ANNALS
ACADEMY OF MEDICINE, SINGAPORE
COMMITTED TO SPECIALIST EDUCATION AND TRAINING SINCE 1957

VOLUME 48 | NUMBER 6 | FREE PAPERS | JUNE 2019 MCI (P) 050/07/2018

"Opportunity is always coming but never knocks on the door. You have to get up and meet him."

Bangambiki Habyarimana
The Great Pearl of Wisdom
Rwandan writer and blogger

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Editorial

Post-Traumatic Stress Disorder in Road Traffic Accident Survivors – Can We Do More?

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Medicine and technology are closely intertwined. Technology has opened a plethora of possibilities to medical treatments with better imaging and diagnostic devices, novel intervention techniques and countless medication choices. It has also enhanced the standard of living and created ease and accessibility in modern-day commute. Traditional means of transportation such as cars and motorcycles have been equipped with more powerful engines that are able to accelerate faster and attain higher speeds in a shorter time. Personal mobility devices (PMDs) such as electronic scooters, motorised wheelchairs and power-assisted bicycles are now commonly used and can reach cruising speeds of up to 50 km/h. While technology has no doubt improved the quality of life, it has proven to be a double-edged sword and created a new set of problems. The number of more severe road traffic accidents (RTAs) have spiked and survivors often present with long-term psychiatric disabilities and impaired health-related quality of life.[1]

Unfortunately, it is difficult to prevent RTAs. In a highly congested city-state such as Singapore with its dense population and heavy vehicular traffic, it only takes a momentary lapse in judgement by a driver or pedestrian before a RTA occurs. When it happens, victims are promptly evacuated from the accident scene and rushed to the nearest hospital where they undergo medical interventions and are stabilised. Upon discharge, they are usually given a follow-up consultation with a physician.

Up to 13% of RTA survivors[1] present with symptoms of acute stress disorder (ASD) within the first month of RTA and up to 21% have subclinical presentations of ASD. ASD can present intrusion symptoms such as recurrent, involuntary and intrusive distressing memories of the traumatic event, recurrent distressing dreams, dissociative reactions, persistent inability to experience positive emotions and intense or prolonged psychological distress or marked psychological reactions in response to internal or external cues that symbolise or resemble an aspect of the traumatic event. Survivors may also experience dissociative symptoms such as altered sense of reality of one's surroundings or of oneself, inability to remember an important aspect of the traumatic event and avoidance symptoms including avoiding distressing memories, thoughts or feelings about or closely associated with the traumatic event or external reminders that may arouse them. Lastly, they may have arousal symptoms and may experience sleep disturbances, irritability, hypervigilance, poor concentration and exaggerated startle response. Without intervention, 78% of ASD and 60% of subclinical ASD[1] patients develop post-traumatic stress disorder (PTSD) 1 month after a RTA.

A meta-analysis of 15 studies that included 6804 RTA survivors has found a pooled PTSD prevalence of 22.25% (95% confidence interval, 16.71-28.33).[2] Eventually, 10% of survivors developed chronic depressive or anxiety disorders.[3] Trauma severity, perceived threat, dissociation during the accident, female gender, prior emotional problems and litigation subsequent to an RTA were identified as predictors of PTSD.[4,5]

A retrospective review of 1038 RTA fatalities in Singapore from 2000 to 2004 showed that the mean age of victims was 36 years old, 78% of whom were from the economically productive age group of 15 to 65 years old.[6] RTA survivors often share the same demographics and PTSD threatens to pose a long-term financial, health and social burden on them.[7,8]

Various legislations and measures have been implemented by the authorities to reduce RTA. They include lowering the cruising speed of motor vehicles, erecting traffic signals that demarcate vehicular and pedestrian traffic, handing out harsher fines and issuing public sanctions to deter reckless behaviour. After several accidents that involved PMDs, the Active Mobility Act was legislated in 2017 to arrest the spike in the number of reported incidents. PMDs of all types are now restricted to a standard size and capped at a maximum speed of

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25 km/h to reduce the severity of injuries sustained in an accident. Owners of PMDs are mandated to register their devices with the authorities. Guidelines on the usage of PMDs on the roads are also disseminated to the public. These measures may help to ameliorate trauma severity, perceived threat and dissociation by reducing RTA rate. They can also reduce the force of impact in an accident and lower the danger such mobility devices pose to the public when they are used in areas other than those designated for their use. They may also lead to lighter sentences for PMD users who are convicted for violating the legislations.

A change in the modus operandi of managing RTA survivors in the hospital emergency setting can lead to early identification and treatment of PTSD and prevent long-term debilitation in patients. Medical resuscitation and stabilisation remained the primary focus in RTA victims in Accident and Emergency services. Since victims may still be in a state of shock and distress, any psychological interventions provided at this point have been shown to be ineffective as they may not respond to them.[9] Early interventions may also disrupt the human body's innate psychological defence against fear and distress. Information and advice on ASD and PTSD may, however, be provided to them to increase their awareness of both conditions.[5]

Screening services can be established in hospitals to review RTA survivors 2 weeks after the incident. Nurses can screen them with a questionnaire such as the Impact of Event Scale-Revised (IES-R).[10] It is easy to administer and provides a structured way for patients to communicate distress when they find it difficult to express themselves. The IES-R comprises 22 questions that address intrusion, avoidance and hyperarousal symptoms. Patients can indicate their response to each question on a scale of 0 to 4. A summary score >24 will benefit from referral to psychiatric services.

After patients are identified in early screening, psychiatrists can institute medical treatments and psychological interventions. ASD progression to full-blown PTSD and, subsequently, chronic PTSD can be halted. Psychiatric comorbidities such as anxiety and depression[3,5]—which often manifest in chronic PTSD—will also be addressed after screening services. The management algorithm for cases that are identified early will become easier and fewer drugs and psychotherapy sessions are also needed. The long-term financial, medical and social effects on patients are reduced and they also enjoy a better quality of life with an earlier return to full functional status. There is also less wastage of resources in hospitals.

Most RTA survivors with chronic PTSD were able-bodied individuals. They were treated by medical services and discharged early since they appeared well during treatment. They could ambulate and talk in a relevant but superficial manner as long as the topic of trauma was not discussed. Their avoidant behaviours are often interpreted and accepted as "normal" since they had experienced a traumatic episode. This acceptance often resulted in aggravation and progression of PTSD symptoms and would eventually incapacitate them, leading to a late referral to psychiatric services. While screening services for asthma, diabetes and hypertension by nursing staff are common in hospitals, it is perhaps time for hospital stakeholders to consider a similar service for RTA survivors to change their clinical trajectory towards a more optimistic outcome.

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Original Article

Multidomain Geriatric Screen and Physical Fitness Assessment Identify Prefrailty/Frailty and Potentially Modifiable Risk Factors in Community-Dwelling Older Adults

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Abstract

Introduction: Frailty begins in middle life and manifests as a decline in functional fitness. We described a model for community frailty screening and factors associated with prefrailty and frailty and fitness measures to distinguish prefrail/frail from robust older adults. We also compared the Fatigue, Resistance, Ambulation, Illnesses and Loss of weight (FRAIL) scale against Fried frailty phenotype and Frailty Index (FI). Materials and Methods: Community-dwelling adults ≥55 years old were designated robust, prefrail or frail using FRAIL. The multidomain geriatric screen included social profiling and cognitive, psychological and nutritional assessments. Physical fitness assessments included flexibility, grip strength, upper limb dexterity, lower body strength and power, tandem and dynamic balance and cardiorespiratory endurance. Results: In 135 subjects, 99 (73.3%) were robust, 34 (25.2%) were prefrail and 2 (1.5%) were frail. After adjusting for age and sex, depression (odds ratio [OR], 2.90; 95% confidence interval [CI], 1.05-7.90; *P* = 0.040) and malnutrition (OR, 6.07; 95% CI, 2.52-14.64; *P* <0.001) were independently associated with prefrailty/frailty. Prefrail/frail participants had significantly poorer performance in upper limb dexterity (*P* = 0.030), lower limb power (*P* = 0.003), tandem and dynamic balance (*P* = 0.031) and endurance (*P* = 0.006). Except for balance and flexibility, all fitness measures differentiated prefrail/frail from robust women. In men, only lower body strength was significantly associated with frailty. Area under receiver operating characteristic curves for FRAIL against FI and Fried were 0.808 (0.688-0.927, *P* <0.001) and 0.645 (0.546-0.744, *P* = 0.005), respectively. Conclusion: Mood and nutrition are targets in frailty prevention. Physical fitness declines early in frailty and manifests differentially in both genders.

Ann Acad Med Singapore 2019;48:171-80

Key words: Elderly, Frail, Function

Introduction

Frailty is a geriatric syndrome characterised by increased vulnerability to adverse health outcomes following minor stressor events.[1] There are 2 established models in the study of frailty: physical frailty phenotype and cumulative deficit model.[2,3] Brief screening instruments have also been developed, but frailty assessment in the community is not widely endorsed. This may reflect concerns about the feasibility of systematic search for cases of frail elderly and uncertainty towards the utility of frailty instruments in informing clinical practice.

Additionally, Comprehensive Geriatric Assessment (CGA) remains the current standard in management of underlying causes of extreme vulnerability,[4] but it is constrained by lack of resources in many contexts. As a multidimensional, inter-disciplinary diagnostic tool to effectively examine multiple health domains—functional, medical and psychological—in a frail elderly person, CGA relies on a core team that comprises a geriatrician, nurse, physiotherapist, occupational therapist and social worker along with appropriate specialty referrals to deliver an individualised care plan. Community CGA programmes

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with a preventive focus have typically involved home assessments and follow-up visits which may not be efficient as they are an expensive model for primary case finding.[5] Instead, outpatient CGA consultations that target patients at higher risk of hospitalisation and address their adherence to programme recommendations are more likely to be effective.[5] Hence, brief evaluation tools such as Rapid Geriatric Assessment[6]—which may be completed without extensive geriatric training—may facilitate wider community screening and referrals for a full CGA.

When measuring frailty, one must ensure that the measurement tool has been validated and its choice is guided by the objectives of the assessment and resources available at one's disposal.[7] The self-reported Fatigue, Resistance, Ambulation, Illnesses and Loss of weight (FRAIL) scale—combining elements from Fried's frailty phenotype and the multidimensional Frailty Index (FI)—appeals because of its sheer simplicity of use and is recommended for clinical use by the International Academy on Nutrition and Aging (IANA).[8] As a rapid screening tool, FRAIL has demonstrated its feasibility to be used as a stepping stone to a more comprehensive evaluation. However, poor follow-up attendance may limit the effectiveness of screening.[9,10] Building on the work of Woo et al,[10] we developed a community programme that integrates screening for physical frailty with its potential determinants to guide targeted interventions.

Unlike frailty, maintenance of functional fitness is associated with successful ageing.[11,12] However, a decline in physical fitness—represented by agility, endurance, flexibility and strength—may begin as early as in middle life. After the age of 50, the annual decline of 1% to 2% in muscle mass is matched by a progressive loss of 1.5% to 3% in muscle strength every year.[13] Additionally, a significant drop in aerobic capacity is observed after the age of 40 and this loss may reach as much as 30% by the age of 65.[14] By convention, weakness in frailty criteria has included only grip strength and it is the most salient feature[15,16] even though loss of muscle strength in the lower limbs is typically greater than in upper limbs.[12,17] It is also interesting to note that physical exhaustion is observed much later in the frailty cycle despite the loss of nearly 10% of aerobic ability after every decade.[15,18] Since deterioration in physical fitness typically precedes functional dependence,[19] a comprehensive physical fitness assessment can be included in conventional measures of frailty to facilitate early detection and prevention of frailty.

We described our experience with a pilot community frailty screening programme that integrates multidomain geriatric screen with a physical fitness assessment. Using data from our pilot cohort, we examined: 1) potentially modifiable factors associated with prefrailty and frailty which were defined using FRAIL; and 2) physical fitness measures that differentiate prefrail and frail older adults from their robust counterparts (with specific reference to gender differences). We hypothesised that a multidomain geriatric screen will allow identification of clinical risk factors for frailty in community-dwelling older adults, and that prefrail/frail older adults will perform poorer across a battery of physical fitness tests. Finally, we compared the diagnostic performance of FRAIL against Fried's frailty phenotype and FI.

Materials and Methods

The Individual Physical Proficiency Test for Seniors (IPPT-S) is a community-based programme that was designed to promote fitness and prevent or delay frailty progression in older adults. For ease of access, we designed IPPT-S as a mobile platform based at the void decks of public housing blocks, senior activity centres (SACs), senior care centres (SCCs) or community clubs. The platform is maintained at each site for 2 to 3 weeks and is managed by members of our multidisciplinary team. Each site is visited yearly for follow-up. This is an ongoing prospective cohort study and participants have provided written informed consent. Ethics approval was obtained from SingHealth Institutional Review Board.

Eligible participants must be ≥55 years old, community-dwelling and ambulate independently (with or without walking aid). Individuals who were unable to ambulate at least 4 m independently were excluded, as well as residents of sheltered and nursing homes. As a pragmatic programme that seeks to extend frailty assessment to the community, we worked systematically to reach seniors through all the SACs and resident committees located in the northeastern region of Singapore which is served by a regional healthcare facility, Sengkang General Hospital.

Multidomain Geriatric Screen

The multidomain geriatric screen included frailty screening and cognitive, psychological and nutritional assessments using a structured questionnaire administered by a trained interviewer. We used the 5-item FRAIL scale to assess self-reported fatigue, resistance, ambulation, illnesses and weight loss[9] and to categorise participants as frail (score of 3-5), prefrail (1-2) or robust (0). Cognition was assessed using the locally validated version of Chinese Mini Mental State Examination (CMMSE).[20] Mood was assessed using the 15-item Geriatric Depression Scale (GDS).[21] Nutritional status was assessed using the Mini Nutritional Assessment-Short Form (MNA-SF) questionnaire.[22,23]

To assess social vulnerability in our participants, we adapted questions from Woo et al.[24] The questions exam-

ined 3 groups of social determinants: socioeconomic status (question on job type was modified to active employment status and housing type was included as another surrogate of socioeconomic status in the local context), lifestyle factors (questions on dietary intake were excluded since nutrition was assessed separately in our study) and social support and network.[24]

Functional performance in activities of daily living (ADL) and instrumental ADL (IADL) was evaluated using the Barthel Index and Lawton and Brody's scale, respectively.[25,26] Data on falls in the past year was captured via standardised questions.

Frailty Phenotype and Cumulative Deficit Model

We modified Fried's criteria to assess physical frailty with the use of 5 components: exhaustion (using the question on fatigue from FRAIL scale), slow gait, weak grip strength, low body mass index (BMI) <18.5 kg/m^2 and low physical activity.[2] Frailty is indicated when the result is positive for 3 components and prefrailty is identified when 1 to 2 components are present.

Grip strength was measured with a JAMAR Plus Hand Dynamometer (Sammons Preston, Bolingbrook, IL, USA). The higher reading taken from 2 trials for each hand was used for analysis. Gait speed was measured based on duration of walking 10 m at a normal pace. Weakness (<18 kg for women and <26 kg for men) and slowness (≤0.8 m/s) were measured against reference values described in the Asian Working Group for Sarcopenia.[27] We used Physical Activity Vital Sign to quantify engagement in moderate to vigorous physical activity[28] and used the lowest quartile as cut-off for physical inactivity.

FI was constructed based on 34 items that included medical comorbidities, functional performance, cognitive and sensory impairment and psychosocial problems. They were derived from data captured in the multidomain geriatric screen.[29] FI was tabulated based on the number of deficits identified in each participant against the maximum number of deficits listed in the scale. Based on their FI results, participants were designated frail (≥0.25), prefrail (>0.08 and <0.25) or robust (≤0.08).[30]

Physical Fitness Assessment

The physical fitness test was a modified version of the Senior Fitness Test.[31] Participants who reported feeling unwell during preassessment were exempted from fitness tests. Lower body strength and power was measured using the chair stand test. In this test, participants were instructed to rise as quickly as possible from a seated to a standing position, all the while keeping their arms folded across their chests.[32] The duration taken to complete 5 chair stands and their number completed within 30 seconds were documented.

Upper limb dexterity was assessed using the box-and-block test. Participants were instructed to briskly pick up blocks from 1 side of a box and place them on another side across a barrier. The number of blocks transferred within 1 minute was recorded.[33] Similar to grip strength, the higher reading taken from 2 trials for each arm was used for analysis.

Flexibility in the upper and lower body was measured using the back scratch and chair sit-and-reach tests, respectively.[31,34] Similarly, the higher reading from 2 attempts in each test was used in the analysis. In the back scratch test, participants were asked to place 1 hand over a shoulder and the other up the middle of their back with the fingers extended. The distance (in centimetres) in which the middle fingers of both hands overlapped with each other or failed to meet was recorded as positive (+) and negative (-) scores, respectively. In the chair sit-and-reach test, participants sat on the edge of a chair with 1 leg extended before them and reached forward to touch their toes with their fingers. Likewise, the distance (in centimetres) in which the extended third finger reached beyond the toe or failed to touch the toe was documented as positive (+) and negative (-), respectively.

Dynamic balance or agility was assessed on the Timed Up and Go (TUG) test. In this test, participants were requested to rise from a seated position, walk briskly round a cone that was placed 3 m away from their chair, return to the chair and resume a fully seated position.[35] Additionally, we used the side-by-side, semi-tandem and full-tandem standing tests in the Short Physical Performance Battery (SPPB) to assess their balance.[36]

Cardiorespiratory endurance was evaluated with the 6-minute walking test (6MWT). Participants had to walk down a 20-metre path with constant encouragement throughout the test. The distance traversed in 6 minutes was recorded and participants were allowed to rest at any time during the test.[37] We scored each participant on SPPB for a composite measure of physical performance and applied established cut-offs in the individual tests of gait speed, balance and chair stand.[36]

Statistical Analysis

Univariate analyses that compared robust against prefrail/frail subjects were performed with independent samples t-test and Mann-Whitney U test for parametric and non-parametric continuous variables. Chi-square and Fisher's Exact tests were performed on categorical variables. To identify risk factors that were independently associated with prefrailty/frailty, multiple logistic regres-

sion analysis was performed on univariate variables with P <0.1 and adjusted for age and gender.

To examine raw agreement between FRAIL against Fried and FI, kappa test was used to correct for chance agreement. Receiver operating characteristic (ROC) curve analysis was used to examine area under ROC curve (AUROC) for FRAIL against Fried and FI. Statistical analysis was performed using SPSS software version 24.0 (IBM, Armonk, NY, USA). All statistical tests were two-tailed and a value of $P \leq 0.05$ was considered statistically significant.

Results

A total of 135 participants with a mean age of 70.0 years were screened in 2 SACs. FRAIL showed 99 (73.3%) were robust, 34 (25.2%) were prefrail and 2 (1.5%) were frail. Since only 2 subjects were frail, they were grouped with prefrail participants for comparison against the robust group. Age, ethnicity and gender were similar between the robust and prefrail/frail groups.

We observed a trend of more prefrail/frail older adults who reported living alone than in the robust group (22.2% vs 10.1%, P = 0.067) and lacked a confidant (16.7% vs 8.1%, P = 0.082). Cognitive performance was similar in both groups (Table 1). However, prefrail/frail participants were significantly more likely to have GDS ≥5 (52.8% vs 16.2%, P <0.001) and at risk of malnutrition or were malnourished (P <0.001).

Of the 96 female participants, 23 (24.7%) were prefrail/frail. They were significantly more likely than their robust peers to live alone (30.4% vs 9.6%, P = 0.014) with higher prevalence of depression (52.2% vs 17.8%, P = 0.001) and malnutrition (P <0.001). In male participants, prevalence of prefrailty/frailty was 33.3% (Table 1). Prefrail/frail men reported less frequent contact with relatives or friends (P = 0.054). Compared to their robust counterparts, depression was significantly more prevalent in prefrail/frail men (53.8 vs 11.5%, P = 0.008) and they were significantly more likely to be at risk of malnutrition (53.8% vs 7.7%, P = 0.003).

Using prefrailty/frailty as the outcome variable, multiple logistic regression analysis of the entire cohort—which included social factors (living alone and lack of confidant), mood and nutritional status, as well as age and gender—revealed that depression (odds ratio [OR], 2.90; 95% confidence interval [CI], 1.05-7.90; P = 0.040) and malnutrition (OR, 6.07; 95% CI, 2.52-14.64; P <0.001) remained independently associated with prefrailty/frailty (Table 2).

In the fitness tests, 12 participants did not complete the full assessment after individual components (n = 7) or the full battery (n = 5) were omitted. They tended to be prefrail/frail compared to those who completed the full battery of fitness tests (6.1% vs 16.7%, P = 0.056).

Grip strength was similar in both groups but robust participants demonstrated superior performance in the box-and-block test against their prefrail/frail peers (mean ± standard deviation [SD], 45.5 ± 9.4 vs 41.4 ± 8.6; P = 0.030). Prefrail/frail participants took longer to complete 5 chair stands with a median time of 12.36 seconds (interquartile range [IQR], 9.72-16.57) against 10.48 seconds (IQR, 8.30-12.32) in their robust peers (P = 0.003). They also achieved significantly fewer stands in 30 seconds. Gait speed was significantly slower in the prefrail/frail group and they had significantly poorer (median, 10.69; IQR, 8.29-14.67) performance in tandem and dynamic balance than their robust (median, 9.33; IQR, 7.79-10.61) counterparts in the TUG test (P = 0.031). In 6MWT, en-durance was significantly worse in the prefrail/frail group than the robust group (mean ± SD, 367.8 ± 143.7 m vs 449.4 ± 121.2 m; P = 0.006). Total SPPB score was significantly lower in prefrail/frail subjects than in robust participants. When the analyses were repeated after frail participants were excluded, all fitness measures—with the exception of flexibility and grip strength—remained significantly worse in prefrail subjects than their robust peers (Table 3).

In female participants, all physical fitness components except balance and flexibility revealed significant differences between the robust and prefrail/frail groups. The latter group also had significantly lower SPPB scores. In men, only lower body strength and power significantly differentiated the robust from prefrail/frail subjects, although male prefrail/frail participants also exhibited lower endurance (P = 0.063).

On the FI, 6 participants had missing data. In the remaining 129 subjects, FI was significantly higher in the prefrail/frail compared to the robust (mean ± SD, 0.215 ± 0.092 vs 0.105 ± 0.066, P <0.001). The overall agreement between FRAIL and FI was 45.7% (kappa = 0.137, P = 0.013). A total of 126 participants fulfilled Fried's criteria and the overall agreement between FRAIL and Fried was 64.3% (kappa = 0.264, P = 0.001). In subjects who were identified as robust on FRAIL, 52.6% were prefrail on FI and 5.3% were frail. Against Fried, 36.2% of subjects who were assessed as robust on FRAIL would be considered prefrail but none of them met the criteria as frail (Table 4). AUROC for FRAIL against FI and Fried were 0.808 (0.688-0.927, P <0.001) and 0.645 (0.546-0.744, P = 0.005), respectively.

Discussion

Our study supports the feasibility of a community programme to detect prefrailty/frailty and its potentially

Table 1. Clinical Characteristics Associated with Prefrailty/Frailty

Variable	Aggregate (n = 135)			Women (n = 96)			Men (n = 39)		
	Robust (n = 99)	Prefrail/Frail (n = 36)	*P* Value	Robust (n = 73)	Prefrail/Frail (n = 23)	*P* Value	Robust (n = 26)	Prefrail/Frail (n = 13)	*P* Value
Age	69.2 (7.4)	68.4 (7.4)	0.586	68.8 (7.0)	70 (7.3)		70.3 (8.5)	65.6 (6.9)	0.093
Female gender (%)	73 (73.7)	23 (63.9)	0.264						
Ethnicity (%)			0.169			0.195			0.494
Chinese	80 (80.8)	25 (69.4)		60 (82.2)	15 (65.2)		20 (76.9)	10 (76.9)	
Malay	6 (6.1)	7 (19.4)		5 (6.8)	5 (21.7)		1 (3.8)	2 (15.4)	
Indian/Others	13 (13.2)	4 (11.1)		8 (11)	3 (13)		5 (19.2)	1 (7.7)	
Education (%)			0.904			0.853			0.919
Primary and below	57 (57.6)	19 (54.3)		50 (68.5)	15 (65.2)		7 (26.9)	4 (33.3)	
Secondary	33 (33.3)	12 (34.3)		19 (26)	6 (26.1)		14 (53.8)	6 (50)	
Tertiary	9 (9.1)	4 (11.4)		4 (5.5)	6 (6.3)		5 (19.2)	2 (16.7)	
Housing type (%)			0.185			0.455			0.109
1 – 2 room flat	35 (35.4)	19 (52.8)		26 (35.6)	11 (47.8)		9 (34.6)	8 (61.5)	
3 – 4 room flat	43 (43.4)	11 (30.6)		30 (40.1)	9 (39.1)		13 (50)	2 (15.4)	
5 room flat/private	21 (21.2)	6 (16.7)		17 (23.3)	3 (13)		4 (15.4)	3 (23.1)	
Active employment (%)	18 (18.2)	5 (13.9)	0.557	11 (15.1)	4 (17.4)	0.751	7 (26.9)	1 (7.7)	0.229
Disposable income (“fair/more than enough”, %)	58 (59.2)	20 (55.6)	0.706	42 (57.5)	11 (47.8)	0.414	16 (64)	9 (69.2)	1.00
Social support (%)									
Living alone	10 (10.1)	28 (22.2)	0.067	7 (9.6)	7 (30.4)	0.014	3 (11.5)	1 (7.7)	1.00
Attends religious/community activities	87 (87.9)	31 (86.1)	0.784	67 (91.8)	22 (95.7)	1.00	20 (76.9)	9 (69.2)	0.704
Lack of confidant	8 (8.1)	6 (16.7%)	0.082	6 (8.2)	4 (17.4)	0.209	2 (7.7)	2 (16.7)	0.577
Weekly contact with friends/relatives	53 (54.6)	11 (37.9%)	0.114	40 (56.3)	10 (52.6)	0.773	13 (50)	1 (10)	0.054
Current/ex-smoker	13 (13.1)	7 (19.4)	0.361	3 (4.1)	0	1.00	10 (38.5)	7 (53.8)	0.361
CMMSE									
0 – 28	24.7 (3.0)	24.3 (3.0)	0.502	24.5 (3.2)	24.1 (3.3)	0.597	25.2 (2.7)	24.6 (2.6)	0.523
<21 (impaired, %)	12 (12.1)	6 (16.7)	0.492	10 (13.7)	5 (21.7)	0.354	2 (7.7)	1 (7.7)	1.00
GDS									
0 – 15	2.3 (2.3)	5.8 (4.0)	<0.001	2.4 (2.5)	5.8 (4.0)	<0.001	2.1 (2.0)	5.6 (4.3)	0.014
≥5 (depression, %)	16 (16.2)	19 (52.8)	<0.001	13 (17.8)	12 (52.2)	0.001	3 (11.5)	7 (53.8)	0.008

BI: Barthel Index; BMI: Body mass index; CMMSE: Chinese Mini Mental State Examination; GDS: Geriatric Depression Scale; IADL: Instrumental activities of daily living; MNA-SF: Mini Nutritional Assessment-Short Form

Table 1. Clinical Characteristics Associated with Prefrailty/Frailty (Cont'd)

Variable	Aggregate (n = 135)			Women (n = 96)			Men (n = 39)		
	Robust (n = 99)	Prefrail/Frail (n = 36)	*P* Value	Robust (n = 73)	Prefrail/Frail (n = 23)	*P* Value	Robust (n = 26)	Prefrail/Frail (n = 13)	*P* Value
MNA-SF									
0 – 14	13 (12 – 14)	11 (9 – 13)	<0.001	13 (12 – 14)	11 (8 – 13)	<0.001	13.5 (12.75 – 14)	11 (9.5 – 14)	0.058
12 – 14 (normal, %)	86 (86.9)	15 (41.7)	<0.001	62 (84.9)	9 (39.1)	<0.001	24 (92.3)	6 (46.2)	0.003
8 – 11 (at risk of malnutrition, %)	12 (12.1)	16 (44.4)		10 (13.7)	9 (39.1)		2 (7.7)	7 (53.8)	
<8 (malnourished, %)	1 (1)	5 (13.9)		1 (1.4)	5 (21.7)		0	0	
BMI	25.1 (3.8)	26.4 (7.6)	0.330	25.1 (4.2)	26.9 (6.9)	0.244	25.2 (2.5)	28.4 (5.4)	0.055
Consequences									
BI	20 (20 – 20)	20 (19 – 20)	0.001	20 (20 – 20)	20 (18 – 20)	<0.001	20 (0 – 20)	20 (19.5 – 20)	0.713
IADL	23 (21 – 23)	22 (20 – 23)	0.206	23 (22 – 23)	23 (20 – 23)	0.362	23 (20 – 23)	22 (19.5 – 23)	0.648
>2 falls in past year (%)	2 (2.0)	4 (11.1)	0.076	1 (1.4)	2 (8.7)	0.095	1 (3.8)	2 (15.4)	0.018

BI: Barthel Index; BMI: Body mass index; CMMSE: Chinese Mini Mental State Examination; GDS: Geriatric Depression Scale; IADL: Instrumental activities of daily living; MNA-SF: Mini Nutritional Assessment-Short Form

modifiable determinants, particularly depression and malnutrition, for targeted intervention in older adults. Physical fitness—in addition to conventional measures of grip strength and gait speed—also declines early in the frailty continuum and may manifest differentially in older men and women.

In our cohort, the prevalence of prefrailty (25.2%) and frailty (1.5%) on FRAIL is lower than other studies that employed similar criteria.[9,38] This finding may be attributed to the younger profile of our cohort whose cut-off age of 55 is lower than age 65 in earlier studies.[10,38] Additionally, our participants were predominantly well and functionally independent and this was reflected in their high ADL and IADL scores. They have a low prevalence of frailty (1.6%) on Fried criteria. However, a higher prevalence of prefrailty (44.4%) was observed but this finding was consistent with studies that employed the phenotypic definition.[39]

By focusing on physical frailty as a specific syndrome in the multidomain geriatric screen, we were able to explore other domains that could potentially contribute to frailty. Our finding that depression and malnutrition contribute to frailty—even in the early prefrail state—concurs with similar findings in current literature and reinforces the clinical importance to assess both conditions when screening for frailty in the community.[39-41] Despite their poor nutritional status, higher BMI in prefrail/frail older men has the same impact as sarcopenic obesity on frailty in healthy community-dwelling older individuals.[42] The impact of social isolation on frailty is well reported and it is supported by the association between prefrailty/frailty and living alone or lack of a confidant in our participants.[40,43] Although prefrail/frail women were more likely to live alone in our study, contact with friends or relatives was notably less frequent in older prefrail/frail men. This suggests that social vulnerability may manifest differently in older men and women.

Contrary to our findings, a recent study from Hong Kong had found that the impact of living alone on frailty was positively associated in older men but was inversely associated in older women.[44] The apparent disparity may reflect culturally unique social factors and a need to further explore social support networks in our community-dwelling older adults.

Compared to muscle strength, muscle power exerts a greater impact on functional tasks such as navigating stairs and rising from a chair. The loss of power typically precedes—and even exceeds—a decline in strength with ageing.[45,46] This may explain the observed differential performance in lower limb power between robust and prefrail/frail older adults despite similar grip strength. The chair stand test—a measure of lower limb strength and

Table 2. Multiple Logistic Regression Analysis of Prefrailty/Frailty

Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Age	0.79 (0.920 – 1.042)	0.512
Female gender	0.454 (0.170 – 1.213)	0.115
Living alone	1.915 (0.490 – 7.480)	0.350
No one to turn to for help or confide in	1.669 (0.397 – 7.022)	0.485
Depression	2.898 (1.052 – 7.984)	0.040
Malnutrition risk/malnourished	6.069 (2.515 – 14.643)	**<0.001**

R^2 = 0.356 (35.6% of variability in prefrailty/frailty status is attributed to variables in the multiple regression model)

power—was the only test that consistently demonstrated poorer performance in our prefrail/frail participants in both genders. Yet, weakness in frailty criteria has typically been represented by grip strength, although the Study of Osteoporotic Fracture (SOF) has included inability to perform the chair stand test as one of its criteria.[47]

The modest correlation between handgrip and quadriceps strength in older people suggests that upper and lower limb strength measurements cannot be used interchangeably, but are associated with distinct health outcomes to distinguish the most vulnerable subpopulation of elderly.[48] Poor performance on the sit-to-stand test had been associated with Fried's frailty criteria,[49] similar to our observation of impaired lower limb strength in the prefrail/frail group. This finding provides further impetus to evaluate lower body strength and power separately.[49]

Falls also feature in adverse outcomes associated with frailty,[50] plausibly secondary to deterioration in balance and agility observed in our prefrail/frail group. Since aerobic endurance impacts on strength, balance and mobility,[51] a decline in 6MWT score in the prefrail state means endurance training is needed to improve cardiorespiratory fitness to prevent frailty. Interestingly, while grip strength and gait speed are intrinsically connected with frailty phenotype, both were associated with prefrailty/frailty only in the women in our study. The differential performance in lower body strength and power between robust and prefrail/frail older men is a strong indicator of developing frailty in men. This finding is consistent with reports of greater loss of muscle mass and strength in lower limbs than upper limbs in older men.[52]

Earlier studies that compared FRAIL against other frailty measures have largely focused on their predictive value. In our study, we observed low to modest agreement among FRAIL, FI and Fried phenotype, suggesting that different frailty tools may have been capturing distinct—but overlapping—populations.[53] Indeed, a recent scoping review on frailty measurement in Singapore has suggested that the identification of frailty is influenced by the tools and constructs employed by researchers.[54] Nonetheless, the validity of FRAIL as a screening tool is supported by significantly higher FI in prefrail/frail subjects compared to robust older adults. The higher prevalence of prefrailty and frailty on FI is expected since it encompassed multiple domains. In contrast, FRAIL and Fried are confined to physical frailty.

Although FRAIL was intended as a rapid screening tool after it was adapted from Fried, AUROC for FRAIL was lower when referenced against Fried compared with FI. This may be attributed to higher frailty prevalence detected on FI than on Fried and the psychological and social indicators captured by FI. An earlier local study had observed similarly high AUROC for FRAIL against FI, but in a population of acutely ill hospitalised older adults.[55] Unlike Fried which employs grip strength as an objective indicator of frailty, the use of lower—rather than upper—limb strength measures to differentiate the robust from the prefrail/frail group is similar to the question on weakness in FRAIL which assesses difficulty in navigating stairs.

Xue et al have demonstrated substantial discordance between physical frailty phenotype and FI in individuals, suggesting that these frailty measures may not be used interchangeably.[56] In our cohort, 40% and 3% of prefrail participants identified by FRAIL were actually considered frail in FI and modified Fried, respectively, and 5% of those assessed as robust on FRAIL would have been frail on FI with none of them considered as frail on modified Fried. Our findings suggest that FRAIL may be used as a rapid screening tool, but future studies should evaluate its cut-off for frailty in our local elderly.

Our study has several limitations. The under-representation of males could have contributed to type 2 error in associations between fitness measures and frailty in men. Participants in our study were neighbourhood residents and those who were not able to ambulate at least 4 m independently were excluded. This could have underestimated frailty prevalence in our study since frail individuals might not have been able to visit our study site. The cross-sectional analysis also limits our inference on causality. However, this study presents pilot data from an ongoing programme and longitudinal follow-up will clarify the temporal relationship between frailty and its

Table 3. Association between Physical Fitness Tests and Prefrailty/Frailty

Variable	Aggregate (n = 135)			Women (n = 96)			Men (n = 39)		
	Robust (n = 99)	Prefrail/Frail (n = 36)	*P* Value	Robust (n = 73)	Prefrail/Frail (n = 23)	*P* Value	Robust (n = 26)	Prefrail/Frail (n = 13)	*P* Value
Flexibility (mean ± SD)									
Back scratch test	6.51 ± 16.59	4.85 ± 25.27	0.728	4.84 ± 14.73	3.60 ± 24.97	0.829	11.32 ± 20.65	7.04 ± 26.78	0.596
Chair sit-and-reach	1.67 ± 10.5	0.77 ± 14.2	0.370	3.36 ± 9.72	2.67 ± 12.41	0.787	3.22 ± 11.19	6.79 ± 15.65	0.431
Strength and power									
Upper limb									
Grip strength (kg)	23.8 (6.7)	22.8 (8.2)	0.517	21.6 (4.6)	18.7 (5.3)	0.017	30.1 (7.7)	30.1 (7.3)	1.00
Weak grip (%)*	21 (21.6)	11 (33.3)	0.178	13 (18.1)	9 (42.9)	0.019	8 (32)	2 (16.7)	0.445
Lower limb (chair stand)									
Median duration of 5 stands (IQR)	10.48 (8.30 – 12.32)	12.36 (9.72 – 16.57)	0.003	10.94 (8.76 – 12.34)	12.51 (10.00 – 16.88)	0.019	9.70 (6.68 – 12.50)	12.0 (9.56 – 16.60)	0.024
Stands completed in 30 seconds (mean ± SD)	14.4 ± 4.9	12.4 ± 3.7	0.036	13.8 ± 4.4	12.4 ± 3.7	0.208	16.1 ± 5.8	12.3 ± 3.9	0.055
Dexterity (box-and-block test, mean ± SD)	45.5 ± 9.4	41.4 ± 8.6	0.030	46.5 ± 9.1	41.0 ± 9.4	0.017	42.4 ± 9.8	42.1 ± 7.4	0.912
Mobility									
Gait speed (mean ± SD)	1.38 ± 0.27	1.19 ± 0.35	0.001	1.37 ± 0.28	1.15 ± 0.28	0.002	1.41 ± 0.25	1.25 ± 0.45	0.265
Slow gait (%)*	–	5 (15.2)	0.001	–	3 (14.3)	0.001	–	2 (16.7)	0.099
Balance and agility									
Standing balance (>10 seconds, %)									
Side-by-side	96 (99)	32 (97)	0.445	71 (98.6)	20 (95.2)	0.403	25 (100)	12 (100)	–
Semi-tandem	95 (97.9)	31 (93.9)	0.267	70 (97.2)	19 (90.5)	0.219	25 (100)	12 (100)	–
Tandem	84 (86.6)	22 (66.7)	0.036	62 (86.1)	14 (66.7)	0.121	22 (88.0)	8 (66.7)	0.093
Dynamic balance									
Median TUG (IQR)	9.33 (7.79 – 10.61)	10.69 (8.29 – 14.67)	0.031	9.39 (7.79 – 10.61)	10.43 (8.65 – 15.78)	0.088	9.30 (7.85 – 10.84)	10.74 (8.04 – 14.29)	0.215
Endurance (6MWT, mean ± SD)	449.4 ± 121.2	376.8 ± 143.7	0.006	446.0 ± 125.1	379.7 ± 149.2	0.041	459.5 ± 110.7	371.4 ± 155.2	0.063
Median SPPB score (IQR)	12 (11 – 12)	11 (8.25 – 12)	0.011	11.5 (10 – 12)	11 (8.25 – 11.75)	0.031	12 (11 – 12)	11 (8 – 12)	0.195

6MWT: 6-minute walking test; IQR: Interquartile range; SD: Standard deviation; SPPB: Short Physical Performance Battery; TUG: Timed Up and Go test
*Based on cut-off for weak grip strength (<18 kg in women and <26 kg in men) and slow gait speed (≤0.8 m/s) from the Asian Working Group for Sarcopenia.

Table 4. Agreement between FRAIL, Frailty Index and Fried Phenotype

FRAIL (%)	Frailty Index					Fried Phenotype				
	Robust (≤0.08)	Prefrail (0.08 – 0.25)	Frail (≥0.25)	Total	Kappa (*P* Value)	Robust	Prefrail	Frail	Total	Kappa (*P* Value)
Robust	40 (42.1)	50 (52.6)	5 (5.3)	95 (73.6)		60 (63.8)	34 (36.2)	0	94 (74.6)	
Pre-frail	2 (6.3)	17 (53.1)	13 (40.6)	32 (24.8)		8 (26.7)	21 (70)	1 (3.3)	30 (23.8)	
Frail	0	0	2 (100)	2 (1.6)		1(50)	1 (50)	0	2 (1.6)	
Total	42 (32.6)	67 (51.9)	20 (15.5)	129	0.137 (0.013)	69 (54.8)	56 (44.4)	1 (0.79)	126	0.264 (0.001)

multiple antecedents. Although frailty screening is recommended in individuals >70 years old, we adopted a lower cut-off age (55 years old) since the antecedents of frailty may manifest as early as in middle age.[57] The exclusion of seniors who reside in sheltered or nursing homes—and who are expected to be more frail—from our study may also limit the generalisability of our findings.

Conclusion

We have shown that an integrated community screening programme that screens frailty and its concurrent risk factors such as mood, nutrition and social support can facilitate targeted intervention in older adults after it identifies them as prefrail. Additionally, the use of physical fitness tests provide older adults with an opportunity to monitor their own functional fitness and to promote healthy ageing in them. The test can also be used to create customised exercise programmes for older adults that target early decline in their physical fitness and early frailty.

Acknowledgements

This study was funded with grants (CGAug16C027 and GAug16M011) from National Medical Research Council. The authors would like to thank Germaine Chng, Steven Lim, Hannah Lim, Alice Lee and Enan Goh from the Strategic Planning Department in Sengkang General Hospital and Mohamad Rizal for their assistance in the operationalisation of IPPT-S. They also thank the staff of Ang Mo Kio Family Service Centre (Rivervale) and Pacific Activity Centre (Punggol Ripples) for their help with the attendance of the senior participants in IPPT-S.

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Original Article

High Thyroid Stimulating Receptor Antibody Titre and Large Goitre Size at First-Time Radioactive Iodine Treatment are Associated with Treatment Failure in Graves' Disease

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Abstract

Introduction: Our study aimed to identify the factors associated with successful first-time radioactive iodine (RAI) treatment in patients with Graves' disease (GD). Materials and Methods: This is a retrospective study of patients with GD who were treated with RAI. Treatment success was defined as onset of permanent hypothyroidism or euthyroidism after 1 dose of RAI at 1-year follow-up. Results: There were 388 GD patients who underwent RAI treatment between January 2014 and December 2015. Of these, 74% achieved treatment success. Median time to achieve permanent hypothyroidism was 2 months. Male gender, smoking, higher antithyroid drug dosage, lower thyroid stimulating hormone (TSH) level, large goitre size and TSH receptor antibody (TRAb) titre at time of RAI were significantly associated with treatment failure. Multivariate analysis showed that larger goitre size and higher TRAb titre were associated with lower first-time RAI success. Conclusion: Larger goitre size and higher TRAb titre predict lower success of RAI therapy in GD patients. Treatment decisions and strategies should be customised for patients who present with these characteristics.

Ann Acad Med Singapore 2019;48:181-7

Key words: Autoimmune thyroid disease, Hyperthyroidism, TSH receptor antibody

Introduction

Graves' disease (GD) is the most common cause of endogenous hyperthyroidism. Remission with medical therapy ranges from 20% to 60% after 1 to 2 years of treatment.[1] Definitive treatment options include radioactive iodine (RAI) and thyroidectomy, with the latter associated with complications of surgery and general anaesthesia. As such, the preferred mode of definitive therapy in uncomplicated GD is RAI.[2] The goal of RAI in GD is to render the patient hypothyroid or euthyroid. Ideally, 1 dose of RAI should achieve this goal in a predictable manner to allow timely initiation of thyroxine and to minimise symptoms associated with prolonged hypothyroidism. In most instances, post-RAI treatment hypothyroidism occurs from 4 weeks after treatment, most commonly between 2 to 6 months post-treatment.[3]

In the literature, the success of RAI therapy ranged from 61% (with 5.4 mCi) to 86% (with 15.7 mCi).[4] Although multiple studies have tried to determine the clinical or biochemical factors that influence the success of RAI treatment, current evidence is conflicting. The factors purported to be associated with reduced success of RAI treatment include younger age, antithyroid drug (ATD) pretreatment, male gender, higher thyroid stimulating hormone receptor antibody (TRAb) titre, higher free thyroxine (FT4) level and larger thyroid gland size.[1,4-7] Additionally, the specific role of TRAb in predicting RAI outcome is also not clear, unlike its role in medical therapy whereby a higher TRAb titre is associated with a lower likelihood of remission.[8]

Our study aimed to examine factors that may predict the success of first-time RAI in the treatment of GD to aid physicians to recommend more customised treatment options to their patients.

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Materials and Methods

Medical records of all GD patients treated with RAI between January 2014 and December 2015 in the Department of Nuclear Medicine and Molecular Imaging in our institution were retrospectively reviewed. The diagnosis of GD was based on elevated FT4 with suppressed thyroid stimulating hormone (TSH) level and clinical examination findings (such as diffusely enlarged goitre, thyroid eye disease and typical signs and symptoms of hyperthyroidism) with documented presence of thyroid autoantibodies. Cases were excluded when the underlying diagnosis was not clear or a patient has a concomitant toxic nodule. Patients who were not followed up for up to 1 year were also excluded.

The data included demographics, thyroid size at RAI, smoking status, GD duration, ATD dose before RAI, first incidence of GD or relapsed disease, presence of GD at time of RAI, use of steroid prophylaxis, empirical or calculated RAI dose, repeat RAI treatment and time to onset of permanent hypothyroidism. Biochemical data such as FT4 and TRAb titre at time of RAI were collected. FT4 was determined on UniCel DxI 800 Access immunoassay system (Beckman Coulter, Inc., Chaska, MN, USA; normal range, 8.8-14.4 μmol/L) using chemiluminescence detection methods. TRAb titre was measured using a second-generation TBII kit using recombinant human TSH receptor (B•R•A•H•M•S Diagnostics, Berlin, Germany; normal range, 0-1.5 IU/L).

Most patients received an empirical RAI dose based on estimated thyroid volume measured by clinical palpation according to the World Health Organization's classification of goitre: small (Grade 0, no palpable or visible goitre), moderate (Grade 1, a mass in the neck that is consistent with an enlarged thyroid which is palpable but not visible when the neck is in the normal position) and large (Grade 2, a swelling in the neck that is visible when the neck is in the normal position and is consistent with an enlarged thyroid when the neck is palpated).[9] Generally, the RAI dose for these 3 goitre sizes are 10-15 mCi, 15-20 mCi and 20-30 mCi, respectively. A small number (n = 25) of patients received a calculated dose using ultrasound for thyroid volumetry and subsequent RAI doses were based on the Marinelli formula with fixed assumptions for maximum thyroid uptake ratios.[10] RAI was ordered in the form of liquid sodium iodide (GE Healthcare, Amersham Place, UK; ANSTO, Sydney, Australia; and POLATOM, Otwock, Poland).

Titrations of RAI dose were performed in our nuclear medicine laboratory by an experienced clinician who measured radioactivity levels using an Atomlab™ 500 Dose Calibrator (Biodex Medical Systems, NY, USA) with an error acceptance rate of ± 5%. This was fed to patients via ingestion using a straw with more water for top-up.

The presence of GD is considered if eyelid retraction occurs in association with thyroid dysfunction, exophthalmos, optic nerve dysfunction or extraocular muscle involvement and when other confounding causes such as idiopathic orbital inflammation are excluded.[11] Steroid prophylaxis is defined as at least 2 weeks of treatment with a pharmacological dose of glucocorticoids. Patients with pre-existing GD or risk factors for GD progression and those with large goitres were given steroid prophylaxis to reduce the risk of GD progression and post-RAI thyroiditis, respectively. ATDs available in our institution are carbimazole, thiamazole and propylthiouracil. ATDs were titrated to equivalent dosage of carbimazole which is 10:1 for propylthiouracil to carbimazole and 2:3 for thiamazole to carbimazole.[1,12] In our institution, ATDs are routinely discontinued 4 to 7 days prior to RAI treatment and restarted after 3 days at the discretion of the treating nuclear medicine physician. Additionally, patients were instructed to strictly follow a diet low in iodine for up to 1 week following the same period of discontinuation of ATDs for RAI treatment.

Successful RAI outcome was defined as achievement of permanent hypothyroidism (requiring thyroxine initiation) or euthyroidism (cessation of all ATDs) after 1 dose of RAI at 1-year follow-up. As such, individuals who had transient hypothyroidism (initially hypothyroid after RAI but became euthyroid or hyperthyroid at 1 year after RAI) had treatment failure.

Statistical analysis was performed using SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean ± standard deviation or median (interquartile range) for continuous variables and as count (percentage) for categorical variables. The primary outcome of interest was successful RAI after first-time RAI treatment. Univariate test of factors associated with outcomes were done using Mann-Whitney U test and chi-square test for continuous and categorical data types, respectively. Significant results were defined as $P < 0.05$.

Logistic regression analysis was used to identify factors that predict success of RAI therapy. The dependent variable includes successful RAI outcome after first-time RAI treatment. The independent variables include age at RAI, gender, smoking status, pre-existing GD, duration of diagnosis, TSH and TRAb titre at RAI, ATD pretreatment, ATD dose, steroid prophylaxis, goitre size and RAI dose.

The study was approved by SingHealth Institutional Research Ethics Committee.

Results

There were 388 patients with GD who were treated with RAI during the study period. The main indication for RAI treatment was relapsed GD in 68.3% of patients. Other indications include patient's treatment choice, allergy to ATDs and definitive treatment due to complications from thyrotoxicosis such as thyroid storm or thyrocardiac disease.

A total of 273 (70.4%) patients became permanently hypothyroid and 14 (3.6%) were euthyroid at 1-year follow-up. As such, 73.7% of GD patients in our study had a successful RAI outcome after the first treatment. Median time to onset of hypothyroidism in patients who achieved permanent hypothyroidism after first-time RAI treatment was 2 months (95% confidence interval, 1.9-2.1) as shown in Figure 1. In patients who failed first-time RAI, 24 (6.2%) remained on long-term ATDs and 77 (19.8%) underwent a second RAI treatment. A total of 73 patients became permanently hypothyroid after the second RAI treatment. Of the remaining 4 patients who underwent the second RAI treatment, 1 was euthyroid and 3 were placed on long-term ATDs. Table 1 shows the baseline characteristics of patients who had a successful outcome after first-time RAI treatment (achievement of euthyroidism or permanent hypothyroidism) against those who remained hyperthyroid after 1 treatment.

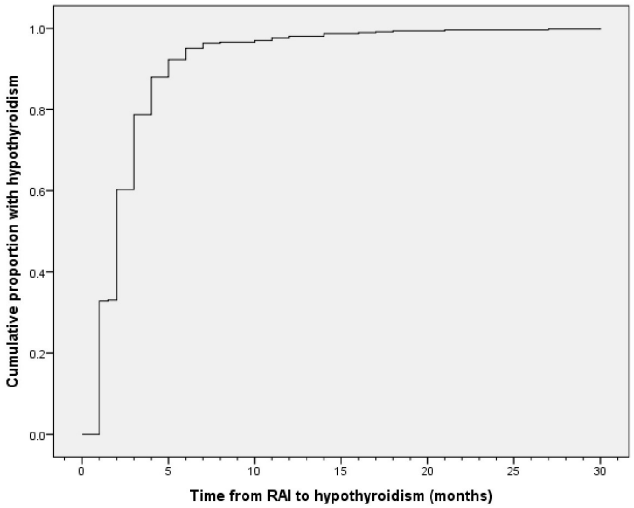

Fig. 1. Cumulative incidence of hypothyroidism seen in patients after first-time RAI therapy. RAI: Radioactive iodine.

Male gender, smoking, higher ATD dosage, large goitre size, lower TSH and higher TRAb titre at RAI treatment were significantly associated with RAI treatment failure (Table 1). There were significantly more male than female smokers (68.4% vs 31.6%, P <0.001). The proportion of patients on each ATD who had a successful outcome after first-time RAI treatment against those who remained

Table 1. Baseline Characteristics of Patients after First-Time RAI Therapy

Variable	Euthyroid or Hypothyroid (n = 286)	Remained Hyperthyroid (n = 102)	*P* Value
Age at diagnosis (years, mean ± SD)	45 ± 14	45 ± 13	0.928
Male gender (%)	67 (23.4)	35 (34.3)	0.032
Smoker (%)	35 (15.7)	22 (24.2)	0.037
Median duration of diagnosis (months, IQR)	65 (34 – 117)	81 (37 – 125)	0.319
Relapsed Graves' disease (%)	192 (67.1)	73 (71.6)	0.433
Pre-existing Graves' ophthalmopathy (%)	53 (18.5)	28 (27.5)	0.057
ATD pretreatment (%)	263 (92.0)	99 (97.1)	0.077
ATD dose (mg/day, mean ± SD)	10.8 ± 9	13.2 ± 9	0.025
Duration of ATD treatment before RAI (months, mean ± SD)	12 ± 5.34	18 ± 5.37	0.238
RAI dosing (%)			
Empirical dosing	265 (92.7)	95 (93.1)	-
Calculated dosing	18 (6.3)	7 (6.9)	0.860
Goitre size (%)			
Small	175 (61.2)	42 (41.2)	-
Moderate	80 (28.0)	34 (33.3)	-
Large	29 (10.1)	25 (24.5)	<0.001
Steroid prophylaxis (%)	68 (23.8)	33 (32.4)	0.090
Median dose of first RAI (mCi, IQR)	18 (15 – 20)	20 (16 – 23)	0.056
Median TSH at RAI (IU/L, IQR)	0.050 (0.015 – 1.000)	0.026 (0.010 – 0.345)	0.013
Median TRAb titre at RAI (IU/L, IQR)	5.9 (2.5 – 16.4)	11.9 (5.3 – 29.8)	<0.001

ATD: Antithyroid drug; IQR: Interquartile range; RAI: Radioactive iodine; SD: Standard deviation; TRAb: Thyroid stimulating hormone receptor antibody; TSH: Thyroid stimulating hormone

hyperthyroid were, respectively, 80.8% versus 82.2% for carbimazole, 4.5% versus 3.0% for thiamazole and 6.6% versus 11.9% for propylthiouracil. The remaining patients (6.7%) were either on non-ATD drugs such as lithium and cholestyramine or not on any form of treatment. The comparison of usage of ATD types between groups did not reach statistical significance. A total of 21 (5.4%) patients had transient hypothyroidism.

Multivariate analysis showed that large gland size and higher TRAb titre at RAI treatment had an odds ratio (OR) of 0.244 (P = 0.003) and 0.969 (P = 0.004), respectively, and were associated with a lower probability of successful first-time RAI treatment outcome after controlling for other factors (Table 2).

Discussion

Our study demonstrated that RAI is effective in 73.7% of patients who achieved a successful outcome (permanent hypothyroidism or euthyroidism) after receiving a first-time median RAI dose of 19 mCi. The onset of post-RAI treatment hypothyroidism is often unpredictable in clinical practice. As such, the duration of follow-up after RAI is often dependent on the attending physician. It has been recommended that assessment of FT4 should be performed between 2 to 6 weeks after RAI therapy to avoid GD exacerbation.[13,14] In our study, the median time to hypothyroidism was 8 weeks after RAI therapy and this finding concurred with that of other studies.[3] This suggests that patients who are treated with RAI should be followed up within 2 months for development of hypothyroidism.

We have demonstrated that TRAb titre—measured at RAI treatment—was significantly associated with treatment failure of first-time RAI. Notably, every 1 IU/L increase in TRAb was associated with a 3.1% reduction in treatment success. This association persisted even after adjustment for multiple factors had been made. Some studies have proposed a link between higher TRAb titre and failure of RAI treatment (Table 3). It has been postulated that functioning thyroid cells that remained after RAI treatment are still being stimulated by TRAb which contributes to the persistence of hyperthyroidism.[15,16]

One finding of our study is that larger goitre size is associated with treatment failure and this finding remained significant in multivariate analysis. Several studies have shown that a larger thyroid gland is associated with a higher risk of treatment failure (Table 3). Although it is difficult to ascertain the exact cause of failure due to differences in dosage in various studies and the complex interactions between thyroid size and other disease risk factors, a larger thyroid gland intuitively implies a higher burden of autonomously functioning thyroid tissue and greater resistance to RAI therapy.

In our study, there were fewer male patients who became euthyroid or hypothyroid after first-time RAI treatment. Male smokers with GD have a poorer response to ATD treatment.[1] There were significantly more male smokers than female smokers in our study. It is plausible that smoking can impact on the treatment outcome of RAI therapy. Smoking may promote immune activation and increase TRAb levels which can lead to resistance to RAI.[17] While the 2 large series by Alevizaki et al and Boelaert et al had demonstrated that male gender was associated with reduced response to RAI treatment, this finding has not been replicated in other studies.[18,19]

Table 2. Multivariate Logistic Regression of Factors that Predict Successful First-Time RAI Therapy

Factor	Odds Ratio (95% Confidence Interval)	*P* Value
Age at RAI (years)	0.990 (0.969 – 1.011)	0.345
Male	0.679 (0.358 – 1.289)	0.237
Smoker	0.651 (0.311 – 1.365)	0.256
Pre-existing Graves' ophthalmopathy	0.634 (0.309 – 1.302)	0.215
Duration of diagnosis (months)	1.001 (0.998 – 1.004)	0.572
TSH at RAI	1.203 (0.994 – 1.456)	0.057
ATD pretreatment	0.393 (0.094 – 1.637)	0.200
ATD dose	0.999 (0.969 – 1.031)	0.958
Steroid prophylaxis	1.379 (0.671 – 2.835)	0.382
Goitre size at RAI		
Small	1.000	-
Medium	0.582 (0.299 – 1.132)	0.111
Large	0.244 (0.097 – 0.611)	0.003
First RAI dose (mCi)	1.042 (0.961 – 1.130)	0.314
TRAb titre at RAI (IU/L)	0.969 (0.948 – 0.990)	0.004

ATD: Antithyroid drug; RAI: Radioactive iodine; TRAb: Thyroid stimulating hormone receptor antibody; TSH: Thyroid stimulating hormone

Table 3. Studies of Goitre Size and TRAb on Outcome of RAI Therapy

First Author (Year)	Number of Patients	Study Design	Goitre Size	TRAb
Davies et al (1982)*	43	Retrospective	ND	+
Marcocci et al (1990)†	274	Retrospective	+	ND
Kung et al (1990) ‡	827	Retrospective	+	ND
Kaise et al (1991) §	109	Retrospective	+	+
Murakami et al (1996)‖	52	Prospective	ND	+
Chiovato et al (1998)¶	31	Prospective	+	+
Sabri et al (1999)#	207	Prospective	–	–
Howarth et al (2001)**	58	Prospective	+	ND
Allahabadia et al (2001)††	813 (321 with GD)	Retrospective	+	ND
Andrade et al (2001)‡‡	61	Prospective	+	–
Alexander and Larsen (2002)§§	261	Retrospective	+	ND
Zantut-Wittmann et al (2005)‖‖	82	Retrospective	+	ND
Boelaert et al (2009)¶¶	1278 (543 with GD)	Cohort	+	ND
Zheng et al (2012)##	796	Retrospective	+	+
Sapienza et al (2015)***	91	Prospective	+	ND
Sfiligoj et al (2015) †††	724	Retrospective	+	ND
Yang et al (2018)‡‡‡	325	Retrospective	+	–

GD: Graves' disease; ND: Not determined; RAI: Radioactive iodine; TRAb: Thyroid stimulating hormone receptor antibody
+: An association was observed between RAI treatment failure and larger goitre size and/or high TRAb.
–: No association was observed between RAI treatment success and goitre size and/or TRAb.
*Davies TF, Platzer M, Farid NR. Prediction of therapeutic response to radioactive iodine in Graves' disease using TSH-receptor antibodies and HLA-status. Clin Endocrinol (Oxf) 1982;16:183-91.
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§Kaise K, Kaise N, Yoshida K, Fukazawa H, Mori K, Yamamoto M, et al. Thyrotropin receptor antibody activities significantly correlate with the outcome of radioiodine (^{131}I) therapy for hyperthyroid Graves' disease. Endocrinol Jpn 1991;38:429-33.
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¶Chiovato L, Fiore E, Vitti P, Rocchi R, Rago T, Dokic D, et al. Outcome of thyroid function in Graves' patients treated with radioiodine: role of thyroid-stimulating and thyrotropin-blocking antibodies and of radioiodine-induced thyroid damage. J Clin Endocrinol Metab 1998;83:40-6.
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¶¶Boelaert K, Syed AA, Manji N, Sheppard MC, Holder RL, Gough SC, et al. Prediction of cure and risk of hypothyroidism in patients receiving ^{131}I for hyperthyroidism. Clin Endocrinol (Oxf) 2009;70:129-38.
##Zheng W, Jian T, Guizhi Z, Zhaowei M, Renfei W. Analysis of ^{131}I therapy and correlation factors of Graves' disease patients: a 4-year retrospective study. Nucl Med Commun 2012;33:97-101.
***Sapienza MT, Coura-Filho GB, Willegaignon J, Watanabe T, Duarte PS, Buchpiguel CA. Clinical and dosimetric variables related to outcome after treatment of Graves' disease with 550 and 1110 MBq of ^{131}I: results of a prospective randomized trial. Clin Nucl Med 2015;40:715-9.
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However, in our study, subsequent multivariate analysis showed that male gender and smoking did not predict treatment outcome of RAI therapy after accounting for other clinical factors.

Patients who remained hyperthyroid after RAI treatment were on a much higher dose of ATDs and had lower serum TSH at RAI treatment compared to those who became euthyroid or hypothyroid after RAI (Table 1). Lower TSH at RAI treatment likely reflects increased disease severity and lesser likelihood of treatment success. TSH at time of RAI was not significant on multivariate analysis (OR, 1.203; $P = 0.057$). It is postulated that this is because patients with lower TSH and more severe disease are more likely to have higher TRAb titres.

The main limitation of our study is its retrospective design. While we acknowledge that transient hypothyroidism has previously been demonstrated as a potential marker of treatment failure, its low incidence of 5.4% in our study made it improbable as a predictor of treatment failure.[20] Our institution does not routinely perform radioiodine uptake or measure the iodine status of all patients before RAI treatment. The absence of this information prior to the determination of empirical RAI treatment dose could potentially affect treatment outcome in our patients. However, a recent study had demonstrated that the efficacy of RAI therapy in GD was not compromised by iodine nutritional status even when patients presented with urinary iodine excretion that is compatible with mildly excessive iodine ingestion.[21]

Another limitation of our study is the lack of uniform strategies in the selection of RAI dosage to treat patients. Many institutions in Europe prefer the use of empirical over calculated RAI dosing strategies.[22] Our institution generally follows similar principles and only a small number (<5%) of patients are treated using a calculated RAI dosage strategy. Studies have shown that estimation of goitre size by manual palpation demonstrates a good correlation with ultrasonographic measurements when it is performed by experienced clinicians.[23] More importantly, both empirical and calculated RAI dosing strategies have achieved comparable outcomes.[23,24]

Conclusion

Our study demonstrated that larger goitre size and higher TRAb titre are associated with failure of first-time RAI therapy. Identification of the predictors of RAI treatment failure will help to moderate the expectations of patients and physicians on the response and outcome of RAI therapy. This information can also guide treatment selection in GD patients such as recommending thyroidectomy or long-term ATDs over RAI in patients with large goitre size or high TRAb titre.

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Commentary

Megatrends in Infectious Diseases: The Next 10 to 15 Years

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Abstract

It has been about 100 years since the Spanish influenza pandemic of 1918-19 that killed an estimated 50 million individuals globally. While we have made remarkable progress in reducing infection-related mortality, infections still account for 13 to 15 million deaths annually. This estimate is projected to remain unchanged until 2050. We have identified 4 megatrends in infectious diseases and these are "emerging and re-emerging infections", "antimicrobial resistance", "demographic changes" and "technological advances". Understanding these trends and challenges should lead to opportunities for the medical community to reshape the future. Further inroads will also require broad approaches involving surveillance, public health and translating scientific discoveries into disease control efforts.

Ann Acad Med Singapore 2019;48:188-94

Key words: Antimicrobial resistance, Demographic changes, Emerging infections, Technological advances

Introduction

Microbial threats to human health have existed for thousands of years.[1,2] In the past, infectious diseases presented some of the most defining challenges of human existence.[3] Great pandemics and local epidemics have influenced wars and the fate of countries and empires.[4] As recently as 30 years ago, the human immunodeficiency virus (HIV) epidemic caused devastating loss of at least 1 generation of adults in some African countries, setting back years of progress.[5]

Infectious diseases have long been associated with poverty. Rapid economic and scientific progress of the 1960s and the subsequent reduction in infectious disease mortality likely prompted the infamous quote: "It is time to close the book on infectious diseases and declare the war against pestilence won." Though often attributed to William H Stewart, the 10th United States (US) Surgeon General, the source remains controversial. Controversy notwithstanding, the resulting complacency in public health efforts has been blamed for antimicrobial resistance, emerging and re-emerging infections.

More than 1400 species of pathogens cause diseases in humans.[6] With global effort, we have eradicated just 1 (smallpox) but have made significant progress controlling many others. However, microbial threats continue to emerge and re-emerge. Under "favourable" conditions, the previously obscure Zika virus—first discovered in the 1960s—emerged in 2015 to infect millions in Central and South America, resulting in thousands of cases of congenital Zika syndrome and is expected to be a long-term public health challenge.[7]

Nowhere in the world have infectious diseases become negligible.[8,9] Outbreaks and epidemics will continue to grab headlines. The Ebola epidemic that began in 2013 ravaged many countries in West Africa. It captured global attention prompting the World Health Organization (WHO) to declare the infection a public health emergency of global concern.[10] Even as the world catches its breath, a new Ebola outbreak

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was declared in the Democratic Republic of Congo in May 2018—and it rages on. Clearly, investing resources and time in the prevention and control of infectious diseases need to be ongoing.

In this article, we review the significant historical events in infectious disease, primarily the scientific progress that have enhanced our understanding of pathogens, their epidemiology, prevention and treatment. We emphasise that significant changes have occurred and that there has been an epidemiological transition in infectious diseases globally.[11] The direction of these changes and the forces they unleash will define the future world. We express what we know and put forward 4 important "megatrends" in infectious diseases that will be ongoing challenges in the next 10 to 15 years. These trends, if harnessed well, will also serve as opportunities to reshape the future.

Megatrend 1: Emerging and Re-Emerging Infections

The Institute of Medicine (now called Health and Medicine Division at the National Academies of Sciences, Engineering and Medicine, United States of America) published a landmark report entitled "Emerging Infections: Microbial Threats to Health" in January 1992 and brought global attention to the ongoing threat of infections to human health.[12] Since then, many new pathogens have been identified. Some of the newly identified viruses that caused outbreaks in Singapore are Nipah virus in 1999,[13] severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003[14] and *H1N1* influenza virus in 2009.[15]

There are many drivers of emerging and re-emerging infections.[16,17] These can be broadly categorised into "microbial factors", "human host factors", "environmental factors" and "others". For "microbial factors", genetic adaptation of the microbe may allow it to infect a different host or result in the development of antimicrobial resistance. "Human host factors" that drive emerging and re-emerging infections include individuals with increased susceptibility to infection (such as those who are immunocompromised and the elderly) and individuals with occupational exposure. Spread within healthcare facilities, human migration and lifestyle issues (including travel for business or leisure) are also implicated. "Environmental factors" include increased population density, climate change (impacting vector habitats and population), changes in land use and development, international trade, changing ecosystems and changing animal populations. Wars, famines, poverty are also other external factors that can impact on emerging and re-emerging infections.

International travel and the global food chain are factors especially relevant to Singapore. The SARS-CoV outbreak in Singapore was linked to a Singaporean who acquired the infection during travel to a North Asian city.[18] More recently, the first Zika case notified in Singapore in April 2016 was a traveller who returned from a business trip to Brazil.[19] Interestingly, the subsequent outbreak of over 400 cases that started in August 2016 was linked to the Southeast Asian strain of the Zika virus.[20] In recent years, our healthcare system has been on heightened alert against the introduction of avian influenza, Middle East respiratory syndrome coronavirus (MERS-CoV) and Ebola.

International travel has also been associated with the spread of multidrug-resistant bacteria.[21] In late 2008, a Swedish diabetic visiting India developed a gluteal abscess and required hospitalisation in New Delhi. A day after his transfer to a Swedish hospital, urine cultures grew a carbapenem-resistant *Klebsiella*. This led to the characterisation of the New Delhi metallo-lactamase gene, which had been unknown hitherto.[22] In Holland, a Dutch man developed fever 2 weeks after returning from a 2-month stay in the Philippines. Blood cultures grew *Salmonella typhi* that carried the SHV-12 extended-spectrum beta-lactamase (ESBL).[23] Indeed, multiple studies demonstrate that travel can be associated with acquisition of ESBL-producing organisms.[24]

With Singapore importing most of its food, the country is vulnerable to infections transmitted by food. A recent example was the Listeria outbreak that occurred in Australia in early 2018 that was linked to infected rock melon. In April 2018, Singapore's Ministry of Health (MOH) reported that 2 out of 5 persons infected with Listeria in Singapore since the beginning of 2018 were in fact infected with the strain that had caused the outbreak in Australia.

In December 2015, the WHO led a panel of experts and published a priority list of 8 pathogens that were expected to cause severe outbreaks in the future. These were Ebola, Marburg, Lassa, Rift Valley, Crimean-Congo, Nipah, MERS-CoV and SARS-CoV.[25] The priority pathogens are all viruses and are zoonoses. This list will be reviewed annually in response to any "new" threats that emerge. Clearly, we need to pay greater attention to the threat of zoonotic infections. The concept of "One Health" is a collaborative and inclusive effort involving human health, animal health and the environment.[26]

The issues of climate warming and environmental perturbation are also critical factors in emerging infectious diseases.[27,28] Climate change will increase exposure to Aedes-borne viruses and the risk of the resurgence of dengue, Chikungunya and Zika infections.[29] Recently, there have been large outbreaks of measles and mumps in developed and developing countries. Vaccine hesitancy— especially with the measles, mumps, rubella (MMR) vaccine—has been implicated[30] but the issue is likely to be much more complex with waning immunity and other considerations.[31,32]

Somewhere out there, there are emerging or re-emerging microbial threats lurking. When the "right" conditions

converge, it will unleash itself onto the global population who will have no immunity to this "new" pathogen. This will present as a "black swan" event as with SARS-CoV, or more insidiously, as with HIV.[33]

Adequate preparations will prevent an "incident" from escalating into a "crisis". In Singapore, it is likely that the pathogen will be imported. Whilst these "imported" infections may be daunting, especially if "unknown", the possible routes of transmission are well defined and measures to prevent the spread of "unknown" infections can often follow a broad range of standard procedures. Our restructured hospitals are regularly put through outbreak simulation exercises where such procedures are practised.

Active surveillance for such threats is critical to ensure that outbreaks are quickly detected and contained. Containment will involve a multi-agency effort that will include the restructured hospitals as well as the National Centre for Infectious Diseases, MOH, National Environment Agency, Singapore Food Agency and research institutes like the Genome Institute of Singapore, Defence Science Organisation Laboratories, Agency for Science, Technology and Research and the relevant departments of our local universities.

In essence, we are unlikely to see eradication of the threat of infections to humans and we need to continue with efforts in disease control and mitigation.

Megatrend 2: Antimicrobial Resistance

The discovery of penicillin and the subsequent development of antibiotics must be one of mankind's greatest triumphs. The widespread use of antibiotics has saved countless human lives. In a recent publication on lower respiratory tract infections in the Global Burden of Disease Study 2016, the authors estimated that increased antibiotic availability could still prevent 30% of lower respiratory infection deaths.[34] However, the universal use of antibiotics for lower respiratory tract infections is not tenable. Microbes adapt, resist the medication used and develop antimicrobial resistance (AMR). In the past few decades, antibiotic resistance—a subset of AMR—has emerged to the extent that some bacterial infections are becoming untreatable. The dramatic increase in the proportion and absolute numbers of bacterial pathogens resistant to multiple antibiotics in recent years has prompted many regulatory agencies including the US Centers for Disease Control and Prevention, the WHO and the European Centre for Disease Prevention and Control to highlight this issue. At the 68th World Health Assembly in May 2015, the WHO declared AMR a global health threat and proposed a multiyear action plan to reduce AMR. The "Global Action Plan on AMR" has 5 strategic objectives: 1) To improve awareness and understanding of AMR; 2) To strengthen surveillance and research; 3) To reduce the incidence of infection; 4) To optimise the use of antimicrobial medicines; and 5) To ensure sustainable investment in countering AMR.

Without exception, all antibiotics, antivirals, antifungals and antiparasitic agents have inherent weaknesses that allow microbial pathogens to evolve and develop resistance mechanisms.

Emergence of resistant micro-organisms by mutation and acquisition of mobile transferable genetic elements carrying resistant genes may take place spontaneously or under selective pressure in the presence of antimicrobial agents. In recent decades, the driving force has been the use and misuse of antibiotics in humans and livestock and leakage into the environment. It has been estimated that antibiotic consumption increased 30% from 2000 to 2010. Antibiotic use has amplified the development of AMR.

If AMR is left unchecked, common bacterial infections will become difficult to treat and "simple" infections will once again kill many. Sophisticated medical interventions such as organ transplantation, joint replacement and cancer chemotherapy will become more dangerous to perform.

Clinical trials on new antibiotics and combination therapy have failed to keep up with the rapid emergence of drug-resistant bacterial, fungal and viral pathogens. Hence, improving how we prescribe antibiotics is critical. Antimicrobial stewardship programmes are now well established in the restructured hospitals in Singapore and many developed countries. These programmes have been demonstrated to be safe and effective in improving appropriate antimicrobial use.

AMR is a widespread and complex issue. The factors have been identified and the measures proposed to reduce AMR are not novel and have shown measurable success in selected settings. Successful implementation requires all stakeholders—policymakers, public health officials, regulatory agencies, pharmaceutical companies and scientific community—to work together. We also need to improve public awareness (Table 1). This may galvanise concerned citizens to work towards avoiding the worst-case scenarios where the end of modern medicine occurs as a result of AMR.

Table 1. Important Public Health Messages on Antimicrobial Resistance

• Antibiotic resistance is one of the biggest threats to global health, food security and development today.
• Antibiotic resistance can affect anyone, of any age, in any country.
• Antibiotic resistance can occur naturally, but misuse of antibiotics in humans and animals is accelerating the process.
• A growing number of "common" infections—such as skin infections, pneumonia, tuberculosis and gonorrhoea—are becoming harder to treat as the antibiotics used to treat them become less effective.
• Antibiotic resistance leads to longer hospital stays, higher medical costs and increased mortality.

Megatrend 3: Demographic Changes

Demographic changes in the next 10 to 20 years will have a major impact on infectious diseases. The 3 global demographic trends worthy of note are: 1) Increase in the elderly population; 2) Increase in the number of immunocompromised patients; and 3) Increase in the migrant population, especially refugees and asylum seekers.

Globally, the elderly—defined as those above 65—is expected to reach 2.1 billion in 2050. In Singapore, this is keenly felt with the elderly projected to reach 20% of the population by 2030. It was 9.4% in 2007 and 14.4% in 2017.[35] With multiple comorbidities and immunosenescence, they have a higher risk of acquiring infections and the diseases resulting from the infections are often more severe. Furthermore, recovery will often be slow and incomplete, resulting in physical deconditioning, impairment of activities of daily living and loss of independence.

Advances in medicine have improved the survival of patients with cancer, organ failure and autoimmune diseases. This patient population will continue to grow but their immunocompromised state puts them at higher risk for infections.

The clinical course of some malignant diseases, once thought to be fatal, is being transformed by new therapeutic approaches. A shining example is multiple myeloma which has become a chronic disease through the combination of novel therapeutics and haematopoietic stem cell transplantation.[36] For practising physicians, this transformation has necessitated a change in the approach towards "infections in myeloma". Older review articles emphasised the importance of encapsulated organisms in untreated patients and nosocomial gram-negatives in those receiving chemotherapy, but the newer therapies have led to infections such as aspergillosis and varicella zoster.[37,38] In fact, viral infections have been reported to assume increased importance in myeloma patients treated with daratumumab, a recently approved drug.[39]

The entry of a migrant population may significantly change a previously stable incident infection rate. The wave of asylum seekers into several European countries has raised not only social anxieties but also concerns about the transmission of infectious diseases to the indigenous population. In reality, infectious diseases in the refugee population usually reflect poor living conditions, especially in transit areas. Hence, "outbreaks" are more likely confined to the migrant communities. One point to note is that the "migrant population" is heterogeneous and the infections they carry or suffer from can vary considerably between students, skilled and unskilled workers and refugees. The disease epidemiology of the country of origin will help to determine the type of screening that the migrants should undergo. In a recent review, Eiset and Wejse reported that latent tuberculosis, hepatitis B and malaria were the major concerns.[40] Outbreaks due to measles, cutaneous diphtheria and shigellosis have also been reported in refugees and asylum seekers.

While we do not have a refugee issue in Singapore, we have a sizeable migrant worker population (estimated at 1.4 million). In a recent article, Sadarangani et al reported that a large proportion of malaria, enteric fevers, hepatitis A and E and tuberculosis involved migrant workers.[41]

Megatrend 4: Technological Advances

Technological advances have made a huge impact in the way we work, live and interact with each other. Similarly, technology has been a major force in the evolution of healthcare. In the context of infectious diseases, we highlight the following: 1) The revolution in microbiological diagnosis especially in "hard-to-culture" infections; 2) Novel advances in therapeutics; and 3) Data mining and artificial intelligence (AI).

Microbiological diagnosis has undergone a revolution with the use of nucleic acid amplification tests. The increasing use of syndromic multiplex polymerase chain reaction (PCR) tests has helped us diagnose viral infections more readily. Multiplex PCR tests in common use include those for respiratory tract, gastrointestinal and central nervous system infections. These platforms are being miniaturised and will increasingly become available as point-of-care tests. Improved diagnosis of viral infections in febrile illnesses may reduce empiric antibiotic use and hopefully reduce the development of AMR. Indeed, the promotion of rapid diagnostic kits was one of the major suggestions made for reducing AMR in the report of a study on AMR commissioned by the British government.[42] However, in practice, the use of rapid diagnostic kits has yielded mixed results. In 1 study, though antibiotic prescriptions fell in the presence of a positive result for influenza, 62% of patients with influenza were still prescribed an antibiotic.[43] Similarly, 40% of patients with sore throat and a negative test for Group A *Streptococcus* still received antibiotics.[44]

Next-generation sequencing (NGS) is likely to play a significant role in several areas of medicine. In clinical infectious diseases, it may find a niche in the diagnosis of "hard-to-grow" organisms. In the field of emerging infections, it has already distinguished itself by helping researchers in "first human cases" reports.[45] In epidemiology, its discriminatory power has helped to upend conventional thinking on "epidemiological links".[46]

NGS platforms are now less expensive, more readily accessible and hence are likely to be increasingly deployed in the diagnostic microbiology laboratory in the coming years. Whole-genome sequencing (WGS), in particular, may well revolutionise outbreak investigations. Snitkin et al have

described how WGS helped them understand transmission routes in a prolonged outbreak of carbapenemase-producing *Klebsiella pneumoniae* in their hospital. It turned out that the temporal sequence in which patients manifested as being colonised/infected was not the sequence by which infection was transmitted.[46] They also emphasised the importance of integrating genomic information with epidemiological data, showing that sagaciously combining cutting-edge technology with established methods could lead to impressive results.

As our understanding of the human microbiome improves, therapeutics involving manipulation of the microbiome will increase. We are familiar with faecal microbiota transplant (FMT) for recurrent *Clostridium difficile* infections. Recently, FMT has also been used selectively for patients colonised and infected with resistant organisms.[47] Clinical trials now being planned may confirm if FMT can treat other diseases. Beyond FMT, there is also research on microbiome manipulation in patients with atopic dermatitis and dysbiosis on their skin.[48] We envisage more microbiome manipulation in other areas of medicine.

It would be remiss of us not to touch on the changes that will be wrought by the massive increase in computing power. The impact that data mining and AI will have on the practice of medicine cannot be dealt with in a few paragraphs. We are also not the appropriate experts to comment on these advances. However, we offer a clinician's analysis.

Mining "big data" gives researchers unparallelled statistical power. We will cite just 1 example. Investigators wanted to understand the interaction between trimethorprim-sulfamethoxazole (TMP/SMX) and spironolactone. Randomised-controlled trials recruiting more than 10,000 patients are rare and massively costly. In this exercise, however, the researchers were able to identify 206,319 patients who were prescribed spironolactone over a 17-year study period. They tapped into several large databases—Ontario Drug Benefit Database, Canadian Institute for Health Information's Discharge Abstract Database, Ontario Health Insurance Plan Registered Persons Database, National Ambulatory Care Reporting System and Ontario Office of the Registrar General's database. They were able to conclude that compared with amoxicillin, TMP/SMX use did increase the risk of sudden death[49] in persons on spironolactone.

With the digitisation of medical records, our hospitals also now contain a wealth of information. Mining the data intelligently will enable us to monitor outcomes, track infection rates and do many other things that are currently unimaginable (or that currently require expensive manpower to manually obtain the information by sampling, for example).

AI is both promising and worrying. At the moment, available technologies are still human-driven. Watson for Oncology (WfO), for example, is a programme developed in conjunction with oncologists at Memorial Sloan Kettering (MSK). After an oncologist keys in patient information, WfO will suggest a treatment regimen, based on published literature, as well as the experience at MSK (all taught to WfO). A hospital in Bangalore compared Watson's decisions against those of a multidisciplinary tumour board and found 93% concordance.[50]

Although exciting, WfO is, in a sense, limited by humans. One of the oncologists who helped to develop the software (in effect, training Watson), mentioned that it had been a struggle.[51] But will it necessarily always be as difficult? Our vision of the future is limited by our minds. Perhaps there is some technology that will mine the data in our hospital's database and also all the studies in PubMed®, and then dish out a recommendation for a patient's breast cancer. As we know, the problem of long queues at taxi stands was not solved by any number of incentives or disincentives but by Uber and Grab, and without rocket scientists. AI does promise disruption. For a detailed analysis of how AI will affect the professions, including ours, we recommend the book, "The Future of the Professions: How Technology Will Transform the Work of Human Experts".[52]

Discussion

Megatrends are transformative global forces that define the future world and have far-reaching impact on businesses, societies, the macroeconomy and the individual. Megatrends have been identified in business, investment and technology and will have different meanings for different industries. In the context of infectious diseases, megatrends represent fundamental sustained forces in the future that will impact infections in mankind.

A fundamental question is: why have we not been more successful in controlling infectious diseases? With access to clean water, sanitation and antibiotics, there has been a steady decrease in infection-related mortality in most segments of the population, except possibly the elderly. Thirteen to 15 million persons are projected to die every year due to infectious diseases up to 2050.[8] This high mortality reflects some of the concerns we have raised in this article. Global population growth has certainly contributed to these high numbers and the challenge is how to push these mortality figures down.

The megatrends that we have outlined may not be exhaustive or mutually exclusive. They serve as a blueprint for the future as healthcare planning and investments often lag behind impact. Often, focus is lost after the hype surrounding a new outbreak like Zika. Instead, ongoing preparations including investment in infrastructure should permit a comprehensive response that ensures

quick interruption of transmission. Beyond infrastructure, equipment and training, previous outbreaks have taught us that the medical community needs more than "research and response".[53,54] We need better organisation, leadership, communication and community action.

Conclusion

We have made remarkable progress in diagnosing, treating and preventing infectious diseases. Our successes in meeting the threats of pathogens come not only from scientific breakthroughs but also from broad approaches on many fronts including surveillance, public health efforts and translating new discoveries into disease control efforts. The future is not a given. We must continue to improve our processes, enhance our tools and infrastructure. The challenges of infectious diseases are perpetual and so must our efforts.

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Intussusception: It's Not Always Ileo-Colic

A 5-year-old boy presented with intermittent episodes of central abdominal pain and vomiting for 3 days. Despite this, he was well hydrated with a soft non-tender abdomen on clinical examination. There was past history of intussusception 8 months prior, which was successfully reduced with fluoroscopic-guided air enema reduction. At presentation, an abdominal ultrasound was performed to investigate the abdominal pain (Fig. 1).

What is the diagnosis?

A) Ileo-colic intussusception
B) Ileo-ileo-colic intussusception
C) Ileo-ileal intussusception
D) Jejuno-jejunal intussusception
E) Colo-colic intussusception

Findings and Diagnosis

The ultrasound images (Fig. 1) show a mass-like lesion demonstrating a "target sign" in the middle left abdomen. Normal vascularity is preserved within the walls of the intussusceptum and intussuscipiens. There is a polypoid structure with a vascular stalk seen within the intussusceptum, consistent with a polyp. The caecum and appendix are noted to be in normal position, in the right iliac fossa. The overall features are compatible with colo-colic intussusception with a polyp acting as the lead point.

Subsequently, the patient underwent successful reduction of the colo-colic intussusception using air enema procedure. Further evaluation with colonoscopy and endoscopic resection revealed a 2.8 cm juvenile polyp at the junction of the descending and sigmoid colon.

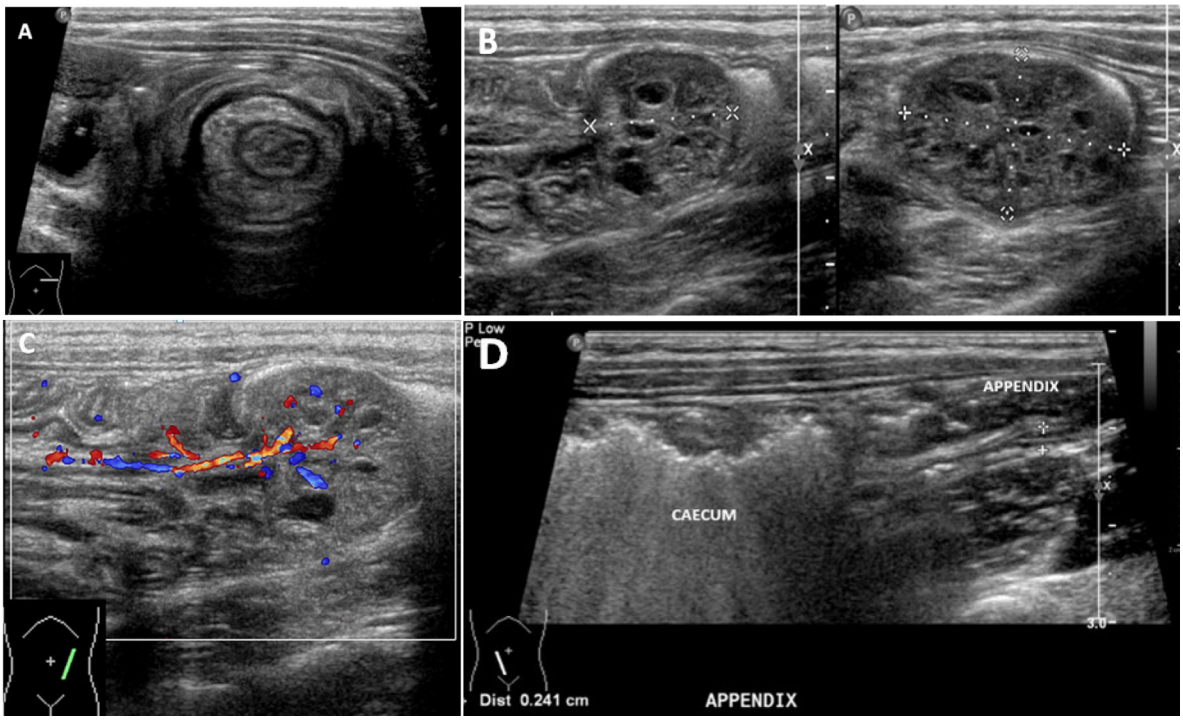

Fig. 1. A) A mass-like bowel lesion in the left upper quadrant of the abdomen with a "target sign" is seen. B & C) A polypoid mass with a vascular pedicle is seen within the intussusceptum. D) Caecum and appendix are detected at normal position in the right iliac fossa.

Answer: E

Discussion

Intussusception is the telescoping of a segment of bowel (the intussusceptum) into another segment of the bowel (the intussuscipiens).[1] It is the most common cause of bowel obstruction in the paediatric age group, occurring most commonly between the ages of 6 months and 2 years.[2] In our case, the child was above the typical age group for intussusception and has experienced recurrent episodes of intussusception. This raises the suspicion of a pathological lead point as a cause of the intussusception.

The classical triad of colicky abdominal pain, vomiting and passage of "red currant jelly" stool is present in less than 50% of cases.[3] A 3-year review by Lai et al demonstrated that 56.3% of patients presented with a palpable abdominal mass.[4] Early diagnosis is crucial for adequate management and prevention of complications. If left undiagnosed and untreated, bowel infarction or perforation may occur.

Plain abdominal radiographs have a limited role in diagnosis of the intussusception due to its low sensitivity (48%) and specificity (21%).[5] However, they are helpful in the detection of complications such as small bowel obstruction and perforation.

Ultrasound is the diagnostic modality of choice, due to its high sensitivity (97.9%) and specificity (97.8%),[5] with a high negative predictive value of 100%.[3] Abdominal sonography may demonstrate a soft tissue mass comprising alternating hyperechoic and hypoechoic rings, known as the "target" or "doughnut" or "bull's eye" sign.[3] "Crescent-in-doughnut" sign is the presence of a hyperechoic crescent-like area at the centre of the alternate hyperechoic and hypoechoic rings, due to the invagination of the mesenteric fat.[3] In addition, mesenteric lymph nodes can be detected within the crescentic mesenteric fat. Occasionally, a pathological lead point can be identified on ultrasound. Navarro et al showed in a study that ultrasound can detect 64% of the pathological lead points.[6] Preservation of vascularity within the intussusception can be observed on colour Doppler. Small amount of free intraperitoneal fluid is frequently seen on ultrasound.

Computed tomography and magnetic resonance imaging are not routinely used to diagnose intussusception in children although both are highly accurate in the diagnosis of the condition. These modalities are reserved for evaluation of selected patients with an atypical sonographic appearance, suggesting a pathological lead point such as lymphoma or a bowel mass.

Treatment options include image-guided enema reduction and surgical reduction. Contraindications for non-surgical management are dehydration, haemodynamic instability, peritonitis and perforation on abdominal X-ray.[7] The 2 most common techniques for image-guided enema reduction are fluoroscopy-guided pneumatic reduction and ultrasound-guided hydrostatic reduction. Overall, a success rate of 80% to 95% can be achieved by image-guided enema reduction.[7] Complications of image-guided reduction include perforation, with an overall rate of less than 1%.[7] Recurrence of the intussusception can occur in approximately 10% of cases, in which 50% will occur within 48 hours after initial reduction.[7,8] If image-guided reduction is not successful after 3 attempts, surgical reduction may be required.

There are different types of intussusception, depending on the region of the affected bowel; these include ileo-colic, ileo-ileo-colic, colo-colic and small bowel (jejuno-jejunal and ileo-ileal) intussusception.[3] The most common type is the ileo-colic variant, without a pathological lead point seen in a majority of the cases. According to Blake Lock et al, intussusception in children with a pathological lead point as a cause ranges from 1.5% to 12%.[9]

In the literature, the frequency of small bowel intussusception (ileo-ileal) varies between 1.6% to 25% of all cases of intussusception. Most of these cases are transient[10] and are treated conservatively.

Colo-colic intussusception is an unusual variant of a common paediatric condition, with only a few cases reported in the current literature. Review of 5 articles—published between 1978 to 2010 by Takahashi et al—showed that the mean age at diagnosis was 9.5 years (range, 7-11 years), with an increased prevalence in females.[11]

Most paediatric colo-colic intussusception cases occur with a lead point such as polyp(s)[12] or neoplasm (lymphoma).[3] Other rare causes reported in the literature have occurred in the clinical setting of Henoch-Schonlein purpura,[8] inflammatory bowel disease, adenocarcinoma, ganglioneuroma and hereditary angioneurotic oedema.

Image-guided enema reduction may be difficult in the presence of a pathological lead point, with a lower success rate and higher chance of recurrence. After successful reduction, further investigation with colonoscopy is recommended to evaluate the nature of the pathological lead point. Thus, it is important to accurately diagnose the colo-colic intussusception initially.

Ultrasound can help differentiate between ileo-colic and colo-colic intussusception. In ileo-colic intussusception, the normal caecal pole is not identified in the right iliac fossa due to invagination of the ileum through the ileocaecal valve into the caecum/colon. With careful scanning, the appendix may also be seen within the intussusceptum (Fig. 2). In contrast, in colo-colic intussusception (as in our case), the caecal pole and appendix remain at the normal position in the right iliac fossa (Fig. 1). In addition, the presence of a pathological lead point such as a polyp within the intussusceptum raises suspicion of a colo-colic intussusception.

In our case, the ultrasound features demonstrate the target sign, consistent with an intussusception. A polypoidal structure, a polyp with a vascular pedicle was seen within the intussusceptum. The appendix and caecum were noted in the right iliac fossa, thus excluding an ileo-colic intussusception.

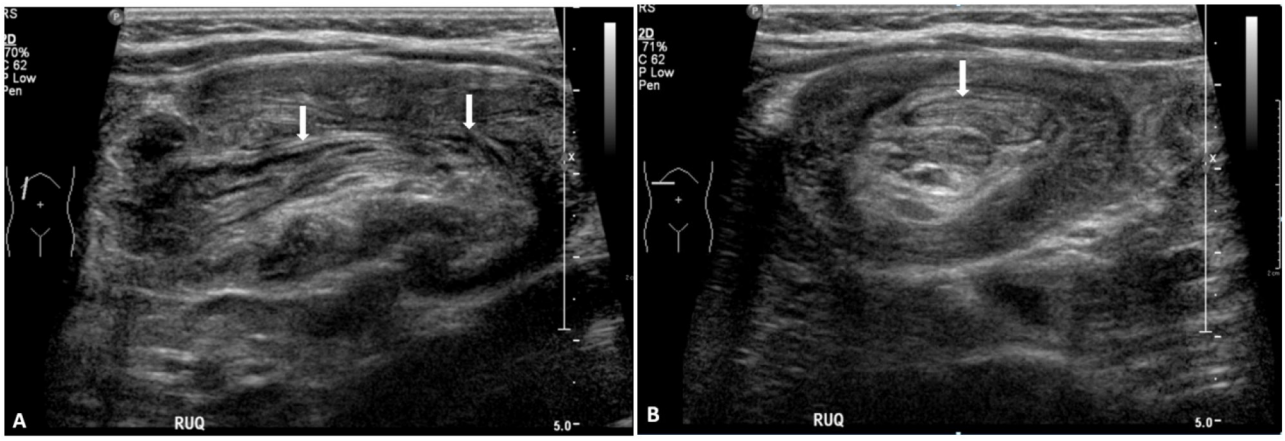

Fig. 2. Typical ileo-colic intussusception in the right upper quadrant of the abdomen. A) Longitudinal view shows a linear tubular structure (arrows) within the intussusceptum in keeping with the appendix. B) On transverse view, tip of the appendix (arrow) can be seen.

The diagnosis was that of colo-colic intussusception, with a polyp as a pathological lead point. It was successfully reduced with fluoroscopic-guided air enema reduction and no immediate complications occurred. The presence of a polyp at the junction of the descending and sigmoid colon was confirmed on colonoscopy performed at a later date (Fig. 3) and this was confirmed to be a juvenile polyp on histology.

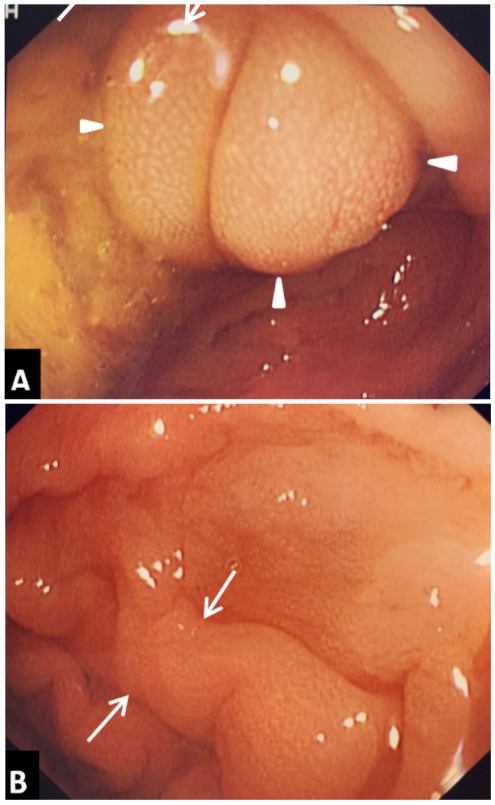

Fig. 3. Colonoscopy images show a polyp at the junction of the descending and sigmoid colon (arrowheads in A) with a stalk (arrows in B).

Conclusion

Intussusception is the most common cause of paediatric bowel obstruction. There are different types of intussusceptions. Most cases of ileo-colic intussusception are idiopathic in aetiology. The colo-colic intussusception is invariably associated with a pathological lead point, which may result in difficulty in its reduction as well as a higher chance of complications and recurrence. We have demonstrated that in older children (above the typical age group), with recurrent intussusception, a pathological lead point is usually the cause of the intussusception. Ultrasound imaging is crucial not only in the initial diagnosis of intussusception, but also in the accurate differentiation between the different types of intussusception as well as identification of a pathological lead point. In this way, the patient can be adequately managed without significant delay.

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