19]

Patients with endocarditis who develop CHF, acute valve dysfunction, paravalvular abscess, cardiac fistula, sepsis or embolization of vegetations despite adequate antibiotic therapy should receive surgical intervention. Patients with prosthetic valve endocarditis, especially mechanical valves, who are infected with *S. aureus have* better outcomes with early surgery.[9,13]

Table 1 - Modified Duke criteria for diagnosis of infective endocarditis.[16]

Definite infective endocarditis
Pathologic criteria
(1) Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
(2) Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis
Clinical criteria
(1) 2 major criteria; or
(2) 1 major criterion and 3 minor criteria; or
(3) 5 minor criteria
Possible infective endocarditis
(1) 1 major criterion and 1 minor criterion; or
(2) 3 minor criteria
Rejected
(1) Firm alternate diagnosis explaining evidence of infective endocarditis; or
(2) Resolution of infective endocarditis syndrome with antibiotic therapy for 4 days; or
(3) No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for 4 days; or
(4) Does not meet criteria for possible infective endocarditis, as above

Patients undergoing urgent heart surgery for endocarditis often have poor heart function and the surgical procedure is both lengthy and complex. In patients with infection limited to the cusps of the aortic valve, the native valve should be removed and replaced with a prosthesis. There is no evidence whether mechanical or bioprosthetic valves are superior in endocarditis patients, and treatment will ultimately depend on the preference of the surgeon and the patient.[23] In young patients, some surgeons prefer the use of pulmonary autografts.[24]

Involvement of the aortic annulus, whether necrosis or inflammation, needs to be surgically resected before implanting a prosthetic valve and patched over with autologous pericardium or glutaraldehyde fixed bovine pericardium.[25,26] In extensive destruction of the aortic root, all infected tissues should be resected and replaced with a pulmonary autograft.[27] The effects of infection associated with endocarditis are unpredictable, and as such different parts of the heart will need to be resected, repaired or replaced depending on the degree of damage.

Postoperatively, patients should be observed closely. Sepsis, coagulopathy and hemorrhage are common postoperative complications. Coagulopathy and bleeding should be treated with antifibrinolytic agents, fresh frozen plasma, platelets, and cryoprecipitate as needed. Resection of an aortic root abscess can lead to heart block and patients may require implantation of pacemakers. Further surgical treatment may be required for metastatic abscesses and vegetative embolisms to other organs, requiring collaboration with other surgical specialties.

Conclusion

Infective endocarditis is a serious infection, leading to destruction of the aortic valve and resulting in a host of symptoms. Prompt diagnosis can be made by careful history, echocardiography and blood cultures. Effective antibiotic therapy with a minimum duration of 6 weeks is the mainstay of treatments; surgical interventions are reserved for those with uncontrollable sepsis, structure-related heart failure, abscess formation, large vegetations and prosthetic valve endocarditis.

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Infection with H5N1 virus: presentation and vaccine development

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Introduction to influenza A (H5N1)

Avian flu, or Influenza A (H5N1), is an RNA virus belonging to Influenzavirus A, one of the five genera classified under the Orthomyxoviridae family. Influenzavirus A has only one species, Influenza A, which has been responsible for all worldwide influenza pandemics.[1] These viruses are further subdivided according to two important surface protein antigens, hemagglutinin and neuraminidase. Variations within these proteins have been responsible in pandemic strains of influenza such as the Spanish Flu (H1N1), which claimed upwards of 20 million lives.[2] Human cases of Avian flu primarily belong to the H5N1 subtype, though rarer subtypes others have been noted.[1] The presentation and vaccine development of the H5N1 subtype is contrasted to H1N1, but the same applies for H3N2, the other major subtype of human influenza virus.

H5N1 human infection was discovered in 1997 and subsequently re-emerged in 2003-2004 in poultry and human populations in several Asian countries.[1] Patients present with symptoms 2-4 days after exposure but may be asymptomatic for up to 8 days.[1,2] Unlike seasonal influenza, the nature of virus shedding in these cases is unknown at this point. Besides the common symptoms of cough, fever and shortness of breath, there are several features unique to infection with H5N1. Unilateral pneumonia progressing into a bilateral pattern within the span of 4 days is more common and can be detected on an X-ray. This is different from the cases of pneumonia which develop subsequent to H1N1 infection as they are quite rare. The mortality of patients infected with H5N1 approaches 60% and death occurs due to respiratory failure secondary to fulminant bilateral pneumonia.[2] It should be noted that this rate has been obtained from reported cases and that the actual number might be higher. As opposed to H1N1, H5N1 might involve extrapulmonary sites as well. For example, viral RNA has been isolated from the blood of patients who died from H5N1 infection.[3] Furthermore, viral RNA has also been detected in areas such as the liver, lymph nodes and brain.[4] This may explain why H5N1 infection also produces gastrointestinal symptoms such as diarrhea, vomiting and abdominal pain.

In the event of an outbreak of H5N1 infection, the modes of transmission of the virus must be examined in order to initiate effective countermeasures. The H5N1 virus is present in poultry and most cases of human infection have occurred in situations where there is close contact with live or dead birds.[3] There is also the possibility that infection occurs via the gastrointestinal tract as viral RNA has been found in feces of infected individuals.[6] Finally, there have been very few cases of human-to-human spread at present and these cases involved lengthy contact with infected individuals.[7] In summary, both animal-to-human and human-to-human spread remains inefficient at present but this could change if a mutation occurs in the H5N1 virus.

Vaccine development

The World Health Organization monitors influenza activity throughout the world and makes a recommendation for the seasonal influenza vaccine every year.[8] Postinfection ferret sera are tested in an assay called the hemagluttination-inhibition (HI) test where hemagluttinin from

different strains of H1N1 are tested to see which elicits the highest immune response. This data is used to make a recommendation around February for the upcoming influenza season.

An ideal vaccine for H5N1 infection should induce a strong mucosal antibody (IgA) response as the primary site of H5N1 infection is the respiratory tract.[9] Due to the extrapulmonary nature of H5N1 infection, a vaccine which induces a cell-mediated response as well would help protect from systemic manifestations of infection. This cell-mediated response needs to be generated against conserved elements of the virus such as matrix and nucleoproteins as other components mutate rapidly. Finally, this vaccine should be easy to produce as large amounts will be needed in the event of a potential or imminent pandemic.

Inactivated H1N1 influenza viruses are used for prophylaxis against seasonal influenza.[9] This approach is restricted to a humoral immune response only. Live attenuated H1N1 viruses were developed to overcome this hurdle as they induce cell-mediated responses as well. These approaches are not helpful for H5N1 human infection because of the long period of time required to produce these vaccines due to the requirement of chicken eggs to complete the process. Another problem with using live attenuated viruses for H5N1 infection prophylaxis is that there is the chance of developing a deadlier strain if they undergo genetic reassortment with another strain. Live attenuated H5N1 viruses have been shown to induce immunity in chickens when challenged to H5N1 infection however and will most likely be used as a last resort during a pandemic. [10]

The use of adenoviruses as vectors provides an attractive alternative to develop vaccines for H5N1 human infection.[11] Specifically, adenovirus serotype 5 can be genetically engineered to express hemagluttinin specific to H5N1. The production of adenovirus vectors is faster than that used for influenza vaccines since they do not require the use of chicken eggs. These vaccines can be administered intranasally and this eliminates the need for specialized personnel to administer them in the event of a pandemic. The main drawback to this modality is that a certain segment of the world population is immune to this subtype of adenovirus and this may dampen the response to hemagluttinin required as the virus may be cleared quickly. However, it has been shown that even in people who possess natural immunity, the vaccine induces antibody production against hemagluttinin.[11] Once large-scale studies examining the safety profile and efficacy of adenovirus-vectored vaccines is complete, they can be produced in large quantities to be used as prophylaxis during a pandemic.

The role of influenza A (H5N1) vaccines in a global pandemic

A potential H5N1 pandemic can be a serious threat to global health. Applying data from the 1918 flu pandemic, a computer model has been developed that predicts between 50 and 80 million people worldwide could be victims to H5N1.[12] Preventing a pandemic of this magnitude requires controlling it and containing it as early as possible. Vaccines play an important role in controlling H5N1, and the World Health Organization (WHO) has announced that they will be stockpiling vaccine in preparation for a global pandemic.[13] The current plan put forth by the WHO is to stockpile 50 million vaccines, which would protect 25 million people at two doses per person.[14] The WHO is charting new territories with regards to stockpiling vaccines. Usually, vaccines for pandemics cannot be prepared until the particular strain of virus makes its way into the population. Using current vaccine development technology, this could take at least 4-6 months after the WHO declares a particular strain of virus to be a pandemic.[15] The current strategy is to stockpile "prepandemic" vaccines. This involves preparing vaccines with currently circulating H5N1 strains, but with cross-reactivity to other emerging strains. For the development of an effective vaccine, it is essential to monitor H5N1 strains as well as any drift which occurs by the accumulation of mutations in H and N antigens. This would require rapid testing of patients at the level of individual communities. Cultures should be obtained from patients in

designated clinics which are representative of the community.[16] This information should then be escalated to a local public health office. Patients receiving the vaccine would be primed towards H5N1, buying time until a more specific booster is developed and administered.[17] To adapt to other strains, cross-reactivity is elicited by adding certain adjuvants to the vaccine, which also induce a stronger immune response and require lower doses of vaccine to be administered. GlaxoSmithKline is developing an inactivated, prepandemic vaccine for H5N1 which has undergone phase I and II clinical trials, and has been found to be safe in healthy adult volunteers.[18]

There are logistical issues surrounding stockpiling not limited to distributing of millions of vaccines and making vaccines available to the developing world. It is a global responsibility to ensure that the developing world receive vaccines and will require global cooperation. The WHO has not come up with a specific plan regarding the stockpile use, and admit to still working on one. Another issue is the lack of data regarding vaccine safety and efficacy in large human clinical trials. There is little research on the vaccine in paediatric and elderly populations, which are considered to be at the highest risk for H5N1. Careful thought and planning must go into making decisions not only at the level of the laboratory, but in policy to ensure that stockpiling vaccines can be taken seriously as a solution to prevent a worldwide H5N1 pandemic.

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Respiratory infections in the homeless

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Many people are affected by homelessness worldwide, in Canada and the U.S. Homelessness is associated with an increased risk of health problems due to overcrowding in shelters and host factors such as substance abuse, HIV co-infection, poor nutrition and hygiene, mental illness and trauma. Respiratory infections are among the most common problems that the homeless may present with and are associated with high morbidity and mortality. Certain respiratory infections are more common among homeless individuals and may be associated with complications unique to this population. Most of the literature in the field focuses on tuberculosis in the homeless or on specific outbreaks of respiratory infections. This article discusses the prevalence, risk factors, complications, treatment and prevention of tuberculous and non-tuberculous respiratory infections such as influenza and pneumonia caused by *S pneumoniae*, *S aureus*, *H influenzae b*, and anaerobes.

Introduction

Homelessness is an alarming social problem that affects up to 100 million people worldwide.[1] The 2001 Canadian census counted 14,145 individuals living in shelters, however, this largely underestimates the number as many homeless may not stay in shelters.[2] Homelessness is also a significant health problem. Crowded shelters are favorable environments for infection and host factors such as poor nutrition, obesity, sedentary lifestyle, poor hygiene, alcoholism, drug use, smoking, mental illness, abuse, trauma, or HIV co-infection increase susceptibility to illness and may diminish immune systems.[3,4,5,6] These factors, combined with decreased financial and personal resources, make the seeking out of medical help and compliance with treatment less likely. As a result, homeless people are more likely to suffer from respiratory infections, skin and foot infections, hepatitis, HIV, STI's, and chronic disease.[5]

Respiratory infections are among the most common medical issue that homeless individuals seek help for and shelters can be sources of outbreaks of tuberculosis and pneumonia.[7] Respiratory infections account for 33-42% of presenting complaints and 20% of total deaths in the homeless.[3,8,9] The mortality due to respiratory illness is about seven times greater than expected in the homeless.[9,10] This is compounded by the increased rate of chronic respiratory illness such as bronchitis (11.4%), asthma (8.6%) and COPD (5%). Several factors specifically predispose this population to respiratory infections including crowding, increased exposure to pathogens, smoking, alcohol and drug abuse, HIV seropositivity and chronic lung disease.[3,6,9] This article will examine both tuberculous and non-tuberculous respiratory infections such as pneumonia and influenza in the homeless as they are not only more common but are associated with greater morbidity, mortality and complications.

Tuberculosis

Tuberculosis is the most common respiratory infection among the homeless that is discussed in the literature. The estimated annual pulmonary TB rate for Canada and the U.S. is 2 per 100,000.[11] The urban homeless comprise a disproportionate burden of tuberculosis. The prevalence of active tuberculosis among the homeless in the U.S. is 1.6% to 6.8% and 18% to 51% for latent disease.[8]

As with other respiratory infections, poverty, malnutrition and overcrowding are all risk factors for tuberculosis. Larger, more crowded shelters with increased people sharing the same breathing space increases transmission and poor ventilation or recirculation of air compounds this risk.[8] HIV co-infection and alcoholism commonly complicate the course of infection. HIV is the single-most important risk factor for latent disease progressing to active disease and it is recommended that all individuals with TB be tested for HIV.[5,8] Some studies link multi-drug resistance to homelessness, although contradictory data disputes this.[5,12] Homelessness is associated with poor adherence, loss to follow-up and is an independent risk factor for no contacts.[12,13] Contact tracing is accomplished by mass screening in shelters as opposed to searching for named contacts.[3]

Screening and detection in the homeless is important for preventing TB resurgence.[14] The CDC recommends that the detection of tuberculosis be given first priority as opposed to screening asymptomatic individuals.[8] City-wide symptom screening programs have been implemented in Philadelphia shelters on intake to ensure that symptoms such as prolonged cough, night sweats, fever, and weight loss are further investigated.[15] Mass screening in shelters has also been widely used with resulting decreases in tuberculosis transmission. No consensus has been reached about the most effective screening tool.[1] Tuberculin skin testing (TST) is likely the simplest and least expensive to administer, but lacks specificity and results in many false negatives in the immunocompromised.[1,16] Mandatory skin test screening in one U.S. study resulted in a decreased incidence of TB from 510 to 121 cases per 100,000 per year.[1] Spot sputum is also a fairly rapid screening technique but 50% of smears are negative and subsequent tracing of patients is difficult.[1,8] Studies in incarcerated individuals show that chest radiography is likely to be the most cost-effective method. Annual snapshot screening for tuberculosis in shelters using combinations of these methods has been undertaken in Los Angeles and Marseille with great effectiveness.[1] Certain shelters, as in Barcelona, imposed mandatory screening with chest radiography, TST and sputum culture upon shelter admission before access to free meal services.[17]

Lack of treatment compliance is a common problem among the homeless. A 48% non-compliance rate was reported in New York in 1991 leading to increased length of treatment (560 versus 324 days) and decreased completion of treatment. Directly observed therapy (DOT) and supervised housing programs are both effective methods used to increase compliance.[5,8,18] Other novel solutions include financial or food incentives, transportation assistance and education using a peer health advisor.[5,8,19] More dramatically, incarceration has also been evaluated as a method for treating patients refusing treatment.[8,20]

Pneumonia

Pneumonia affects over 1 million Americans annually and is the 6th leading cause of death with a 14% mortality rate among hospitalized patients.[21] This burden is disproportionally shared by the homeless. An Edmonton-based study from 2000-2002 showed a pneumococcal infection rate among the homeless of 266.7 per 100,000 contrasted with 9.7 per 100,000 in the general population. Outbreaks of pneumococcal pneumonia more commonly occur in crowded shelters with high pneumococcal carriage rates of up to 60%. Shelter outbreaks in Chicago, Boston, Paris and the UK as well as in several provinces of Western Canada have been described in the literature.[20,22]

In addition to homelessness, risk factors for pneumonia include smoking, drug or alcohol use, HIV, asthma and COPD; all frequent comorbidities in the homeless. It is estimated that 78% of homeless individuals are smokers and 60% abuse alcohol.[3,9,22,23] In two shelter outbreaks in Boston and Paris, the majority of those infected were alcoholics, smokers or had chronic bronchitis.[9,24] Outbreaks of Hib pneumonia are also mostly found among alcoholic homeless patients.[3,9]

The most common organisms responsible for community acquired pneumonia in the homeless are *Streptococcus pneumoniae, Staphylococcus aureus,* and *H influenzae b.* Aspiration pneumonia is also frequent and organisms include anaerobes like peptostreptococcus, *Fusobacterium nucleatum*, Prevotella and bacteroides species. *Pneumocystis carinii* can be found in HIV positive individuals.[20,21,22]

Vaccination against pneumococcal pneumonia is one method of reducing invasive pneumococcal disease in shelters.[25] The Canadian National Advisory Committee on Immunization (NACI) recommends the use of 23-valent pneumococcal polysaccharide vaccine (PPV-23) in the homeless, those who use illicit drugs, HIV infected individuals and those with other chronic conditions such as COPD that are disproportionately higher in the homeless. Vaccination of hard to reach populations like the homeless can be challenging and a 1999 vaccination campaign in Edmonton addressed this issue by targeting as many sites as possible including single room occupancy hotels, soup kitchens, community agencies, needle exchanges, pubs, parks and alleys. The year following the campaign, there was a decrease in the amount of emergency department visits for pneumonia (863 compared to 646), and a decrease in admissions for pneumonia.[22] Vaccination is also the best way to prevent Hib pneumonia in at-risk persons who are not immune.[23]

Special considerations for pneumonia in the homeless include keeping a high index of suspicion for aspiration in those who abuse drugs and alcohol. One must also consider the difficulty of completing antibiotic regimens especially those with frequent dosing. Furthermore, there is often no safe storage for medications or a place to convalesce with closures of shelters during the day. Hospitalization or admission in a medical respite unit is worthwhile to ensure proper treatment.[21] Smoking cessation is another important arm of prevention although it is often overlooked in the homeless due to falsely assumed lack of motivation.[6]

Influenza

Influenza affects millions of Americans per year and results in 100,000 hospitalizations and 36,000 deaths annually. Influenza can result in secondary pneumonia and exacerbations of COPD or asthma.[26] Despite the large morbidity and mortality associated with the virus, influenza among the homeless is very poorly studied. A New York-based study of 3 shelters evaluated 4,319 charts for influenza-like illness with 59 recorded cases, less than one fourth of which had been vaccinated. Vaccination against influenza has been advocated for in those at increased risk of influenza and pneumonia including the homeless, HIV-infected and those with COPD.[27] Influenza vaccination remains underutilized and organized efforts concentrated over a day or week to vaccinate all shelter residents and staff is suggested.[26] Various strategies for improving vaccination rates include educational campaigns, improving patient-provider interactions, broadening the provider base, adoption of standing orders for immunization administration, and promoting wider availability and access to vaccine at the structural level.[28]

Conclusion

Homeless individuals are at increased risk of respiratory infections such as tuberculosis, influenza and pneumonia due to *S pneumoniae, S aureus, H influenzae b* and anaerobes. Risk factors include overcrowding, increased pathogen exposure and host factors such as alcoholism, smoking, drug abuse, HIV co-infection and chronic lung disease. Morbidity, mortality and complications are greater in these specific populations and outbreaks are common. Diagnosis and treatment non-compliance are serious challenges. It is important to remember that respiratory infections and their complications in the homeless are largely influenced by social factors. Mindfulness of the unique risks and challenges associated with this population is important. It is only through comprehensive programs that involve initiatives like screening, immunization, low threshold for hospitalization, smoking cessation, and incentives or education to increase compliance, that effective prevention and

treatment of respiratory infections in the homeless can be attained.

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A case of a middle-aged man with a neck mass

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The differential diagnosis of a neck mass can be extensive. In this short publication we will focus on an unusual neck mass whose features suggested that of extrapulmonary tuberculosis (TB). Though TB is endemic is some developing parts of the world, its rates of infection have drastically decreased in developed countries and the prevalence has remained relatively low. However with the emergence of AIDS and multi-drug resistant tuberculosis, we have seen a resurgence of TB infections. Though pulmonary TB is by far the most common presentation of tuberculosis, several extrapulmonary manifestations can present clinically. The presentation of interest that will be discussed in this article is Scrofula – the involvement of TB in the lymphatic system of the neck.

A 45-year-old man of Indian ethnicity presented to the General Surgery Outpatient Clinic complaining of a left-sided, palpable, non-tender mass above the clavicle. The swelling had developed over a period of several weeks and had been progressively increasing in size. He was concerned about malignancy. There was no history of recent viral infections, fever, chills, weight loss, sweats, or any other systemic symptoms. He was otherwise healthy, active and worked at a marketing firm. The patient's past medical and surgical history was unremarkable. He lived alone in an apartment and had no pets. Two years previously he visited India for one week. The patient did not appear sick and was in no discomfort. His oral temperature was $36.7^{o}C$, pulse 70bpm with a blood pressure of 140/70mmHg. A left-sided slightly indurated, non-tender 5cm supraclavicular mass was present just lateral to the sternocleidomastoid muscle. The overlying skin was slightly erythematous but there was minimal tenderness. The oral cavity, face and scalp were normal. There was no enlargement of axillary or inguinal nodes and no hepatosplenomegaly.

The white blood cell (WBC) count was normal and the erythrocyte sedimentation rate (ESR) and C-reactive protein were mildly elevated. An urgent contrast-enhanced computed tomography (CT) scan of the neck and chest showed a 2.8 cm x 5.3 cm well delineated soft tissue mass with a central area of lower attenuation. It was interpreted as a necrotic lymph node and lymphoma, metastatic cancer and infection were listed in the differential diagnosis. There was no mediastinal adenopathy and no pulmonary nodules. Four days after the initial consultation the mass was larger and fluctuant. Using local anaesthesia it was incised and thick pus without any odour was drained. Gram stain of the pus showed no organisms and routine anaerobic and aerobic cultures were negative. Stain for Acid Fast bacilli was negative and the culture for TB are still pending. When seen three weeks after the drainage, mass had resolved and the site of the incision was almost closed.

Because of the patients presentation with a "cold abscess" (lack of locally marked findings of redness and tenderness and absence of systemic findings of inflammation), scrofula was entertained in the initial differential diagnosis. Scrofula is the term for tuberculous cervical lymphadenitis. Its origin is the latin word meaning "brood sow". Scrofula has been known to afflict people since antiquity. In the middle ages it was believed that the royal touch of the king could cure the disease, hence it was known as the King's Evil. Kings were thought to have

received this power due to their descent from Edward the Confessor. Elaborate healing rituals were performed by monarchs to heal the afflicted of this disease. In 1768, the Englishman John Morley produced a handbook "Essay on the nature and cure of scrophulous disorders" which first described the typical symptoms and prognostic factors.[1] Epidemiologically, 95% of the scrofula cases in adults, and 8% of cases in children, are caused by Mycobacterium tuberculosis. The rest are caused by atypical mycobacterium or nontuberculous mycobacterium (NTM). With the vast decrease of tuberculosis in the second half of the 20th century, scrofula became a very rare disease, however with the appearance AIDS it has shown a resurgence, and presently affects about 5% of severely immunocompromised patients. TB is responsible for up to 43 percent of all of peripheral lymphadenopathy in the developing world. Tuberculous lymphadenitis occurs in more than 4 children per 1000.[2]

The most usual signs and symptoms are the appearance of a chronic, painless mass in the neck, which is persistent and progressive. The mass is referred to as a "cold abscess", because there are minimal findings of acute inflammation accompanying local and the overlying skin acquires a violaceous color. Scrofula caused by Mycobacterium tuberculosis is usually accompanied by other symptoms of the disease, such as fever, chills, malaise and weight loss in about 43% of the patients. As the lesion progresses, skin becomes adherent to the mass and it may rupture spontaneously, forming a sinus and an open wound.[3]

The diagnosis of scrofula definitively is made by histology and culture of lymph node material. Other supportive tests that may be useful to raise suspicion include a positive PPD skin test and chest radiography indicating pleural thickening and apical fibrosis suggestive of previous TB.[4] Fine needle aspirate (FNA) in seronegative HIV patients using conventional cytology, microscopy and culture has lead to inconsistent results,[5] but one study report a sensitivity of 77 percent and specificity of 93%.[6] It is generally accepted that FNA is more valuable

in HIV-infected patients.[7] With new polymerase chain reaction (PCR) techniques some studies have found FNA to be almost equally sensitive to a lymph node biopsy.[8] Ziehl-Neelsen staining of FNAs was positive in 87 percent patients with a final diagnosis of TB according to one study.[9] Excisional node biopsy can be performed if FNA and PCR are negative. A finding of caseating granulomas on histopathology is highly suggestive of TB.[10] Finally TB can also be elusive to culture taking up to 4-6 weeks but sensitivity testing can perform on the isolated organisms.[11] In the patient described here, cultures for TB are still pending to confirm the diagnosis as mentioned earlier.

The mainstay of treatment for Scrofula has shifted from excisional biopsy to antitubercular agents. Treatment should be initiated before confirmative cultures return from the lab. The optimal duration has been found to be six months with multi-drug therapy including isoniazid, rifampin and pyrazinamide.[12] Often patients return early after initiation of treatment because of a paradoxical increase in the lymph node size due to an immune response to the mycobacteria.[13] Response to therapy is excellent with relapse rates reported at 3.5%.[14]

His preliminary microbiology results were negative for acid-fast bacilli and cultures up to one month did not show any organisms, however TB can be difficult to culture and the lab keeps cultures up to eight weeks to be certain. Resolution of the inflammatory mass after drainage would be expected, but a persistent draining sinus would be expected if TB is the underlying organism. Our suspicion of scrofula remains probable given the classical clinical presentation, negative cultures for typical aerobic and anaerobic bacterium, and negative chest X-ray for active pulmonary disease.

Due to international travel and the prevalence of TB worldwide scrofula is important to investigate especially due to the high mortality of disseminated TB and curative potential antitubercular medications. HIV positive patients and travellers to regions with high prevalence of TB should raise the suspicion of scrofula since

these groups are at higher risk.[15] Therefore, as long as TB is around Scrofula should remain on the differential for unexplained neck masses.

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Antibiotic resistance knowledge in the elderly

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Antibiotic resistance (ABR) is a growing health care problem. Literature suggests a lack of awareness may lead patients to pressure physicians towards inappropriate prescribing practices. Very little is known about what seniors know about ABR. This pilot study investigated knowledge of antibiotic use, expectations regarding the prescription of antibiotics and awareness of ABR in a community dwelling elderly population. Thirty-eight subjects (age ≥65) were interviewed at a London senior's centre using a structured survey tool that explored knowledge and expectations about antibiotic use. Results reveal that 66% of respondents were familiar with the term 'antibiotic resistance' and that 90% felt it was an important health care issue. Fifty-six percent of respondents obtained this information through media-related sources, and only 17% through their family physician (FP). However, the majority of respondents (90%) felt that it was the role of the FP to inform the general public about the issue. Regarding patient knowledge, 26% of respondents believed that antibiotics would help them recover from a common cold and 50% expected to receive antibiotics if they visited their FP for a cold. Of those patients who had recently been prescribed antibiotics, only 50% completed their prescribed course. These results illustrate the lack of knowledge held by elders regarding appropriate use of antibiotics and a significant discord between their expectations of their FP and the role FPs might play in educating patients about proper antibiotic use. Study methods and the survey tool should be validated in larger future studies.

Introduction

ABR is an important healthcare issue that has significant implications for both the individual patient and for society as a whole.[1-5] Several studies have shown that knowledge of ABR is lacking in some of the more educated segments of the North American population; however, literature regarding the knowledge of ABR among the elderly population, a group which uses a disproportionately large amount of antibiotics, is limited. Further, many physicians lack knowledge of proper prescribing practices.[6-7] Improper antibiotic prescribing practices may lead to their unnecessary use and subsequently may contribute to the proliferation of resistant bacteria. Thus, correcting these practices could lead to a slowed increase in antibiotic resistance.

The lack of patient knowledge regarding proper antibiotic usage has been shown in several studies to directly influence patient expectations from their physician encounters.[8-9] Lack of education among patients often leads to pressure on physicians to prescribe inappropriately. Research has shown that physicians are especially likely to comply with such requests from elderly patients within their practice.[10-13] One recent study found that 46% of general internists in a US hospital believed that patient expectations was one of the most important causes of antibiotic resistance.[7]

Another significant cause of ABR is widespread misunderstanding regarding the importance of completing prescribed courses of antibiotics.[10,14] This knowledge is particularly lacking among older adults, as is health care knowledge in general.[15] Studies have shown that increased knowledge about medications leads to significant improvement in adherence and compliance with treatment regimens. This emphasizes the importance of assessing the knowledge of elderly patients regarding ABR and

educating this patient population about the importance of adhering to a prescribed antibiotic regime.[9]

With the current lack of information on the knowledge of ABR and patterns of antibiotic use among the elderly, we designed a pilot study to better understand this important healthcare issue, specifically targeting a sample of community dwelling elders in London, Ontario. We sought to understand patient expectations of their physicians regarding the prescription of antibiotics, patient attitudes towards antibiotics, antibiotic usage patterns, and patient knowledge and understanding of the concept of ABR.

Methods

A standardized survey tool was administered through personal interviews by the student investigators at a local community centre over a period of three days in March-April 2007. Subjects were excluded if they were less than 65 years of age or residing in a long-term care or retirement home. A community dwelling population was targeted under the premise that they would have more control over their medication usage patterns than those living in more institutional settings.

Participants were not solicited. Rather, study participants voluntarily approached the student investigator's table located in the lobby of the community centre. After obtaining consent, individual interviews were conducted by the student investigators. No personal identifiers were collected and no remuneration was provided. At the completion of the interview, a Letter of Information and a Health Canada information sheet regarding ABR were provided to each study participant to further their

knowledge of this issue.

Approval for this study was obtained from the Office of Research Ethics at The University of Western Ontario.

Results

Thirty-eight elders with a mean age of 77 years (range: 65-92 years) were interviewed. Sixty-eight percent were female, 100% had been employed at some time in their lives, and 97% reported currently having a FP (mean duration of professional relationship: 14.4 years).

Regarding elders' expectations of their physicians, 24% indicated they would visit a physician for common cold symptoms such as cough, runny nose and a fever. Among those who would visit their FP for a cold, 56% expected an antibiotic prescription for their cold. Forty-seven percent of subjects believed that doctors usually prescribed antibiotics if patients felt they were needed.

Regarding participant attitude toward antibiotic use, 87% of respondents felt they should not take antibiotics to prevent them from getting a more serious illness when they had a cold, whereas 26.3% believed that antibiotics would help them to "get better more quickly" from a cold. Half of all elders interviewed believed that if they were sick enough to visit a physician, they would expect an antibiotic prescription (Table 1). Of those interviewed, 16% had used antibiotics within the last 4 weeks, with only 50% completing the course of antibiotics they had been prescribed.

Sixty-six percent of respondents were familiar with the term 'antibiotic resistance'. After

Table 1: Attitudes towards antibiotic use among community-dwelling elders

Item	% Agree	% Disagree	% Unsure
When I get a cold, I should take antibiotics to prevent from getting a more serious illness.	10.5% (4)	86.9% (33)	2.6% (1)
When I get a cold, antibiotics help me to get better more quickly.	26.3% (10)	63.2% (24)	10.5% (4)
By the time I'm sick enough to visit GP from cold, I expect an antibiotic.	50.0% (19)	47.4% (18)	2.6% (1)

Note: the number in the parentheses is the number of study respondents with this response.

being read a paragraph that described ABR, 92% felt this to be an important healthcare issue. When asked who should inform consumers about the issue of ABR, 90% of respondents felt it should be physicians, 55% stated pharmacists and 29% thought the media should educate the public. Of those patients who had heard or read about ABR, most indicated that they received this information through public media (58%), 17% had received this information through physicians and 8% through their pharmacists. Surprisingly, 84% indicated that their FP had never discussed the issue of ABR, and 97% had never received written information about antibiotic resistance from their FP (Table 2).

Discussion

ABR is a growing health care concern. Recent initiatives by Health Canada strive toward educating the public about appropriate antibiotic use and preventing unnecessary antibiotic use. This pilot study set out to investigate the awareness and knowledge surrounding these elders. The majority (92%) of the respondents considered ABR a very important healthcare issue. However, there was large discrepancy between patient expectations and the information about antibiotic use provided by their healthcare professionals.

Almost 90% of respondents felt that FPs should be responsible for informing patients, whereas only 17% of the respondents had actually heard about the issue from their FP. Surprisingly, it was media sources that had exposed most of the respondents to the issue. This is an important finding as the nature of the patient-physician relationship makes it one of the primary vehicles for reducing the number of unnecessary antibiotic prescriptions. Most patients have a strong trust in their physicians and educating elders regarding proper antibiotic use may promote better health outcomes for the patient and slow the increase of antibiotic resistance.

Table 2: Knowledge of antibiotic resistance among community-dwelling elders

(a) Question	% Agree	% Disagree	% Unsure
Are you familiar with the term 'Antibiotic Resistance'?	65.8% (25)	34.2% (13)	0%
Do you think this is an important healthcare issue?	92.1% (35)	2.6% (1)	5.3% (2)
Have you ever heard or read about Antibiotic Resistance?	63.2% (24)	36.8% (14)	0%
Has your Family Physician (FP) ever talked to you about Antibiotic Resistance?	15.8% (6)	84.2% (32)	0%
Has your FP ever given your reading materials about Antibiotic Resistance?	2.6% (1)	97.4% (37)	0%
Does your pharmacist talk to you about your prescription medications?	84.2% (32)	15.8% (6)	0%

Note: the number in the parentheses is the number of study respondents with this response.

(b) Question	Response	
Who should tell people about antibiotic resistance?	Doctor:	89.5% (34)
	Pharmacist:	55.3% (21)
	Media:	29.0% (11)
	Other:	5.3% (2)
Among those who had heard or read about antibiotic resistance (n=24): Where did you get this information?	Media:	58.4% (14)
	Doctor:	16.7% (4)
	Family/Friend:	16.7% (4)
	Pharmacist:	8.3% (2)
	Other:	8.3% (2)
	Nurse:	4.2% (1)

Note: the number in the parentheses is the number of study respondents with this response; percentages do not total 100% as participants could select more than one option.

Although a majority of subjects stated that they were familiar with the term 'antibiotic resistance', our data indicate that this awareness did not necessarily equate to evidence-based antibiotic use. Twenty-four percent of respondents went to their doctor for cold symptoms and half of these patients expected a prescription for antibiotics. While 87% of respondents did not believe that antibiotics could prevent a cold, 37% believed that they could get better faster using antibiotics. These results suggest that even though a large number of subjects were familiar with the term 'antibiotic resistance', this did not translate to an understanding regarding appropriate use of antibiotics or knowledge of appropriate antibiotic use. This is thought provoking considering that the majority of subjects heard about ABR from media sources. Whether education of patients by physicians would lead to improved knowledge and behaviors around the use of antibiotics needs further evaluation.

While this small pilot study raised some interesting points, further research on the topic will be needed to support these initial observations. As with all studies, there are several limitations. Both the small sample size and use of a population attending a community centre make it difficult to generalize these findings to all community dwelling elders. A population regularly attending a community centre may differ significantly from a more sedentary population with respect to knowledge, attitudes, self-advocacy and health behaviors. Further, although the study questionnaire has face validity, further evaluation of the tool is needed.

This study suggests that lack of patient knowledge regarding contributors to the development of ABR, as well as patient expectations of physicians and the prescribing practices of physicians could all be targeted in an attempt to reduce the incidence of ABR. Further research is required to better understand this issue and to evaluate the efficacy of potential strategies in reducing the development of ABR.

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