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An analytical cross-sectional study on the knowledge, attitudes, and practices (KAP) on biomedical waste management among nurses and medical technologists in the Philippines*

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Abstract

Introduction Unregulated biomedical waste management is an emerging public health problem in the Philippines. This study aimed to differentiate the knowledge, attitudes, and practices of nurses and medical technologists toward biomedical waste management.

Methods Using an analytic cross-sectional study design, an online survey of nurses and medical technologists from hospitals around the Philippines was conducted. A 27-item questionnaire covering knowledge, attitudes and practices was used. The percentages of correct answers and mean scores in each domain was compared between the nurses and medical technologists.

Results A total of 196 respondents consisting of 77 registered nurses and 119 medical technologists were included in the study. Medical technologists had significantly better knowledge scores than nurses on disposal procedures for expired blood units and by-products waste (55% vs. 19%, p = 0.026). Both had low correct responses on adequate disposal of human tissue remains, throwing blood waste into domestic waste, and throwing of expired medications in domestic waste. There was no significant difference in the attitude of nurses and medical technologists. Nurses had significantly better practice scores on disposal of liquid waste in bags (84.4% vs. 68.9, p = 0.018), but medical technologists fared better at disposal of human tissue together with other waste (13.0% vs. 2.5%, p = 0.006).

Conclusion Both nurses and medical technologists had adequate knowledge of some aspects but were lacking in others. There was no significant difference in the attitude of nurses and medical technologists towards biomedical waste management. Half of the respondents practiced proper biomedical waste management.

Key words: biomedical waste management, nurses, medical technologists, knowledge, attitudes, and practices (KAP)

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Biomedical waste from hospitals includes needles, scalpel blades, gloves, bandages, cotton, medicine, blood and body fluids, human tissues, radioactive substances, and chemicals. These objects may contain harmful organisms or contaminants that may adversely affect those who come into contact with these wastes. Improper or careless disposal poses a variety of health hazards, therefore they must be properly segregated and disposed. It is of utmost importance that those who handle these objects before disposal, including

nurses and medical technicians, have knowledge of the guidelines on how to properly dispose biomedical waste, have the right attitude towards handling waste, and apply their knowledge and attitude to proper handling procedures. However, studies have shown that not all of those who handle medical waste are aware of or follow these guidelines.

With the emergence of diseases that arise from numerous wastes from the surroundings, it is imperative to look into the Philippine health system's biomedical waste management. The World Health Organization (WHO) defines biomedical waste as composed of organisms that can infect medical personnel, health workers, patients, and the public. The hazardous nature of biomedical waste may be attributed to infectious agents, toxic or hazardous chemicals or pharmaceuticals, sharps, genotoxicity, and radioactive material. These outcomes may arise from inadequate training, absence of waste management or disposal systems, inadequate human and financial resources, and low priority given to biomedical waste management. According to the Department of Health (DOH), significant progress has been made on health care waste management. However, previous studies indicate the need to introduce modifications to existing health care waste management practices.

The objective of the study was to determine and quantify the knowledge, attitude, and practice of nurses and medical technologists regarding biomedical waste management during the 2nd quarter of 2020 in the Philippines. The study also aimed to differentiate the KAP of nurses and medical technologists toward BWM, by determining if there is a significant difference in the knowledge, attitude and practice mean scores between these two groups.

Methods

This is a cross-sectional analytic study to compare the knowledge, attitude, and practice (KAP) of nurses and medical technologists regarding biomedical waste management (BWM). Registered nurses and medical technologists, male or female, aged 21-60 years old, graduates of any school in the Philippines, employees of any hospital in the Philippines, and who practice biomedical waste management were recruited. Any nurse or medical technologist who has been part of their respective facility's waste management committee were excluded. Non-probability convenience sampling was done to acquire participants through online recruitment. The minimum required sample size is 260 each for nurses and medical technologists computed using a proportion of 32% for nurses and 20% for medical technologists with a 95% confidence level and a power of 80% based on a similar study by Olaifa.[1]

A modified survey tool consisting of 27 items (knowledge 11, attitude 4, practice 12) adapted from a questionnaire developed by Olaifa was utilized in this study.[1] Expert validation was conducted by the Chief Health Program Officer for Biomedical Waste of the DOH. Four items from the knowledge domain of the original questionnaire were omitted as advised by the expert since these items were not applicable in the Philippine setting and were not included in the latest DOH manual for biomedical waste. Data collection was conducted online via Google Forms. The responses for each domain were assigned a code and were recorded in Google Sheets. The questionnaire has score values for practices and knowledge domains as 2 for 'correct response', 1 for 'incorrect response', and 0 for 'I don't know response' whereas the score values for attitude domain were as follows: 5 as 'strongly agree' and 4 as 'agree' were coded as 2 for a correct response; 3 as 'disagree' and 2 as 'strongly disagree' were coded as 1 for an incorrect response; 0 for 'I don't know'. Reverse scoring applied for Item 8 on the practice domain and Items 14, 15, and 16 on the attitude domain.

IBM SPSS version 23 was used for the statistical analyses of the encoded responses. Descriptive statistics were used to determine the frequencies and proportions of the nurses and medical technologists' responses for the knowledge, attitudes, and practices in the provided questionnaire. To see if there was a significant difference in the responses per item in each domain of the questionnaire, the chi-square test was utilized with a 95% confidence interval ($p = 0.05$).

The study was approved by the UERM Ethics Review Committee. All participants were required to answer an online informed consent approved by the RIHS ERC before proceeding to the questionnaire. Privacy was ensured by restricting access to the files containing the responses to the researchers alone. Social desirability bias was controlled by providing descriptive questions to verify the respondents' knowledge, attitudes, and practices.

Results

Table 1 shows the demographic data of the study participants which consisted of 77 nurses and 119 medical technologists. Seven out of 10 respondents were female, 70% were 21-25 years old, and almost a third had been working for two years or less. A little more than a third of respondents (34.7%) had received formal training on biomedical waste management.

Table 2 shows that there is a significant difference in the knowledge of nurses and medical technologists concerning the following items: medical technologists had a higher proportion of correct answers on adequate disposal procedures for expired blood units and by-products waste (55% vs. 19%, p = 0.026); more medical technologists received supervision (79% vs 36%, p = 0.008); however, both nurses and medical technologists had low correct responses on the adequate disposal procedures for expired medicines (nurses 33% vs. medical technologists 28%, p = 0.007). Both nurses and medical technologists had low correct responses concerning the following items: the adequate disposal of human tissue remains (nurses 23.4%, medical technologists 26.1%, p = 0.737), throwing blood waste into domestic waste (nurses 7.79%, medical technologists 7.56%, p > 0.999), and throwing of expired medications in domestic waste (nurses 6.49%, medical technologists 12.6%, p = 0.228).

Table 3 shows that there is no significant difference in the attitude of nurses and medical technologists; however, there was a small proportion of both nurses and medical technologists who believe that the containment of sharps does not help in the management of hospital waste (nurses 37.66%, medical technologists 26.89%, p = 0.230). Table 4 shows a significant difference in the practice of nurses and medical technologists concerning the following items: more nurses than medical technologists practice the disposal of liquid waste in bags (nurses 84.42% vs. medical technologists 68.91, p = 0.018); and more nurses disposed of human tissue together with other waste (nurses 12.99% vs. medical technologists 2.52%, p = 0.006). Smaller proportions of nurses and medical technologists disposed of liquid waste together with other wastes (nurses 13.0%, medical technologists 7.6%), disposed of blood waste with other wastes (nurses 9.1%, medical technologists 2.5%), and disposed of expired medicines together with other wastes (nurses 18.2%, medical technologists 10.9%). Table 5 shows that the medical technologists had significantly higher overall mean scores (medical technologists 18.95, nurses 18.09, p = 0.028).

Table 1. Demographic characteristics of nurses and medical technologists (n = 196).

	Nurses	Medical Technologists	Total
Sex			
Female	60 (77.92%)	78 (65.55%)	138
Male	17 (22.08%)	41 (53.25%)	58
Age			
21-25	39 (50.65%)	99 (83.20%)	138
26-30	22 (28.57%)	15 (42.02%)	37
31-35	10 (12.99%)	4 (3.36%)	14
36 and older	6 (7.79%)	1 (0.84%)	7
Biomedical waste management training			
Received training	27 (35.06%)	41 (34.45%)	68
1-2 days	20 (25.97%)	32 (27.59%)	52
3-5 days	6 (7.79%)	4 (3.36%)	10
1 week or longer	0	2 (1.68%)	2
Not indicated	1 (1.30%)	3 (2.52%)	4
No training	50 (64.94%)	78 (65.55%)	128
Duration of present employment			
Less than 1 year	19 (24.68%)	35 (29.41%)	54
1-2 years	22 (28.57%)	50 (42.02%)	72
2-4 years	18 (23.38%)	15 (12.61%)	33
More than 4 years	17 (22.08%)	14 (11.76%)	31
Not indicated	1 (1.30%)	5 (4.20%)	6

Table 2. Comparison of the proportion of appropriate responses to knowledge questionnaire between nurses and medical technologists

	Nurses (n = 77)	Medical Technologists (n = 119)	p-value
Are you able to identify the types of medical waste?	74 (96.10%)	119 (100%)	0.059
Do you recognize the need to sort medical waste during collection?	74 (96.10%)	117 (98.31%)	0.383
Do you know the reason behind sorting (separation of) medical waste?	70 (90.90%)	115 (96.64%)	0.115
Are you aware of risks in dealing with medical waste?	66 (85.71%)	110 (92.44%)	0.151
Have you ever received any formal training on medical waste handling?	22 (28.57%)	45 (37.82%)	0.218
Do you know adequate disposal procedures for expired blood units and by-products waste?	19 (24.68%)	55 (46.22%)	0.003
Do you know adequate disposal procedures for human tissue remains?	18 (23.38%)	31 (26.05%)	0.737
Do you know adequate disposal procedures for expired medicine?	33 (42.68%)	28 (23.53%)	0.007
Do you believe that throwing blood waste into domestic waste is an adequate disposal procedure?	6 (7.79%)	9 (7.56%)	>0.999
Do you receive any form of supervision on the way you handle wastes?	36 (46.75%)	79 (66.39%)	0.008
Do you believe that throwing expired medicine into domestic waste is an adequate disposal procedure?	5 (6.49%)	15 (12.60%)	0.228

Table 3. Comparison of the proportion of appropriate responses in attitude questionnaire between nurses and medical technologists based on the median score.

	Nurses (n = 77)	Medical Technologists (n = 119)	p-value*
Segregation of waste at source increases risk of injury to waste handlers.	47 (61.04%)	75 (63.03%)	0.718
Containment of sharps does not help in safe management of hospital waste.	29 (37.66%)	32 (26.89%)	0.230
Hepatitis B immunization prevents transmission of hospital-acquired infections.	57 (74.03%)	95 (79.83%)	0.300
Reporting of needle-stick injury is an extra burden on work.	61 (79.22%)	103 (86.55%)	0.275

* Chi-square test

Table 4. Comparison of the proportion of appropriate responses in practice questionnaire between nurses and medical technologists

	Nurses (n = 77)	Medical Technologists (n = 119)	p-value*
Do you sort medical waste at source?	77 (100)	118 (99.16)	> 0.999
Do you separate sharp waste from blunt waste?	76 (98.70)	117 (98.34)	> 0.999
Do you use personal protection tools?	77 (100%)	119 (100%)	> 0.999
Do you think the number of people employed to handle waste in the hospital is adequate?	47 (61.04)	89 (74.79)	0.056
Do you dispose of liquid waste in bags?	65 (84.42)	82 (68.91)	0.018
Do you dispose of blood waste in bags?	62 (80.52)	99 (83.19)	0.704
Do you dispose of human tissue remains in separate bags?	63 (81.82)	91 (76.47)	0.476
Do you dispose of liquid waste with other waste?	10 (12.99)	9 (7.56)	0.225
Do you dispose of blood waste together with other waste?	7 (9.09)	3 (2.52)	0.051
Do you dispose of human tissue remains together with other waste?	10 (12.99)	3 (2.52)	0.006
Do you dispose at the source the expired medicines together with other waste?	14 (18.18)	13 (10.92)	0.202
Do you dispose of liquid waste into the sewage system?	27 (35.06)	54 (45.38)	0.182

* Chi-square test

Table 5. Comparison of the mean scores of nurses versus medical technologists on knowledge, attitude, and practice

	Nurses (n = 77)	Medical Technologists (n = 119)	Mean Difference	p-value*
Knowledge	18.09 (2.966)	18.95 (2.389)	0.859 ± 0.385	0.027
Attitude	11.39 (2.014)	11.19 (1.879)	-0.196 ± 0.283	0.488
Practice	19.69 (2.429)	19.32 (2.600)	-0.369 ± 0.371	0.321

* Chi-square test

Discussion

Knowledge

A high proportion of both nurses and medical technologists demonstrated knowledge regarding the identification of different types of medical waste. For nurses, the type of medical waste they could identify the most were sharp wastes, and the least were non-hazardous wastes. Medical technologists were most able to identify infectious wastes and the least able to identify cytotoxic wastes. Tayaben stated that nurses sustain the highest number of percutaneous injuries related to sharps and needles among all surveyed health care workers and this may be linked to the nature of their work and the frequency of needle use.[2] Hence, they are more likely to identify sharp wastes above other types of medical wastes. Rajan found that medical technologists are most likely to identify infectious wastes because the nature of their work is to process and examine body fluids such as blood, serum, urine, sputum, and muscle tissues.[3] They are exposed to these infectious wastes from collection, reception, and up to the examination of the potentially infectious samples.

Medical technologists have a higher proportion of correct answers than nurses concerning the adequate disposal procedures for expired blood units and by-products waste (55% vs. 19%). In a similar study by Mugabi, nurses had poor knowledge on proper disposal of expired units which was attributed to not having formal training on BWM.[4] In the study, nurses and medical technologists, in general, had poor knowledge regarding the presence of recycling services (e.g., waste disposal) in the hospital. Likewise, previous training, availability of training, and awareness of recycling of medical waste scored lowest despite them being knowledgeable on the basics of BWM and handling (e.g., categorization/disposal of waste).

More medical technologists received supervision compared to nurses (79% vs. 36%). Results are in contrast with that from Olaifa who found that lack of supervision and monitoring of BWM practices are common.[1] A reason for this may be that since medical technologists are situated in only one common workplace, the laboratory, more frequent and easier supervision is done by their superiors, compared to the nurses roaming around the hospital.[5] Among nurses, however, the majority stated that they lack supervision; this is congruent with the findings of Olaifa, Sobh, and Muthoni.[1,6,7] These studies indicate that there may be an inadequate effort made to ensure proper knowledge of and compliance with hospital policies on BWM, concluding that there is a need to supervise all aspects of BWM. The difference in response of both groups may be explained by their response on the item where they stated that there are not enough people employed to handle biomedical waste.

However, both nurses and medical technologists had low correct responses on the adequate disposal procedures for expired medicines, though more nurses responded correctly (33% vs. 28%). Although the DOH Manual states that expired medicine should be disposed of in the yellow container with a black band, results showed otherwise.[8] Aside from both groups handling patients, most hospitals have pharmacists and inspectors who facilitate the quality assurance of each medicine dispensed. The primary role of the inspectors is to evaluate drug manufacturing processes and final products in order to ensure their safety and quality. According to the WHO, inspectors should have previous training and practical experience in the manufacture and/or quality control of pharmaceutical products and should be knowledgeable on the procedures for handling returned and time-expired drugs resulting in both respondents not having adequate knowledge on the disposal of expired

medicines.[9] Agaceta found that pharmacists are also in charge of pharmaceutical care (medication counseling and clinical pharmacy).[10]

Similarly, both nurses and medical technologists had low percentage of correct responses on the following items: the adequate disposal of human tissue remains (nurses 23.4%, medical technologists 26.1%), throwing blood waste into domestic waste (nurses 7.8%, medical technologists 7.6%), and throwing of expired medications in domestic waste (nurses 6.49, medical technologists 12.60%). Studies by Jahan, and Adogu and Ubajaka had similar results in which a lower percentage of nurses and medical technologists had knowledge on the use of a yellow disposal container assigned to human tissue remains and infectious material, compared to other biomedical wastes.[11,12] In addition, nurses and medical technologists had poor knowledge of recycling services (e.g., waste disposal) in the hospital.[2] Since the majority of nurses and medical technologists did not receive any formal training on waste management, this resulted in poor knowledge on the proper disposal of human tissue remains for both nurses and medical technologists, which is congruent with responses to the question if both groups received formal training in this matter. Thus, the lack of adequate training on healthcare waste management may also result in inadequate knowledge on pathological (e.g., human tissue remains) waste disposal.

Attitudes

Nurses and medical technologists had the same attitude towards BWM. The results of this study are similar to the findings of Olaifa.[1] This study also showed that both nurses (37.7%) and medical technologists (26.9%) scored low on the negative attitude that containment of sharps does not help in the safe management of hospital waste. Injuries from sharps is a known safety hazard in BWM. Cruz showed that various health consequences related to biomedical waste exposure include sharps injuries.[14] The respondents, therefore, believe that the containment of sharps is necessary and contributed to the safer management of hospital waste.

Practices

More nurses than medical technologists practice the disposal of liquid waste in bags (84.4% vs. 68.9). Both groups comply with the practice of disposing of liquid waste in bags to avoid leakage and is in accordance with the Department of Health Healthcare Waste Manual that waste should be packaged in sealed bags or containers to prevent spillage during handling and transportation for off-site collection.[8] The results are similar to those of Abrol, wherein the majority of healthcare personnel disposed of these wastes in separate puncture-proof bags.[15]

More nurses than medical technologists disposed human tissue together with other waste (13.0% vs. 2.5%). This is in connection with responses on the type of waste the respondents were able to identify, wherein a lower frequency of nurse and medical technologists identified pathological waste. Deress and colleagues stated that the difference might come from the educational level, previous training, use of visual aids, presence of color-coded bins, and presence of guidelines in the department.[17] Jahan had similar results in which a lower percentage of nurses and medical technologists had proper knowledge of the yellow disposal container assigned to human tissue remains and infectious material, compared to other biomedical wastes such as radioactive wastes and sharps.[18] Similarly, Adogu and Ubajaka found that nurses and medical technologists had poor scoring of infectious waste segregation at 24% and 33% of the total respondents, respectively.[10]

Smaller proportions of nurses and medical technologists disposed of liquid waste together with other wastes (nurses 13.0%, medical technologists 7.6%), dispose of blood waste with other wastes (nurses 9.1%, medical technologists 2.5%), and disposed of expired medicines together with other wastes (nurses 18.2%, medical technologists 10.9%). This is consistent with the results of Parida establishing that primary healthcare workers practice segregation of infectious and non-infectious waste.[19] This was attributed to the fact that these healthcare workers were well versed with waste segregation, color coding, and the important health hazards of biomedical waste.[19] If the liquid and blood wastes are infectious, then these wastes should be carefully placed in clearly labeled containers separated from other wastes. This is to decrease health hazards resulting from poor waste management as not only the medical staff are at risk of injury or infection, but also the general public.[20] Expired medicines must not also be disposed of with other wastes as some drugs, such as antineoplastic drugs, may be unstable and may have serious effects

when disposed improperly into the environment with other wastes.[21] Results here are parallel with the knowledge of the participants regarding these disposal procedures. Since they have scored less on knowledge, they also practice less. However, despite the majority of nurses and medical technologists stating they have no knowledge regarding procedures on how to adequately dispose of liquid wastes, the majority of these healthcare workers claim that they practice disposing of these wastes in bags which is in accordance with the DOH guidelines. The result of having poor knowledge but good practice may be attributed to the presence of guidelines, the use of visual aids, and the availability of properly labeled color-coded bins in the facility which have been identified as key factors for effective BWM.[16] The scores may reflect that handling certain types of wastes, despite it being part of hospital policies based on DOH guidelines, are not in the scope of the job of the nurses and medical technologists, as these are usually being handled by nurse aides. This study has identified a knowledge gap that may expose these healthcare workers to occupational risks which appropriate training has the potential to prevent as in a study by Nwanko on hospital cleaners.[22]

Knowledge, Attitude, and Practice

According to Mathur, the knowledge about BWM rules among hospital personnel such as doctors, nurses, and medical technologists is high.[23] A significant difference was found in the knowledge of nurses and medical technologists which may be attributed to the varying scopes and job descriptions within the hospital. The revised Organizational Structure and Staffing Standards for Government Hospitals show that protocols, number of staff, and service structures vary per hospital level, therefore hospitals may not have a standardized protocol on BWM (e.g., bins, treatment facility), and the number of supervisors per department varies per hospital level.[24]

On the other hand, there is no significant difference in the attitude and practices of both nurses and medical technologists regarding biomedical waste management. Hospital protocols, guidelines from the Health Care Waste Management Manual of the DOH, and Ordinance No. 16 Series of 1991, which regulates the management, collection, and disposal of hospital waste and similar institutions in Metro Manila, could be possible explanations as to why healthcare workers have the same attitude and practices of BWM.[25] Since practices of nurses and medical technologists do not differ greatly, this may explain why they have the same attitude towards BWM as well.

In conclusion, the assessment of the participants' knowledge showed that both nurses and medical technologists were able to identify types of medical waste, sort medical waste, state the reasons for waste sorting at the site, and name risks associated with medical waste; however, a significant number of participants did not have knowledge with regards to disposal procedures of expired medicine and expired blood units. The knowledge of nurses and medical technologists differed only regarding their knowledge of supervision. As for attitude, it has been found that there is no significant difference in the attitude of nurses and medical technologists towards biomedical waste management. Lastly, the assessment of the participants' practices has shown that half of the participants practice proper biomedical waste management in terms of sorting waste at source, separating sharp waste from blunt waste, using personal protection tools, and disposing of blood/liquid/human tissue remains in separate bags. The practices of nurses and medical technologists differed only in the disposal of human tissue remains together with other waste.

Given these, the researchers recommend that hospitals of all levels, laboratory clinics, and other medical facilities conduct formal training on medical waste handling as a requirement for all nurses and medical technologists; multiple training sessions may be necessary for the effective and complete practice of biomedical waste management. Topics on medical waste handling should also be included as part of the undergraduate curriculums of colleges and universities not only for nurses and medical technologists but for all other allied healthcare professionals as well. Strict supervision and surveillance should be followed in waste management activities in the hospital.

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Correlation of internet addiction to psychological well-being among high school students from private schools in Metro Manila

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Abstract

Introduction The social environment of adolescents plays a significant role in their psychological well-being, which in turn contributes to their personal development as individuals. This research aimed to determine the correlation between internet addiction and the psychological well-being of high school students in private schools in Metro Manila for the school year 2020-2021.

Methods High school students from Grades 7-12 in private schools in Metro Manila, with at least one account in any social media platform participated. The Internet Addiction Test and The Flourishing Scale were used to determine internet addiction and psychological well-being, respectively. Spearman's rank-order correlation was used to determine the magnitude of correlation between internet addiction and psychological well-being.

Results The prevalence of internet addiction was 46.1% among 128 respondents. The mean psychological well-being score of the participants was 45.9 ± 7.84. There was weak statistically significant negative correlation between psychological well-being and internet addiction ($r_s(126) = -0.346$, $p < 0.001$).

Conclusion Students with higher scores of internet addiction were more likely to have lower scores in psychological well-being. There was weak statistically significant negative correlation between psychological well-being and internet addiction.

Key words: adolescent, internet addiction, psychological well-being

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Internet addiction is characterized by the excessive and poorly-controlled preoccupation, urge, and behavior relating to computer use and internet access that may lead to impairment or distress to the user.[1] Due to the internet's role as a means of modern-day communications and as an access to vast resources of information, dependence on it can develop and eventually lead to internet addiction. The population of internet users had increased from 360 million in December 2000 to 4.5 billion by June 2019, and of

this population, adolescents are found to be more predisposed to internet addiction since they spend more time on the internet than adults.[2,3] In 2013, people aged 24 years and younger accounted for 45% of internet users worldwide.[4] Filipino youths aged 8-18 comprise the highest proportion of children who use electronic tablets as compared to children from Bahrain, Honduras, and Japan, according to a study by Groupe Spécial Mobile Association (GMSA).[5] In addition, a study showed that Filipino youths cannot live without digital media, and that in all of Asia, they are the most inclined to social networking.[6]

The psychological well-being of adolescents is correlated with their social environment to a large extent.[7] In Ryff's psychological well-being theory, self-acceptance, positive relations with others, autonomy, environmental mastery, purpose in life, and personal growth are closely related with psychological well-being.[8] A study discovered that excessive use of the internet can cause a negative effect on face-to-face interactions due to the reduction in time spent with family and friends, leading to an increase in loneliness and depression, and thereby a decrease in psychological well-being.[9]

Since the psychological well-being of adolescents plays a significant role in their personality and development, this study was done to determine the magnitude and direction of correlation between internet addiction scores and psychological well-being scores among private high school students in Metro Manila for the school year 2020-2021. In addition, this also aimed to determine the prevalence of internet addiction among private high school students in Metro Manila and to assess their psychological well-being scores using the Self-Flourishing Scale.

Methods

This was a correlational study among high school students from private schools in Metro Manila. Two questionnaires were used: one measured the independent variable internet addiction and the other measured psychological well-being, the dependent variable. This study was approved by the Ethics Review Committee.

The target population were high school students from Grade 7-12 in private schools in Metro Manila recruited via convenience sampling. The inclusion criteria were: a) male or female aged 10-19 years enrolled in Grade 7-12 in a private school in Metro Manila for the academic year 2020-2021; b) uses at least one type of social media platform (i.e., Facebook, Twitter, Gmail, Instagram, Viber, etc.). The following were excluded: a) students with special needs; b) previously diagnosed with mental disorders (depression, other addictive disorders, obsessive compulsive disorders, generalized anxiety disorders). The minimum required sample size was 163 based on the correlation coefficient of -0.218, confidence interval of 95% and a power of 80% using the correlation coefficient formula.[10]

The Flourishing Scale, an 8-item summary survey of a person's self-perceived success in different aspects of life such as relationships, self-esteem, purpose, and meaning, was used to assess psychological well-being. The Flourishing Scale is a valid test for measuring the psychological well-being of adolescents, adults, and the older population (12-111 years old), and it has a good reliability score ($a = 0.91$).[11] The Internet Addiction Test is a 20-item Likert scale that measures factors associated with the compulsive use of the internet including problems from internet use related to personal, occupational, and social functioning. The test was computed to have a reliability coefficient Cronbach's alpha of 0.90. It is also a valid test to measure an individual's internet addiction.[12]

The participants were invited to participate in the study through online advertisements posted on different social media platforms such as Facebook, Twitter, and Instagram. The hyperlink of the informed consent and assent form were also posted along with the advertisement. When the hyperlink was clicked, it redirected the user to a Google Forms site. Users had three options to select from: 1) parent, 2) below 18 years old, and 3) 18 years old and above. Upon selecting the appropriate answer, the page was redirected to the following: 1) If they were a parent, an informed consent was flashed on the screen. If the parent consented, they were required to give their contact details, either an email address, mobile number, or any social media account handle, their child's name, school, year level for the school year 2020-2021, and contact information. The data collectors informed the parent about their consent and child's participation in the study via text message or email. Attached within the email/message was another hyperlink redirecting them to the checklist of the inclusion and exclusion criteria and assent form to be filled out by their child, along with the main questionnaires. To ensure that the forms were

filled out, the data collectors also sent the child the hyperlink to the assent form and main questionnaire via the contact information given by their parents. 2) If they were below 18 years old, a checklist of the inclusion and exclusion criteria and the assent form were needed to be filled out. After that, they gave their names, contact information, either an email address, mobile number, or any contact details of their parents, as well as their own. The data collectors sent the parents an email or text message via the contact details provided by the student, saying that their child wanted to participate in the study with a hyperlink to the informed consent form. When the parent consented, a hyperlink of the main questionnaires was sent to both the parent and the participant. However, if the participant was together with his/her parent after filling the assent and criteria forms, they may be immediately redirected to the informed consent form and main questionnaires. 3) If they were 18 years old and above, a checklist of the inclusion and exclusion criteria and the informed consent were needed to be filled out, and then the main questionnaires. The questions were set to "required data" on the Google Form to ensure that the participants did not miss answering a question.

The Internet Addiction Test consisted of 20 items rated on an ordinal scale from 0 to 5, representing how often the participant experienced the situation described in the question. The responses were graded as 0 - does not apply, 1 - rarely, 2 - occasionally, 3 - frequently, 4 - often and 5 - always. When added, all the scores displayed a result ranging from 0-100. No internet addiction was considered when the score ranged from 0–49 and those with scores of 50-100 were considered to have internet addiction.

The Flourishing Scale was an 8-item questionnaire rated on a scale from 1 to 7, that represented the participant's degree of agreement in the stated questions. The responses were graded as 1 - strongly disagree, 2 - disagree, 3 - slightly disagree, 4 - neither agree nor disagree, 5 - slightly agree, 6 - agree, and 7 - strongly agree. The scores ranged from 8-56. Those who obtained a low score was considered to have a low psychological well-being, while those who obtained a high score had good psychological well-being. A high score was considered to represent a person with many psychological resources and strengths.

IBM SPSS Statistics 22 was used to process and analyze the data. Frequency distribution was used to analyze the demographic characteristics of the participants, such as age, sex, and grade level. The prevalence of internet addiction was computed by dividing the number of respondents with a score of 50-100 over the total number of respondents who participated in the study. Spearman's rank-order correlation and scatter plot were used to determine the magnitude and direction of correlation between the internet addiction and psychological well-being.

The study was approved by the UERMMMCI Research Institute for Health Science Ethics Review Committee. This study ensured the autonomy of the participants. The participants were informed that the study was completely voluntary. They were also informed about the purpose of the study as well as the risks and benefits involved. Safety and privacy were ensured throughout the data collection process by reassuring participants of their confidentiality.

Results

The study had a total of 161 responses, with 25 respondents whose parents did not consent, one respondent with special needs, one with clinically-diagnosed depression, one whose school was not in Metro Manila, two who did not wish to participate, one who was not currently enrolled, and two parental responses but their child did not wish to participate. The final number of valid responses and participants was 128 high school students. The mean age of the respondents was 15.8 years and there were more females (n = 77) than males (n = 51). Most of the respondents were in Grade 12 (n = 49). (Table 1)

Table 2 shows that out of the 128 participants, 46.1% (n = 59) were found to have internet addiction while 53.9% (n = 69) were classified as having no internet addiction. The computed mean psychological well-being score of the respondents was 45.9 ± 7.84. Figure 1 shows an inverse relationship between psychological well-being and internet addiction based on the line of fit. A Spearman's rank-order correlation, showed a weak negative correlation between psychological well-being and internet addiction, which was statistically significant ($r_s(126) = -0.346$ (-0.494 to -0.178), $p < .001$).

Discussion

In terms of the prevalence of internet addiction among the present study's participants, the results are higher at 46.1%, as compared with other studies. A study in

Table 1. Demographic characteristics of 128 respondents.

Variable	Mean/frequency	Standard deviation/ percentage
Age (year)	15.8	± 2.51
Sex		
Male	51	39.8
Female	77	60.2
Level		
Grade 7	5	3.9
Grade 8	19	14.8
Grade 9	13	10.2
Grade 10	15	11.7
Grade 11	27	21.1
Grade 12	49	38.3

Table 2. Internet addiction among 128 Grade 7 to 12 students in private high schools in Metro Manila.

Variable	Mean/frequency	SD/percentage
Internet addiction score	45.5	±17.41
No internet addiction	69	53.9
With internet addiction	59	46.1

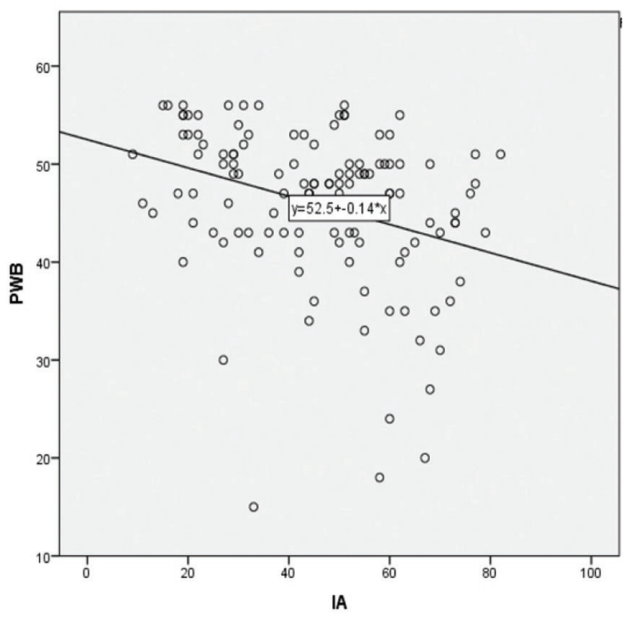

Figure 1. Scatterplot of psychological well-being and internet addiction

China reported an 8.8% rate of internet addiction.[13] Another study conducted in Italy showed a 5.4% rate, while a 1.5% rate was observed in Greek students.[14,15] Several other international studies made use of the term "problematic internet use" (PIU) instead of internet addiction, but both refer to addictive patterns of internet use. Another study from China found that only 5.5% of adolescent students demonstrated problematic internet use.[16] This finding appears to also be largely inconsistent with other studies that used different measures to assess PIU, such as seen in a 3% prevalence among a Korean adolescent sample in 2013, and a 17.6% prevalence among Qatar adolescents.[17,18] Moreover, on a local city scale, the findings of the present study are also higher than that of a study in Baguio City in 2014 where only 24.7% of the adolescent participants met the criteria for internet addiction.[19] While further studies and standardized diagnostic criteria are necessary before direct comparison among studies can be made, the relatively high prevalence estimates suggest that internet addiction is an emerging global mental health problem. With the widespread availability, acceptance, and explosive growth of internet and social networking sites directed at this age group, internet addiction could be a serious concern with a significant public health impact. Alternatively, the higher prevalence of internet addiction in this study may be because students cannot go outside due to quarantine, resulting in longer exposure to the internet or staying online since it may be the only source of entertainment and social interaction.

With regard to the Flourishing Scale, the results of the present study indicated that the psychological well-being mean (45.9) of the participants was higher compared to a similar study in Thailand, where the mean for a sample of university students was 33.3 (SD = 4.90).[20] A relatively higher psychological well-being mean among Filipino adolescents may be explained by Filipino families generally having close ties and being family-centered and child-centric. In a qualitative study that investigated the role of family in Filipino adolescents' behavioral health needs, findings suggest that one's family environment may have a significant influence as the Filipino family is seen as a source of positive support for some Filipino youth.[21]

The present study shows an inverse relationship between psychological well-being and internet addiction. This is consistent with a study in 2016 which revealed that there was a significant

negative correlation between internet addiction and psychological well-being among the youth of Kashmir, India (r = -0.218*, p = 0.03).[10] More recently, a similar study in 2018 in Central India found internet addiction to be significantly negatively correlated to psychological well-being (r = –0.572, p < 0.01).[22] This means students with higher scores of internet addiction are more likely to have lower scores in psychological well-being. Furthermore, this finding is also consistent with that of a 2013 study from Turkey where internet addiction was found to negatively predict psychological well-being, although the participants were university students.[23] There are several possible explanations for a relatively lower psychological well-being mean in relation to higher internet addiction score. For one, the unnecessary use of gadgets has the tendency to limit the amount and reduce the quality of face-to-face interactions. This reduction in time spent with friends and loved ones may lead to dissatisfaction in one's personal relationships. This is supported by a study stating that individuals who use gadgets excessively are likely to have less of a feeling that their social relationships are supportive and rewarding, or less of a feeling that they actively contribute to the happiness and well-being of others.[24] Furthermore, nomophobia (abbreviated form of "no mobile phone phobia"), a term recently coined to refer to the anxieties or feelings of discomfort of losing or being away from one's mobile phone, is believed to be associated with excessive use of mobile phones. Related to this, excessive use of gadgets is also known to often lead to sleep disturbances, which, in turn, may affect a person's psychological well-being. The results revealed a weak inverse relationship between psychological well-being and internet addiction. This means that a higher score on the internet addiction test is correlated to a lower psychological well-being. Findings of this study may be used to formulate health programs and information, education, and communication materials that can educate high school students on the impact of internet addiction on their psychological well-being. High school students can then be informed of several adverse effects of excessive internet use and use this knowledge to prevent internet addiction and thus prevent development of poor psychological well-being.

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Effectiveness of *Saccharomyces boulardii* on diarrhea, a systematic review and meta-analysis

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Abstract

Introduction Probiotics such as *Saccharomyces boulardii* are now advocated for the treatment of diarrhea. The objective of this systematic review and meta-analysis was to determine the effectiveness of *Saccharomyces boulardii* in the treatment of diarrhea.

Methods MEDLINE, EBSCO, Clinical Key, and the Cochrane Library were searched for clinical trials which used *Saccharomyces boulardii* as primary or adjuvant treatment for diarrhea. Outcomes included were treatment success in the form of cessation of diarrhea, decrease in the duration of diarrhea, decrease in hospital days, and improvement of dehydration. The Centre for Evidence-Based Medicine Critical Appraisal tool together with the Cochrane Collaboration tool was used to assess the risk of bias, RevMan 5.4 for encoding, and the Mantel-Haenszel method for analysis to compute a pooled result.

Results Eleven clinical trials involving 1,541 participants were included in the systematic review and meta-analysis. Seven studies showed a non-significant overall decrease in the duration of diarrhea of 1.65 days ($p = 0.25$), five studies showed an overall significant beneficial response (RR = 1.68, $p < 0.001$) in the cessation of diarrhea. There was a statistically significant mean decrease (1.01 days, $p < 0.001$) in duration of hospitalization; and a statistically significant decrease (0.18 days or 4.32 hours, $p = 0.04$) in the duration of vomiting.

Conclusion A systematic review and meta-analysis of 11 clinical trials favors the use of *Saccharomyces boulardii* in the treatment of diarrhea in terms of cessation of diarrhea, decrease in the duration of hospitalization and duration of vomiting.

Key words: diarrhea, probiotic, *Saccharomyces boulardii*

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Diarrhea or loose bowel movement is one of the most common symptoms leading to health care consultation. Hydration and conservative management is recommended when diarrhea is assessed to have a viral cause. One of the modalities being advocated in treating diarrhea is the provision of probiotics. *Saccharomyces boulardii*, a live yeast marketed as a dietary supplement, is a promising therapeutic adjunct for diarrhea. With the numerous drugs being offered to physicians and each drug company espousing the good qualities of their product, a meta-analysis is a valid evidence-based guide for physicians. From 1976 to 2015, there have been 90 randomized controlled trials on *S. boulardii* for treating 15 different disease conditions. The most documented evidence-based uses are the treatment of acute pediatric diarrhea,

prevention of antibiotic-associated diarrhea, and the treatment and prevention of *Helicobacter pylori* infections. A few studies found *S. boulardii* to be effective for the treatment of acute adult diarrhea and the treatment of inflammatory bowel disease. Other disease indications such as adjunctive treatment for *Clostridium difficile* infections, giardiasis, traveler's diarrhea, and enteral nutrition-related diarrhea also show promising outcomes.[1]

This meta-analysis will serve as a guide for Filipino physicians in their decision making in their clinical practice on the use of *Saccharomyces boulardii*. The objective of this meta-analysis was to determine the effectiveness of *Saccharomyces boulardii* in the treatment of diarrhea.

Methods

This meta-analysis was done according to the fundamentals laid in the Cochrane Handbook for Systematic Reviews of Interventions and as stated by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[2,3]

Clinical trials from 1985 onwards, randomized or non-randomized, which compared *Saccharomyces boulardii* at any dose, used as an adjunct or as treatment, compared with a control or placebo in the treatment of diarrhea in children were selected. Only English language articles were considered. Outcomes were indicators of treatment success, such as cessation of diarrhea, decrease in the duration of diarrhea, decrease in duration of hospitalization, improvement of dehydration, and others.

A literature search was conducted on MEDLINE and an academic search on EBSCO, ClinicalKey and the Cochrane Library using the following terms and MESH headings diarrhea/diarrhoea, diarrh*, probiotic*, children, child*, *Saccharomyces boulardii*, and *S. boulardii*. To ensure literature saturation, the team scanned the reference lists of the revtrieved studies or relevant reviews identified through the search. Literature search records were uploaded to RevMan 5.4 and shared among the reviewers. The reviewers developed and tested screening questions and forms for the Level 1 and 2 assessment based on the selection criteria. Training on the use of RevMan 5.4 was provided for the whole team.

Four review authors independently screened each title and abstract yielded by the search. The full text of all titles and abstracts that met the selection criteria, and those that required further scrutiny, were retrieved. Review author pairs then screened the full text articles and decided whether these articles met the selection criteria. Additional information was obtained from the study authors, when necessary, to resolve questions about eligibility. Disagreements were resolved through discussion among all the authors. The reasons for the exclusion of studies were recorded. The review authors were not blinded to the journal titles nor to the study authors or institutions.

Using the RevMan 5.4, three teams of author reviewers extracted the data in duplicate from each eligible study. To ensure consistency across reviewers, all attended training exercises using the RevMan 5.4 training guide. Data extracted from each study included the following: sociodemographic characteristics of the participants, intervention and comparators and their dose, frequency and duration of administration, including the drugs taken in studies where *Saccharomyces boulardii* was used as adjuvant therapy, all reported outcomes including the effect size and the statistical analysis done for the outcomes. The trial design, number of participants for each arm, duration of follow up, attrition rate, and source of financial support were also collected. Data for both the per protocol and the intention-to-treat analysis were extracted. Reviewers resolved disagreements through discussions. Two main authors (JGJ and RLC) adjudicated unresolved disagreements. Study authors were contacted for any uncertainties.

The primary outcome was the number of persons who had successful treatment. Successful treatment was defined as decrease in the length of hospital stay, resolution of the diarrhea, resolution of the dehydration. Secondary outcomes - continuous variables like the decrease in hospital days, increase in weight, quality of life scores, and decrease in the duration of diarrhea, were also extracted. The number of participants experiencing at least one side effect and the number of individuals experiencing each side effect were also noted.

To assess the risk of bias, critical appraisal of each article was done using the Centre for Evidence-Based Medicine (CEBM) Critical Appraisal tool. To facilitate the assessment however, information was collected using the Cochrane Collaboration tool for assessing the risk of bias which covered allocation randomization, concealment, blinding, incomplete outcome data, dropouts, and selective outcome reporting. This was encoded using RevMan 5.4. For each domain in the

tool, a statement or description was encoded to assist the reviewers in assessing the degree of the risk of bias. Two review authors assessed the risk of bias based on the criteria for judging the review of bias. Disagreements were resolved by discussion and if not resolved, was done by arbitration. A table for the risk of bias was generated using RevMan 5.4.

The proportion with successful treatment was extracted from the data. A 2 x 2 table was developed with the frequencies of those who had and did not have successful treatment tabulated. The relative risk was computed for each data set. The data set was encoded in RevMan 5.4 for analysis. The Mantel-Haenszel method was used for pooling together the effect of individual data using relative risk. $P < 0.05$ was used as a statistical significance level together with the 95% confidence interval. A relative risk of > 1.00 was deemed as a positive outcome which would favor the use of *Sacharomyces boulardii*. The use of a random or fixed effects model was determined by the statistical heterogeneity which was evaluated by chi-square and I-tests.[4] An I^2 value of 0 to < 40% was considered as no significant heterogeneity, 30-60% as moderate heterogeneity, 50-90% as substantial heterogeneity and 75-100% as significant heterogeneity. The authors used an I^2 result of > 75% and a X^2 result of $p < 0.01$ as indicative of statistical heterogeneity.[5] Continuous outcomes were analyzed using weighted mean differences (with 95% CI) or standardized mean differences (95% CI) if different measurement scales were used. Skewed data and non-quantitative data were presented descriptively.

The authors evaluated whether selective reporting of outcomes (outcome reporting bias) was present. The fixed effects estimate was compared against the random effects model to assess the presence of small sample bias in the published literature (i.e., in which the effect of the intervention is more beneficial in smaller studies). In the presence of small sample bias, the random effects estimate of the intervention is more appropriate than the fixed effects estimate. The potential for reporting bias was further explored by funnel plots if ≥ 10 studies were available.

Results

A total of 497 titles were identified from the search and 17 more were identified through the references and abstracts. After removal of duplicates, 454 titles remained, of which 370 titles were excluded because the titles clearly identified that the articles were not about effect of *Saccharomyces boulardii* on diarrhea. The full texts of the remaining 84 articles were retrieved and assessed for relevance; 68 titles were excluded for reasons stated in Figure 1. Sixteen full text articles were included in the systematic review but only 11 studies were included in the meta-analysis as five articles had unclear and/or undefined outcome measurements and results (Figure 1).

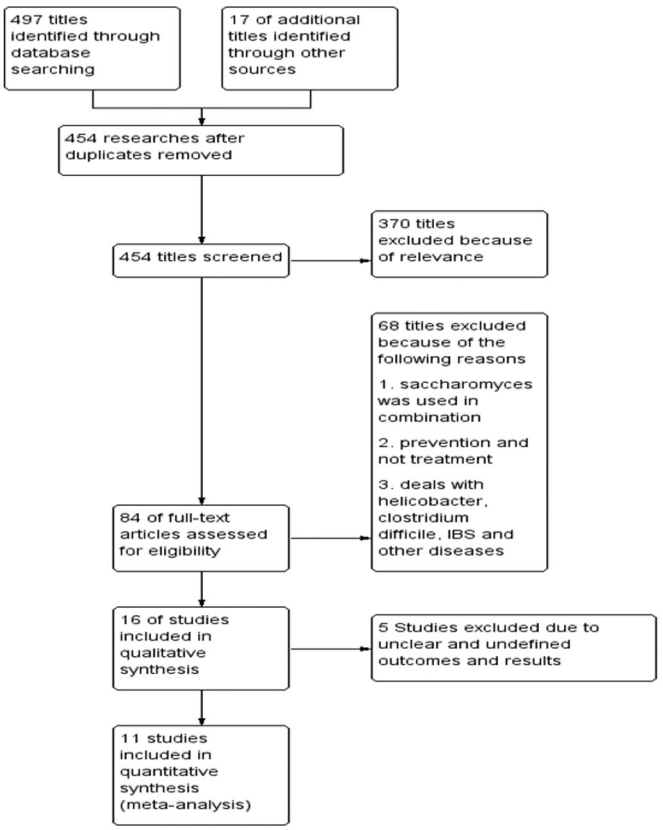

Figure 1. Flow diagram, *Saccharomyces boulardii* for diarrhea

Study Characteristics Table 1 shows the characteristics of the 11 included studies which involved a total of 1,541 participants consisting of 812 participants in the treatment and 729 in the control groups, respectively. The combined study population included infants and children from one month to 14 years of age. The dose of *Saccharomyces boulardii* ranged from 250 to 500 mg in two divided doses given for 5 days except in one study. The most common comparator was a placebo.

The other comparators were oral rehydrating solution (ORS) in three studies, and lactic acid. Seven studies looked at the duration of post-intervention diarrhea and five studies looked at clinical cure or efficacy.

Risk of bias (Figure 2) All except one study had randomization and allocation concealment. One study did not specify allocation concealment. Three studies did not specify if blinding was done. Three studies conducted an intention-to-treat analysis. Attrition ranged from 0 to 16.7%; three studies did not specify if there was any attrition or dropouts.

Results of individual studies and synthesis

Clinical cure/cessation of diarrhea Five studies reported clinical cure or efficacy defined as cessation of diarrhea, with some variations: 1) evacuation frequency < 3 times a day, or stool consistency improved for at least 24 hours; 2) < 3 stools per day or stools with solid consistency only; and 3) appearance

Table 1. Characteristics of 11 included studies

Author, year, country	Total patients	Inclusion criteria	Control	*S. boulardii* dose	Duration (days)	Outcome measured	Etiology of diarrhea
Naflesia[6] 2011, Brazil	176	Children 6-48 months, no other diarrhea episode or antibiotics use 2 weeks before trial, acute diarrhea within 72 hours before hospitalization	Placebo	200 mg BID	5	Clinical cure (evacuation frequency < 3 times per day or stool consistency improved for at least 24 hours.	Rotavirus, non-rotavirus
Asmat[7] 2018,Pakistan	200	Children with diarrhea < 14 days	Lactic acid	150-250 mg/day, 2 divided doses	5	Efficacy - frequency and consistency of stools (not defined)	Undefined
Kurugol[11] 2005, Turkey	200	Children 3 mo-7 yr, with acute diarrhea	Placebo	250 mg/day	5	The duration of diarrhea, i.e., the time from start of treatment until appearance of first normal stool	Mixed
Das[12] 2016, India	58	Children 3 mo-5 yr with acute diarrhea < 48 h duration, moderate to severe dehydration	Placebo	250 mg BID	1	Duration of acute diarrhea (hours)	Rotavirus
Riaz[13] 2012, India	90	Children 3-59 mo with acute onset diarrhea (of less than < 48 h)	Placebo	250 mg BID	5	Duration of post intervention diarrhea	Rotavirus & cholera
Shan[14] 2013, China	42	Children 6 mo-14 yr with diarrhea after antibiotic treatment of URTI	Placebo	250 mg BID		Duration of diarrhea (number of days of continuous diarrhea, from the first diarrheic stool until first normal stool)	Antibiotic associated
Canani[15] 2007, Italy	183	Children 3-36 mo consulting for acute diarrhea. (< 48 hours)	ORS alone	5×10^9 live micro-organisms/dose BID	None	Duration of diarrhea and daily number & consistency of stools	Undefined
Grandy[16] 2010, Bolivia	41	Children 1-23 months with acute diarrhea, rotavirus (+)	Placebo	BID	5	Length of diarrhea (hours), from admission to first formed stool	Rotavirus
Htwe[8] 2008 Myanmar	100	Children 3 mo-10 yr with acute watery diarrhea < 7 days	ORS alone	250 mg BID	5	< 3 stools per day or stools with solid consistency only	Undefined
Vandenplas[10] 2006	88	Infants and children 3 mo-2 yr (urban, middle social class), with acute, mild to moderate diarrhea		250 mg OD or BID	6	Number of stools on day 4 and 7 ('stool output') and the number of patients with diarrhea > 7 days	Undefined
Dinleyici[9] 2015, Turkey	363	Children 3-60 mo, with acute watery diarrhea, 12 to 72 h, requiring hospitalization in Turkey.	ORS alone	250 mg BID	5	Duration of diarrhea (hours) from admission until cessation of diarrhea (first normal stool according to Bristol score)	Undefined

of first normal stool based on the Bristol score. All five studies showed a significant beneficial response to *Saccharomyces boulardii* treatment (RR = 1.28-3.17).[6–10] Rotavirus was identified as the etiology of diarrhea in three studies, while two did not mention the etiology. The study measured cessation of diarrhea from 3 to 7 days. Overall, the study had a total of 923 participants and a significant beneficial (RR = 1.68, 95% CI = 1.48, 1.92; $p < 0.001$) response for *Saccharomyces boulardii* in the cessation of diarrhea. A fixed effects model was used due to the I^2 score of 70% and X^2 of 0.01 (Figure 3).

Duration of diarrhea Seven studies reported a shorter duration of diarrhea (0.43 to 6.66 days), with three citing a significant decrease.[10–16] The overall decrease in the duration of diarrhea was 1.65 days but this was not statistically significant (-4.44-1.15; $p = 0.25$). A random effects model was used due to the presence of heterogeneity ($x^2 < 0.001$).

Duration of hospitalization Four studies revealed a shorter duration of hospitalization in the *Saccharomyces boulardii* groups with a mean decrease ranging from 0.63 to 1.52 days; this was statistically significant in three studies. Overall, the four studies with a total of 519 participants showed a statistically significant (1.25–0.77; $p < 0.001$) mean decrease (1.01 days) in hospitalization with *Saccharomyces boulardii* as compared to placebo. A fixed effects model was used because of the I^2 of 60 and x^2 of 0.06.

Duration of vomiting Three of four studies showed a decrease in the duration of vomiting ranging from 0.10 to 1.61 days in the *Saccharomyces boulardii* group, with two studies citing a statistically significant difference. One study showed no difference in the duration of vomiting between those given *Saccharomyces boulardii* and placebo. Overall, there was a statistically significant decrease (0.18 days or 4.32 hours, $p = 0.04$) in the duration of vomiting among those given *Saccharomyces boulardii*.

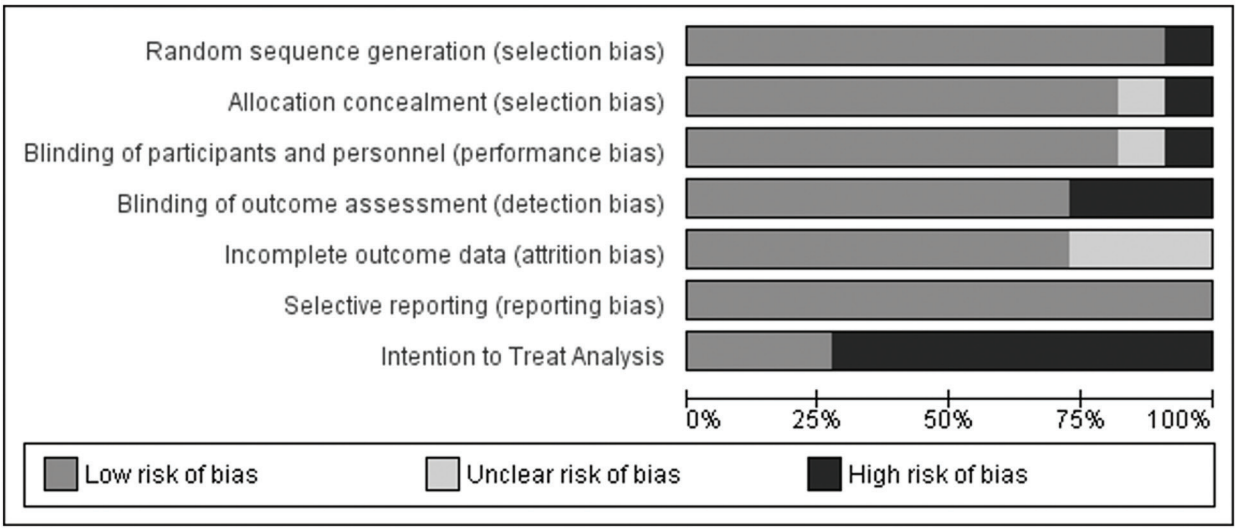

Figure 2. Summary of risk of bias for included studies

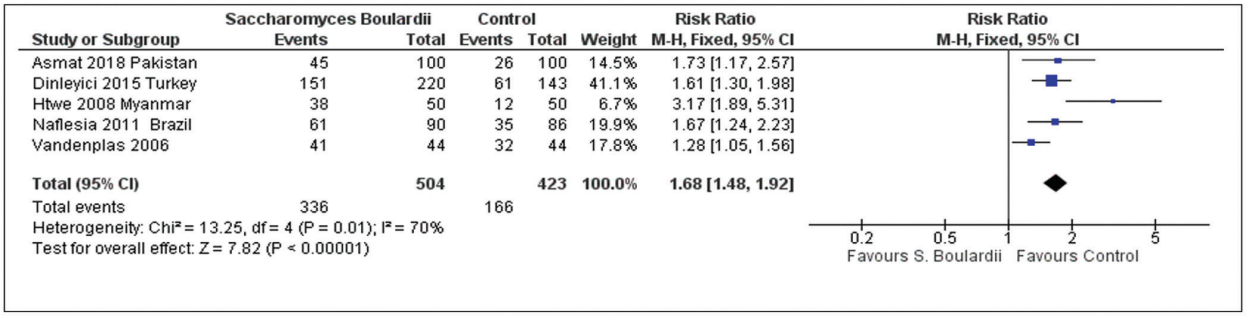

Figure 3. Comparison of clinical cure for *Saccharomyces boulardii* and control

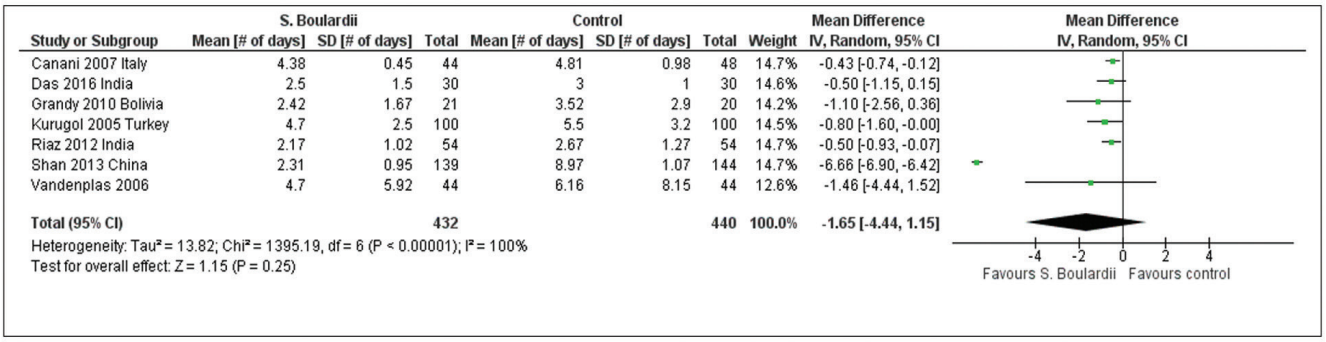

Figure 4. Comparison of duration of diarrhea for *Saccharomyces boulardii* and control

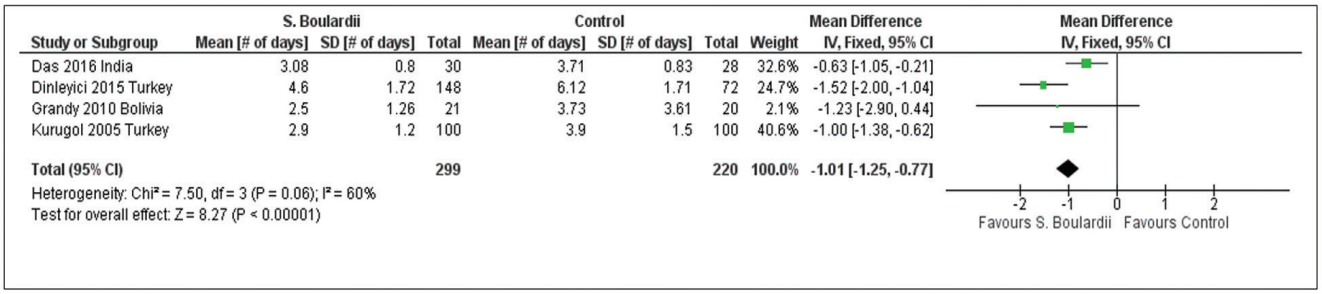

Figure 5. Comparison of duration of hospitalization for *Saccharomyces boulardii* and control

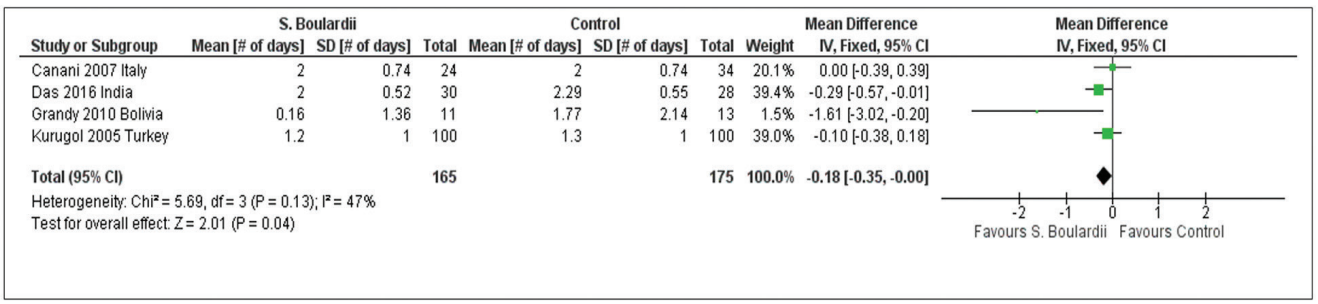

Figure 6. Comparison of duration of vomiting for *Saccharomyces boulardii* and control

Discussion

According to UNICEF Statistics from 2001-2015, annual diarrheal deaths in children less than 5 years of age have been reduced to 9% of total pediatric deaths worldwide. However, 10% of the deaths due to acute diarrhea worldwide are from South Asia, thus it is imperative to find ways to reduce mortality from diarrhea. One of the modalities being advocated for diarrheal treatment is the provision of probiotics. Probiotics are live microorganisms that can be formulated into many different types of products, such as food, drugs, and dietary supplements. Several studies have documented the effect of probiotics on a wide variety of gastrointestinal and extraintestinal disorders, including inflammatory bowel disease, irritable bowel syndrome, vaginal infections, and on immune enhancement.[17]

In this era of probiotics and good and bad bacteria, physicians are overwhelmed with numerous new medications and supplements bearing different forms of pro- and prebiotics and good bacteria, including *Saccharomyces boulardii*. At present, there

are five food supplements available in the Philippines containing *Saccharomyces boulardii*, two of which are also classified as antidiarrheals. The different drug companies have their own claims on the effectiveness of their product.[18]

A total of 11 clinical trials were included in the meta-analysis. For the primary endpoint of clinical cure or efficacy of *Saccharomyces boulardii* in the treatment of acute diarrhea, five studies showed a statistically significant increase in the rate (RR = 1.68) of clinical cure for those who received *Saccharomyces boulardii*. This translates to a number needed to treat of four individuals. For the duration of diarrhea, although previous studies and meta-analyses showed that *Saccharomyces boulardii* provided a statistically significant decrease in the duration of diarrhea, our meta-analysis did not share the same statistically significant result. However, it should be noted that the seven studies still showed a decrease in the duration of diarrhea.

For the duration of hospitalization, four studies showed a statistically significant decrease in the duration of hospitalization in favor of *Saccharomyces boulardii* (mean difference of 1.01 days). For the duration of vomiting, four studies showed a statistically significant decrease in the duration of vomiting in favor of *Saccharomyces boulardii* (mean difference 4.32 hours, p = 0.04). There were no reported adverse events in any of the studies cited. Literature shows that *Saccharomyces boulardii* administration causes *Saccharomyces cerevisiae* fungemia especially in patients with severe general or intestinal disease who had an indwelling catheter.[19,20] Other reviews and clinical trials showed similar moderate favorable results with the use *Saccharomyces boulardii* regardless of clinical outcome measure.[21-25]

S. boulardii is a non-pathogenic probiotic yeast which is naturally resistant to antibiotics and gastric acidity.[26] The mechanisms of action for the beneficial effect of *Saccharomyces boulardii* for diarrhea are as follows: a) antimicrobial activities that inhibit growth and invasion of pathogens and/or their adhesion; b) decreased bacterial gut translocation and improvement in the intestinal barrier function in an animal model; c) stimulation of local immunity by increasing the mucosal immune response and secretory IgA intestinal levels in an animal model; d) the enzymatic effects mediated through the increased release of polyamines, resulting in an increase in disaccharidases; and e) decrease in the inflammatory process through the inhibition of the NF-B translocation into the nucleus.[27-35]

This study has several limitations: most of the articles published have some form of publication bias, as those with neutral or negative results for treatment may remain unpublished; and the attrition of most studies was not reported. This could result in the non-inclusion of those who dropped out in the determination of clinical outcomes, especially if the dropout was due to treatment side effects or ineffective treatment of symptoms. It is also recommended that more studies on supplemental treatment of antibiotic-managed diarrhea be conducted, as most of the studies included involve non-antibiotic treatment of loose bowel symptoms.

A systematic review and meta-analysis of 11 clinical trials involving a total of 1,541 participants, showed a favorable result for the use of *Saccharomyces boulardii* in the treatment of diarrhea in children. Seven studies showed a statistically significant increase in rate of clinical cure among those given *Saccharomyces boulardii*. Four studies each showed a statistically significant decrease in the duration of hospitalization and the duration of vomiting. There was also a decrease in the duration of diarrhea however the results were not statistically significant. The etiology of diarrhea in most studies is also unknown or does not have a bacterial cause, which makes the utility of supplementing treatment with antibiotic therapy inconclusive.

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In vitro susceptibility of bacterial conjunctivitis standard isolates to non-fluoroquinolone ophthalmic medications

Moses Job D. Dumapig, MD and Eric Constantine Valera MD, MSHE

Abstract

Introduction This study aimed to determine the in vitro susceptibility of standard isolates of common pathogens causing bacterial conjunctivitis to non-fluoroquinolone antimicrobial ophthalmic medications.

Methods This is a single-blind experimental study which compared the in vitro susceptibility of *Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa and Staphylococcus epidermidis* to locally available non-fluoroquinolone ophthalmic medications, specifically chloramphenicol, tobramycin, fusidic acid, gentamicin sulfate, sulfacetamide and polymyxin-neomycin. Utilizing the disk diffusion method, zones of inhibition in millimeters for each bacterial isolate was recorded and tabulated. Kruskal-Wallis test was used to determine statistical differences.

Results Both Staphylococci were sensitive to all antibiotics except sulfacetamide. Only chloramphenicol showed activity against all four isolates. Tobramycin showed the largest zone of inhibition against *Pseudomonas aeruginosa*. There was statistically significant difference in the median zone of inhibition in each antimicrobial medication against *Staphylococcus aureus* ($p = 0.002$) and *Staphylococcus epidermidis* ($p < 0.001$) with the largest mean zone of inhibition by fusidic acid of 34 and 38 millimeters, respectively. *Streptococcus pneumoniae* was least susceptible to antibiotics tested; only chloramphenicol and fusidic acid showed activity. There were also significant differences in the median zones of inhibition across the isolates.

Conclusion The standard isolates are susceptible to at least one non-fluoroquinolone ophthalmic medication. The antibiotics tested showed differences in activity against the four isolates. The findings of this study may be used as a basis to review local practice patterns or/and initiate revisions in the guidelines for prescribing initial treatment of bacterial conjunctivitis.

Key words: antibiotics, susceptibility, bacterial conjunctivitis

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Bacterial conjunctivitis is a common health problem in ambulatory clinics. A US National Ambulatory Medical Care Survey in 2005 showed the crude incidence rate of bacterial conjunctivitis to be 1.3% using a base population of 296 million unique visits, translating to 135 per 10,000 visits annually.[1]

More than half of bacterial conjunctivitis cases resolve spontaneously within two to five days.[2-4] Although most symptoms of bacterial conjunctivitis are self-limiting, a seven-day course of topical antibacterial therapy is associated with a shorter infectious period, earlier resolution of clinical signs

and symptoms, and eradication of the pathogen within five days.[3,5,6] A systematic review of randomized controlled trials showed increased microbiological cure rates at 2 to 7 days after early initiation of ophthalmic antibiotics when compared to no treatment or placebo.[2]

The initial medical therapy for mild bacterial conjunctivitis recommended by the American Academy of Ophthalmology (AAO) includes: polymyxin B-trimethoprim combination drops, aminoglycoside or fluoroquinolone drops.[7] Other medications being used are macrolides, fusidic acid, chloramphenicol and sulfa-based topical antibiotics.[4,8] Antimicrobials such as chloramphenicol, sulfonamides, polymyxins, aminoglycosides and early generation fluoroquinolones are still being prescribed despite their limited spectrum and/or development of resistance.[9] Around 19-60% of *Streptococcus pneumoniae* and *Staphylococcus aureus* isolates have been shown to be resistant to macrolide antibiotics, penicillin, and older fluoroquinolones, and 85% of methicillin-resistant *Staphylococcus aureus* isolates are resistant to ophthalmic fluoroquinolones, including the newer fluoroquinolones gatifloxacin and moxifloxacin.[10] Factors contributing to ophthalmic drug resistance include non-compliance, irrational use, and over usage of both systemic and topical antibiotics.[11]

Newer generation fluoroquinolones with their broader spectrum of action against common ocular pathogens are now increasingly utilized as first line therapy for bacterial conjunctivitis.[12] The most commonly prescribed fluoroquinolones are moxifloxacin, ofloxacin, and ciprofloxacin.[12,13] However, studies indicate that fluoroquinolones should not be used routinely and should be reserved for severe, complicated, and resistant cases of bacterial conjunctivitis.[3,8,14]

The authors' literature survey revealed a lack of local data and clinical practice guidelines supporting the use of non-fluoroquinolones in the treatment of mild to moderate cases of bacterial conjunctivitis. Hence, the authors sought to determine the in vitro susceptibility of the standard bacterial conjunctivitis isolates to locally available non-fluoroquinolones.

Methods

This is an experimental comparative study done at the central laboratory of a medical center, testing the susceptibility patterns of stock isolates of the most common pathogens causing bacterial conjunctivitis. Bacterial isolates of *Staphylococcus aureus* (SA), *Streptococcus pneumoniae* (SP), *Pseudomonas aeruginosa* (PA), and *Staphylococcus epidermidis* (SE) were obtained from the central laboratory.

All the media plates for culture were prepared by licensed medical technologists at the laboratory using a standard procedure. MacConkey agar powder was mixed well with triple distilled water and heated to dissolve the agar. The mixture was sterilized in an autoclave at 121°C for 15 minutes. The liquid media was then allowed to cool to 45°C. Under a fume-hood set up, 20 mL aliquots were poured into several sterile petri dishes and allowed to solidify at room temperature. The same steps were done with the blood agar with the addition of 5% sheep blood before pouring into the plates. Inoculation to appropriate agars was done (*P. aeruginosa* to MacConkey agar; *S. pneumoniae, S. epidermidis* and *S. aureus* on blood agar) by using the streaking method with a sterile inoculation loop. The plates were then incubated for 24 hours at 37°C. Five replicates were prepared for comparison and reproducibility of results.

Thirteen antibiotic brands of chloramphenicol, sulfacetamide, gentamicin sulfate, polymyxin B sulfate-neomycin sulfate, fusidic acid and tobramycin listed in the 2019 Monthly Index of Medical Specialties (MIMS) Drug Reference Philippines and currently available were used in this study as listed in Table 1.[15] New unopened, unexpired bottles of each ophthalmic antibiotic brand were obtained. The identities of the antibiotics were masked using coded labels known only to the investigator. 300 uL of each antibiotic were transferred to separate sterile tubes using a micropipette. Each tube contained a labeled 6 mm circular piece of filter paper which was allowed to soak in the antibiotic for 24 hours (Figure 1). The excess solution was allowed to drip off before transferring the filter paper to the prepared agar plates.

The zone of inhibition (ZOI) around each filter paper was measured in millimeters after 24 hours using a caliper under fume-hood light and recorded (Figure 2). Values were interpreted as *susceptible, intermediate*, or *resistant* based on Clinical and Laboratory Standards Institute (CLSI) M100-S29 Performance Standards for Antimicrobial Susceptibility Testing.[16] The pathogen inoculation and measurement of ZOI was carried out by two different medical technologists to ensure blinding.

Table 1. Topical antibiotics and brands tested

Antibiotic	Brand	Manufacturer	Location of manufacturer
Chloramphenicol (Chl)	VistaChlor	E.L. Lab	Laguna, PH
	Celsus	E.L. Lab	Laguna, PH
Sulfacetamide (Sul)	Vistasulf	E.L. Lab	Laguna, PH
Gentamicin sulfate (Gen)	Sensomed Gentamicin Sulfate	E.L. Lab	Laguna, PH
Polymyxin B sulfate-neomycin sulfate (PN)	Isonep	E.L. Lab	Laguna, PH
Fusidic acid (Fus)	Fucithalmic	Amdipharm Ltd.	Dublin, Ireland
Tobramycin (Tob)	Tobrex	Alcon	Texas, USA
	Celsus	E.L. Lab	Laguna, PH
	Nebra	Remington Pharma	Pakistan
	Tobra-V	E.L. Lab	Laguna, PH
	Sensomed	E.L. Lab	Laguna, PH
	Ramitob	Daewoo Pharmaceutical Co., Ltd.	Busan, South Korea
	Tobralcin	Bharat Parenterals, Ltd.	Gujarat, India

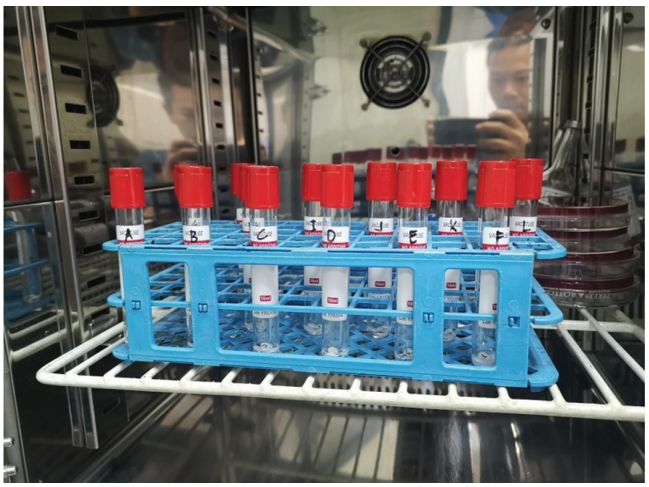

Figure 1. Labeled 6 mm filter paper impregnated with respective antibiotic for 24 hours.

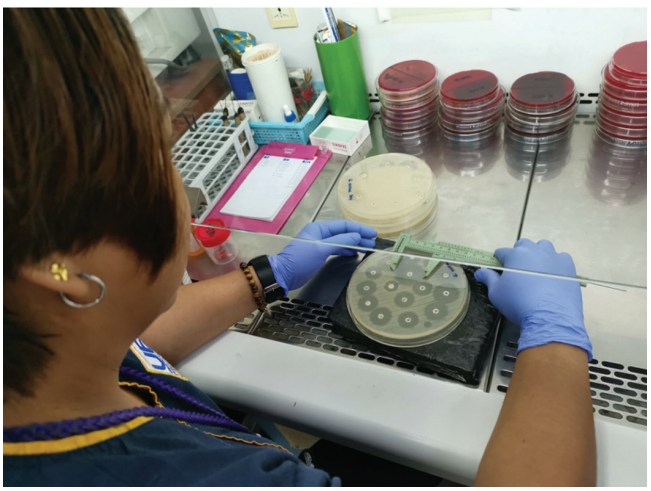

Figure 2. Measurement of zone of inhibition using caliper.

Zones of inhibition were summarized using median values. The Kruskal-Wallis test was used to compare the ZOI of each medication among different isolates and the ZOI of the individual isolates per antimicrobial medications with a 5% level of significance. P-values were adjusted using Bonferroni correction for multiple comparisons. Statistical package for social science (SPSS 23.0) was used to analyze the data.

Results

Table 2 shows the sensitivity of the four bacteria with the different antibiotics tested based on CLSI Performance Standards for Antimicrobial Susceptibility Testing.[16] *S. aureus, S. pneumoniae* and *S. epidermidis* were all sensitive to chloramphenicol. *S. aureus, P. pneumoniae* and *S. epidermidis* were sensitive to gentamicin sulfate. *P. aeruginosa* was resistant to polymyxin B sulfate-neomycin sulfate,

while the three remaining bacteria were all sensitive. *S. aureus*, *S. pneumoniae* and *S. epidermidis* were all sensitive to fusidic acid. *S. aureus*, *P. aeruginosa* and *S. epidermidis* were all sensitive to tobramycin.

As shown in Table 3, fusidic acid and sulfacetamide had the highest and lowest median ZOI against *S. aureus*, respectively. Chloramphenicol had the highest median ZOI against *S. pneumoniae*. Sulfacetamide, gentamicin sulfate, polymyxin B sulfate-neomycin sulfate showed no microbial activity against *S. pneumoniae*. Some brands of tobramycin - Tobrex, Tobra-V, Senosmed, Ramitob and Tobralcin - also showed no microbial activity against *S. pneumoniae*. Tobramycin (Nebra) and chloramphenicol (VistaChlor), respectively, had the highest and lowest median ZOI against *P. aeruginosa*. Fusidic acid and sulfacetamide, respectively, had the highest and lowest median ZOI against *S. aureus*.

Table 4 compares the median ZOI across isolates and across antimicrobial medications and shows that there are significant differences in the median ZOI for each antimicrobial medication. Likewise, there are significant differences in the median ZOI for each of the isolates. In Table 5, pair-wise comparisons among all test antimicrobials showed that fusidic acid had a significantly higher ZOI against *Staphylococcus aureus* compared to each of the other antibiotics. Tobramycin, chloramphenicol, gentamicin sulfate, polymyxin B sulfate-neomycin sulfate, all did not differ significantly in terms of ZOI. Sulfacetamide had a significantly smaller ZOI compared with the other antibiotics.

Tobramycin, sulfacetamide, gentamicin sulfate, and polymyxin B sulfate-neomycin sulfate did not differ significantly in terms of zone ZOI against *P. aeruginosa*. All four antibiotics had significantly wider ZOI compared to chloramphenicol and fusidic acid. Chloramphenicol and fusidic acid did not differ significantly in terms of ZOI (Table 6).

Pair-wise comparisons showed that chloramphenicol had a significantly wider ZOI against *S. pneumoniae* compared to each of the other antibiotics. Fusidic acid had a significantly wider ZOI compared to tobramycin, sulfacetamide, gentamicin sulfate, and polymyxin B sulfate-neomycin

Table 2. Sensitivity of isolates to ophthalmic antibiotics based on CLSI Performance Standards for Antimicrobial Susceptibility Testing

Medication	Brand	SA	PA	SP	SE
Chl	VistaChlor Celsus	Sensitive	*	Sensitive	Sensitive
Sul	Vistasulf	*	*	*	*
Gen	Sensomed Gentamicin Sulfate	Sensitive	Sensitive	*	Sensitive
PN	Isonep	Sensitive	Sensitive	Resistant	Sensitive
Fus	Fucithalmic	Sensitive	*	Sensitive	Sensitive
Tob	Tobrex				
	Celsus				
	Nebra				
	Tobra-V	Sensitive	Sensitive	*	Sensitive
	Sensomed				
	Ramitob				
	Tobralcin				

Chl – chloramphenicol, Sul – sulfacetamide, Gen – gentamicin sulfate, PN - Polymyxin B sulfate-neomycin sulfate, Fus – fusidic acid, Tob – tobramycin; SA – *Staphylococcus aureus*, PA – *Pseudomonas aeruginosa*, SP – *Streptococcus pneumoniae*, SE - *Staphylococcus epidermidis*
*No CLSI values available

Table 3. Zone of Inhibition of test antibiotics against four bacterial isolates

Antibiotics	Brand	Median ZOI (mm)			
		SA	SP	PA	SE
Chl	VistaChlor	25	30	13	28
	Celsus	28	30	15	35
Sul	Vistasulf	10	0	25	14
Gen	Sensomed	25	0	20	27
PN	Isonep	24	0	19	29
Fus	Fucithalmic	34	16	10	38
Tob	Tobrex	28	0	26	33
	Celsus	29	12	27	32
	Nebra	28	11	28	34
	Tobra-V	26	0	26	32
	Sensomed	29	0	27	33
	Ramitob	27	0	25	32
	Tobralcin	27	0	26	33

Chl – chloramphenicol, Sul – sulfacetamide, Gen – gentamicin sulfate, PN - Polymyxin B sulfate-neomycin sulfate, Fus – fusidic acid, Tob – tobramycin; SA – *Staphylococcus aureus*, PA – *Pseudomonas aeruginosa*, SP – *Streptococcus pneumoniae*, SE - *Staphylococcus epidermidis*

Table 4. Comparison of median zone of inhibition (mm) of isolates across antimicrobial medications

	SA	PA	SP	SE	Kruskal-Wallis p-value
Chl	26.5	13.5	30.0	31.5	0.001*
Sul	10.0	25.0	0.0	14.0	< 0.001*
Gen	25.0	20.0	0.0	27.0	0.001*
PN	24.0	19.0	0.0	29.0	< 0.001*
Fus	34.0	10.0	16.0	38.0	< 0.001*
Tob	28.0	27.0	13.0	33.0	< 0.001*
Kruskal-Wallis p-value	0.002*	< 0.001*	< 0.001*	< 0.001*	

Chl – chloramphenicol, Sul – sulfacetamide, Gen – gentamicin sulfate, PN - Polymyxin B sulfate-neomycin sulfate, Fus – fusidic acid, Tob – tobramycin; SA – *Staphylococcus aureus*, PA – *Pseudomonas aeruginosa*, SP – *Streptococcus pneumoniae*, SE - *Staphylococcus epidermidis*
*Significant at $p < 0.05$

Table 5. Pair-wise comparisons of zone of inhibition between each antibiotic against *Staphylococcus aureus* (adjusted p-values)

	Median	Chl	Sul	Gen	PN	Fus	Tob
Median		26.5	10.0	25.0	24.0	34.0	28.0
Chl	26.5	n/a	0.023*	0.380	0.380	0.023*	1.000
Sul	10.0	0.023*	n/a	0.023*	0.023*	0.023*	0.023*
Gen	25.0	0.380	0.023*	n/a	0.577	0.023*	0.459
PN	24.0	0.380	0.023*	0.577	n/a	0.023*	0.459
Fus	34.0	0.023*	0.023*	0.023*	0.023*	n/a	0.023*
Tob	28.0	1.000	0.023*	0.459	0.459	0.023*	n/a

Chl – chloramphenicol, Sul – sulfacetamide, Gen – gentamicin sulfate, PN - Polymyxin B sulfate-neomycin sulfate, Fus – fusidic acid, Tob - tobramycin
* Significant at $p < 0.05$, adjusted for multiple comparisons

Table 6. Pair-wise comparisons of zone of inhibition between each antibiotic against *Pseudomonas aeruginosa* (adjusted p-values)

	Median	Chl	Sul	Gen	PN	Fus	Tob
Median		13.5	25.0	20.0	19.0	10.0	27.0
Chl	13.5	n/a	0.012*	0.012*	0.012*	1.000	0.033*
Sul	25.0	0.012*	n/a	0.023*	0.023*	0.023*	1.000
Gen	20.0	0.012*	0.023*	n/a	1.000	0.023*	0.345
PN	19.0	0.012*	0.023*	1.000	n/a	0.023*	0.345
Fus	10.0	1.000	0.023*	0.023*	0.023*	n/a	0.023*
Tob	27.0	0.033*	1.000	0.345	0.345	0.023*	n/a

Chl – chloramphenicol, Sul – sulfacetamide, Gen – gentamicin sulfate, PN - Polymyxin B sulfate-neomycin sulfate, Fus – fusidic acid, Tob - tobramycin
* Significant at $p < 0.05$, adjusted for multiple comparisons

sulfate against *S. pneumoniae*. Two tobramycin brands (Celsus & Nebra) had significantly wider zones of inhibition against other the tobramycin brands, sulfacetamide, gentamicin sulfate, and polymyxin B sulfate-neomycin sulfate against *S. pneumoniae*. Sulfacetamide, gentamicin sulfate, and polymyxin B sulfate-neomycin sulfate did not differ significantly (Table 7). Fusidic acid had a significant difference in ZOI compared to each of the antibiotics tested against *S. epidermidis*. Tobramycin, chloramphenicol, and polymyxin B sulfate-neomycin sulfate did not differ significantly. Sulfacetamide significantly had the lowest ZOI median score compared to each of the antibiotics tested (Table 8).

Discussion

Microorganisms are naturally occurring on the surface of the eyes as part of the normal flora. However several multiple factors such as a patient's hygiene,

Table 7. Pair-wise comparisons of zone of inhibition between each antibiotic against *Streptococcus pneumoniae* (adjusted p-values)

	Median	Chl	Sul	Gen	PN	Fus	Tob
Median		30.0	0.0	0.0	0.0	16.0	13.0
Chl	30.0	n/a	n/a	n/a	n/a	0.031*	0.000*
Sul	0.0	n/a	n/a	n/a	n/a	n/a	n/a
Gen	0.0	n/a	n/a	n/a	n/a	n/a	n/a
PN	0.0	n/a	n/a	n/a	n/a	n/a	n/a
Fus	16.0	0.031*	n/a	n/a	n/a	n/a	0.045*
Tob	13.0	0.000*	n/a	n/a	n/a	0.045*	n/a

Chl – chloramphenicol, Sul – sulfacetamide, Gen – gentamicin sulfate, PN - Polymyxin B sulfate-neomycin sulfate, Fus – fusidic acid, Tob - tobramycin
* Significant at $p < 0.05$, adjusted for multiple comparisons

Table 8. Pair-wise comparisons of zone of inhibition between each antibiotic against *Staphylococcus epidermidis* (adjusted p-values)

	Median	Chl	Sul	Gen	PN	Fus	Tob
Median		31.5	14.0	27.0	29.0	38.0	33.0
Chl	31.5	n/a	0.023*	0.156	1.000	0.045*	1.000
Sul	14.0	0.023*	n/a	0.023*	0.023*	0.023*	0.023*
Gen	27.0	0.156	0.023*	n/a	0.147	0.023*	1.000
PN	29.0	1.000	0.023*	0.147	n/a	0.023*	1.000
Fus	38.0	0.045*	0.023*	0.023*	0.023*	n/a	0.045*
Tob	33.0	1.000	0.023*	1.000	1.000	0.045*	n/a

Chl – chloramphenicol, Sul – sulfacetamide, Gen – gentamicin sulfate, PN - Polymyxin B sulfate-neomycin sulfate, Fus – fusidic acid, Tob - tobramycin
* Significant at $p < 0.05$, adjusted for multiple comparisons

underlying disease, trauma, pathogen exposure and history of steroid and antibiotic use lead to imbalances that may result in infection.

Su and Tighe identified *Pseudomonas, Staphylococcus, Streptococcus, Propionibacterium, Bradyrhizobium, Corynebacterium, Acinetobacter, Brevundimonas, Aquabacterium, Sphingomonas, Streptophyta,* and *Methylobacterium* as the 12 most common genera causing ocular surface infections.[17] The most common pathogens listed by various authors include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenza, Streptococcus epidermidis* and *Pseudomonas aeruginosa*.[2,6,11]

The selection of antimicrobials to treat ocular surface infections should be based on microbiologic profile and antibiotic sensitivity. Proper antibiotic therapy is essential to achieve resolution of infection and minimize damage to the eye. However, there are no published local guidelines on the treatment of bacterial conjunctivitis. The AAO advises a broad-spectrum topical antibiotic on an empirical

basis.[3] Locally, fluoroquinolones are the commonly prescribed antimicrobial agents to treat bacterial conjunctivitis. Another study reported that 94% of ophthalmologists in India prescribed fluoroquinolone as first line medication for bacterial conjunctivitis. While fluoroquinolones have proven to be effective against common ocular pathogens, there is a risk for resistance due to indiscriminate and irrational use.[10,11] It has been suggested therefore that fluoroquinolones should not be used routinely for bacterial conjunctivitis.

However, there is a lack of local studies to provide a basis for the continued use of non-fluoroquinolones against bacterial conjunctivitis as a viable alternative to fluoroquinolones. To address this, the current study aimed to determine the susceptibility of the common ocular surface bacteria *S. aureus, S. pneumoniae, P. aeruginosa*, and *S. epidermidis* to locally available non-fluoroquinolones ophthalmic antibiotics.

Chloramphenicol inhibits protein synthesis and the protein chain elongation by peptidyl transferase of the bacterial ribosome. It is effective against many Gram-positive and Gram-negative bacteria, including most anaerobic organisms.[11] Several articles report that *S. aureus* (100%), *S. epidermidis* (71.9%) and *S. pneumoniae* are susceptible to chloramphenicol.[18,19] Results of the study are consistent with current literature. *S. aureus, S. pneumoniae*, and *S. epidermidis* were susceptible to chloramphenicol. On the other hand, it had minimal activity against *P. aeruginosa*. Watson recommended chloramphenicol 0.5% eye drops as the initial treatment for bacterial conjunctivitis commonly caused by *S. pneumoniae* and *S. aureus*.[20]

Sulfacetamide is another bacteriostatic agent belonging to the class of sulfonamides; it acts as folate synthesis inhibitor. It stops the bacterial enzyme dihydropteroate synthase, which is responsible for the merging of paraamino-benzoic acid (PABA) with dihydropteroic acid, the precursor of folic acid needed by some bacteria to produce nucleic acid that make up their deoxyribonucleic acids (DNAs).[21] Several disease-causing organisms like *S. aureus*, *Escherichia coli, S. pneumoniae, Streptococcus viridians, Haemophilus influenza, Klebsiella and Enterobacter* species are widely inhibited by sulfacetamide.[22] However, sulfacetamide is not recommended as a first-line ophthalmic drug because it does not cover *Pseudomonas*, and other organisms may easily develop resistance.[18] Current study showed contrasting results as sulfacetamide demonstrated a significant zone of inhibition against *P. aeruginosa* while *Staphylococci spp*. showed small ZOI.

Gentamicin sulfate is an aminoglycoside that prevents the synthesis of the DNA and ribonucleic acid (RNA) of the bacterial protein by binding to both 16S and 23S rRNA molecule of the bacterial ribosime.[18] This agent acts on a wide range of Gram-positive or Gram-negative aerobic bacteria (e.g., *Staphylococcus spp., Haemophilus influenzae* or *P. aeruginosa*). However, it is not active against Streptococci and anaerobic bacteria.[6] This study showed that *S. aureus, S. epidermidis*, and *P. aeruginosa* were susceptible while *S. pneumonia* was resistant to gentamycin based on the ZOI.

The antibiotic combination of polymyxin B sulfate and neomycin sulfate is usually commercially available with a steroid (hydrocortisone) combined to treat or prevent bacterial infection and inflammation of the eyes. Neomycin sulfate is an aminoglycoside, which binds to the 30S subunit to prevent bacterial DNA polymerase. It is bactericidal to many Gram-positive and Gram-negative bacteria but is not effective on *Streptococci* and *P. aeruginosa*. Polymyxin B sulfate increases the permeability of the bacterial cell membrane, resulting in leakage of cell constituents.[23] The addition of polymyxin B sulfate expands antibiotic coverage to Gram-negative bacteria, especially *P. aeruginosa*. The results of the current study showed that *S. aureus, P. aeruginosa* and *S. epidermidis* were sensitive to polymyxin B sulfate-neomycin sulfate while *S. pneumoniae* showed resistance.

Fusidic acid is an ophthalmic drug belonging to the class fusidane that acts as a bacteriostatic agent at lower doses and is bactericidal at higher concentrations.[24] It prevents the bacterial protein synthesis of Gram-positive bacteria, particularly of *S. aureus* by inhibiting the dissociation of complex formed between guanosine diphosphate, elongation factor 2 and the ribosome.[25] It interferes with the amino acid transfer from aminoacyltransfer RNA to protein on the ribosomes.[24] Studies showed that *S. epidermidis* was highly susceptible to fusidic acid.[24,26] The same study of Jackson revealed good compliance of patients who had positive bacterial culture conjunctivitis being treated with fusidic acid compared to those using tobramycin (85% versus 47%, $p < 0.00I$).[24] The results of the current study showed that *S. aureus, S. pneumoniae*, and *S. epidermidis* were susceptible to fusidic acid. However, there was a minimal ZOI against *P. aeruginosa*.

Tobramycin is a bactericidal agent that acts as a protein synthesis inhibitor by binding to the 30S

subunit, which further prevents bacterial DNA and RNA synthesis.[11] Available literature show conflicting reports on the susceptibility of common ocular bacterial pathogens to tobramycin. Tobramycin is an effective antimicrobial agent against most *Staphylococci*, *Proteus* and *Enterobacteriaceae*, but resistant strains can now be seen. Like other aminoglycosides, tobramycin has a limited action against *S. pneumoniae*, group A *Streptococcus* and *Haemophilus*.[18] The survey of Ocular TRUST showed 65.3% of *S. pneumoniae* had resistance to tobramycin while Shrestha reported 100% sensitivity.[27,28] Current study showed that *S. aureus*, *S. epidermidis*, and *P. aeruginosa* were sensitive to tobramycin. It has little to no activity against *S. pneumoniae*.

CLSI also reported that *P. aeruginosa* may develop resistance during prolonged treatment with antibiotics. Isolates that are usually susceptible may become resistant 3-4 days after initiation of therapy.[16] Tobramycin should not be the first line treatment in this type of conjunctivitis since it is reserved for *Pseudomonas* resistant to fluoroquinolone. Hovding, in his review article, suggested that neither fluoroquinolone nor aminoglycoside (gentamicin and tobramycin) should be used to treat uncomplicated acute bacterial conjunctivitis, and topical administration should be restricted to severe eye infections and in bacterial conjunctivitis that are not responsive to fusidic acid or chloramphenicol.[8]

The results of the current study also showed significant differences in the susceptibility patterns of the four pathogens tested to the six non-fluoroquinolone agents based on their ZOI. *S. aureus* and *S. epidermidis* were susceptible to all except to sulfacetamide. *S. pneumonia* was susceptible only to chloramphenicol. *P. aeruginosa* was susceptible to all except chloramphenicol and fusidic acid. There were also significant differences in microbial activity among the six non-fluoroquinolone agents against *S. aureus, S. pneumoniae, P. aeruginosa*, and *S. epidermidis*. Specifically, fusidic acid showed the highest activity in terms of ZOI against *S. aureus* and *S. epidermidis*. Tobramycin and sulfacetamide showed the widest zone of inhibition against *P. aeruginosa*. Chloramphenicol showed the widest ZOI against *S. pneumoniae*.

Limitations of this study include inability to test susceptibility of other common microorganisms such as *Haemophilus influenza* and *Moraxella catarrhalis* due to their unavailability and difficulty to culture. In addition, ophthalmic drops used in patients have a higher concentration than those being used in laboratories during in vitro studies, thus a comparison of both in clinical and microbiological laboratory studies is recommended. Samples taken from patients with bacterial conjunctivitis should be tested using all locally available antibiotics to determine resistance patterns.

This is the first study which evaluated the sensitivity of bacterial conjunctivitis-causing pathogens to non-fluoroquinolone antimicrobial ophthalmic medications. Current study results neither confirm or dispute reports from current literature reinforcing the notion of evolving susceptibility patterns of common ocular surface pathogens to antimicrobials and emphasizing the need for more rational, judicious use these antimicrobial agents. The findings of this study may be used as a simple guide for prescribing based on susceptibility patterns but should be explored further in randomized clinical trials to determine the effectiveness and safety of these antimicrobial agents in the treatment of bacterial conjunctivitis.

The standard isolates are susceptible to at least one non-fluoroquinolone ophthalmic medication. The antibiotics tested showed differences in activity against the four isolates. The findings of this study may be used to review local practice patterns or and initiate revisions in guidelines for prescribing initial treatment for bacterial conjunctivitis.

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Necrotizing fasciitis in a patient with Chiari malformation Type II - a family case analysis

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Abstract

The biopsychosocial approach to healthcare is fundamental to Family and Community Medicine specialists. Using the patient-centered, family-focused, community-oriented (PFC) matrix, the interplay of a myriad of biomedical and psychosocial factors is assessed in order to provide a thorough medical management that is custom-made to meet the needs and inherent values of a patient and his/her family. Family assessment tools are also utilized to better understand the family dynamics of a patient that may impact on the prescribed management plan. In addition, social determinants of health are evaluated to ascertain which ones may facilitate or hamper proper utilization of community resources. This family case analysis documented the medical ordeal of a young professional who had been diagnosed with two rare medical conditions: necrotizing fasciitis and Chiari malformation Type II. Employing the PFC matrix, the Family and Community Medicine specialist was able to provide inter-disciplinary care for the patient and his family in a holistic manner by recognizing patient needs, creating an enabling family support environment, and helping the family unit navigate various community resources.

Key words: biopsychosocial approach to health; patient-centered, family-focused, community-oriented matrix; social determinants of health

Physiology defines homeostasis as the ability of any living organism to keep the conditions inside it the same, despite the myriad of changes in its living environment or the presence of various stimuli, in order to maintain the state of internal balance. In the context of Family and Community Medicine, homeostasis can likewise be defined as the ability of a social unit (e.g., family or community) to respond and adapt to the psychosocial variables that are present, whenever an individual is subjected to a chronic medical condition or physical ordeal. It is assumed that in a functional unit, medical problems can initially shift the balance to one direction, but through the development of positive coping mechanisms among its members, the social unit will eventually regain its homeostasis. In contrast, dysfunctionality of a family often leads to disruptive adaptive behaviors among its members, which can result in further disintegration of social ties of a familial unit during medical crises.

In 1977, American psychiatrist George Engel proposed a biopsychosocial model that included social and psychological factors as crucial determinants of disease and illness. According to his new framework, the subsystems of the body interact to produce

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successively more complex biologic systems, which are simultaneously affected by social and psychological variables. The organism is thus conceptualized in terms of complex interacting systems of biologic, psychological, and social forces, and neither disease nor illness is seen as understandable only in terms of smaller biologic components. Engel believed that systemic interactions of biopsychosocial factors were relevant to all disease processes and to the individual's experience of illness. Accordingly, understanding a person's response to a disease requires consideration of interacting factors such as the social and cultural environment, the individual's psychological resources, and the biochemistry and genetics of the disorder in the population.[1]

The biopsychosocial model was proposed as a scientific paradigm by Engel, who encouraged the clinician to observe biochemical and morphologic changes in relation to a patient's emotional patterns, life goals, attitudes toward illness, and social environment. Engel reasoned that the brain and peripheral organs were linked in complex, mutually adjusting relationships, affected by changes in social, as well as physical stimuli. Within this model, environmental and psychological stress may be viewed as potentially pathogenic for the individual. Emotions may serve as the organism's bridge between the value of stressful events and the changes in physiologic function.[1]

According to the Genetic and Rare Diseases (GARD) Information Center of the US National Institutes of Health, Chiari malformation Type II (CM Type II) involves the extension of the cerebellum and brain stem tissues into the foramen magnum.[2] CM Type II is usually accompanied by a myelomeningocoele, which can result in partial or complete paralysis of the area below the spinal opening. While the severity of CM Type II can vary significantly, it can potentially cause severe, life-threatening complications during infancy or childhood. The exact etiology of CM Type II, unfortunately, is not completely known, but it is believed to be secondary to congenital birth defects during fetal development.

On the other hand, according to the US Centers for Disease Prevention and Control, necrotizing fasciitis is a rare bacterial infection that may have systemic manifestations and can potentially precipitate the premature demise of patients. Others have referred to necrotizing fasciitis as an infectious process secondary to a "flesh-eating bacterium," but public health experts theorize necrotizing fasciitis is most probably caused by group A *Streptococcus*.[3]

This paper documented the case of a young professional who had been diagnosed with two rare medical conditions - necrotizing fasciitis and CM Type II. Specifically, this aimed to describe the natural history of the disease in the context of the biopsychosocial model, and how patient-centered, family-focused, community-oriented healthcare had been provided for the patient and his family.

History of present illness

KUA was a 33-year old licensed physician and a member of the medical academe, Filipino, single, Roman Catholic, who consulted at the emergency room of a tertiary private teaching hospital with a chief complaint of swelling of the left leg of six days duration. He had been previously diagnosed with CM Type II, s/p suboccipital craniectomy (2011), resulting in left-sided motor and sensory deficits. He also suffered from Erb's palsy in the right upper extremity, secondary to shoulder dystocia during birth since he was born as a term macrosomic baby. He was a paraplegic who was dependent on his caregiver for most of his activities of daily living (ADLs) and was recognized to be a person with disability (PWD).

KUA was previously functional, until six days prior to admission (PTA), when he gradually noted progressive pain in both lower extremities associated with Grade II pitting bipedal edema. He also noted intermittent low-grade fever (i.e., maximum temperature of 37.8°C) with chills and gradual swelling of his left leg. There was progression of the edema until the swelling extended to involve the knee area. As a general practitioner, he self-medicated with paracetamol 500 mg every 4 hours for the feverish symptoms and azithromycin 500 mg OD for three days, which provided minimal relief of symptoms.

Four days PTA, the condition persisted, with progression of the left lower leg edema. He also noticed hyperemic skin changes in the left lower extremity, making standing and assisted ambulation more difficult. Still, no official medical consult was done. Three days PTA, the left leg swelling worsened, with development of skin retractions and dimpling in the involved area, similar to a peau d'orange. There were also yellow-orange, non-foul smelling secretions oozing from the intact skin pores in the left leg. This was also associated with uncontrollable hyperreflexia

of the left knee. The condition progressively worsened, resulting in limitation in the range of motion of the left lower extremity, warranting the use of a wheelchair since standing up had become too painful for KUA. One day PTA, there was an increase in the volume of the purulent discharge coming from the lesions in the left leg and knee. He decided to self-medicate with another oral antibiotic - sultamicillin 750 mg BID. A few hours PTA, the symptoms persisted, prompting consult at the emergency room; KUA was subsequently admitted on June 27, 2018 with an initial impression of cellulitis of the lower extremities.

Physical examination on admission (June 2018)

- *General survey*: awake, conversant, coherent, oriented to three spheres with good fund of knowledge, bedridden, morbidly obese
- *Vital signs*: BP = 140/100 mm Hg; CR = 84 beats per minute in sinus rhythm; RR = 17 cycles per minute; T = 36.9°C; O_2 sat = 90% at room air
- *HEENT*: with midline surgical scar in the occipital area; anicteric sclerae, pale palpebral conjunctivae; no nasoaural discharge; no tonsilopharyngeal congestion; no facial asymmetry; no anterior neck mass; no neck vein engorgement; no cervical lymphadenopathy
- *Chest & pulmonary system*: equal chest expansion; equal vocal and tactile fremitus; good air entry; clear breath sounds, no crackles, no wheezes
- *Heart & cardiovascular system*: adynamic precordium; apex beat at 5th intercostal space, left midclavicular line; distinct S1 and S2, no S3 gallop, no murmurs
- *Abdomen & gastrointestinal system*: globular and non-distended abdomen; normoactive bowel sounds; no tenderness, no organomegaly
- *Extremities*: capillary refill time less than 2 seconds; dystrophic nails noted in both upper and lower extremities; with unequal length of upper extremities; swollen bilateral lower extremities with note of erythema and warmth; 50 cm widest leg circumference; purulent discharge from multiple ulcers in the left lower extremity

Course in the hospital

During his hospital stay, KUA was co-managed by the Internal Medicine (Infectious Disease), Neurology, and General Surgery services. Laboratory work-up was immediately done, including culture and sensitivity studies of the wound discharge and blood. Loading doses of intravenous antibiotics and pain medications were given, and he was managed for other medical comorbidities (i.e., hypertension, dyslipidemia, anemia, and impaired fasting glucose).

KUA was confined for 72 days from June 27 to September 10, 2018. He underwent at least six debridement sessions, which he was able to tolerate with no significant complications. Various bacteria were isolated from the wound, including *Pseudomonas aeruginosa*, *Klebsiella aerogenes*, and *Escherichia coli* (heavy growth). Unfortunately, KUA exhibited antimicrobial resistance to penicillins, cephalosporins, fluoroquinolones, carbanems, and chloramphenicol. KUA was likewise positive for extended-spectrum beta-lactamases (ESBL) bacteria, suggesting a fast course of potentially life-threatening sepsis. KUA also had extremely elevated D-dimer levels at 3,737.80 ng/mL, suggesting poor perfusion of blood in his lower extremities. An electroencephalogram (EEG) revealed slow-generalized abnormal waves during awake, drowsy, and somnolent states. A mild diffuse cortical dysfunction was demonstrated, most probably secondary to metabolic or systemic causes.

Magnetic resonance imaging (MRI) of the cervicothoracic spine showed post-operative changes related to prior Chiari decompression, such as synechiae formation within the craniocervical junction, which was noted to be capacious. In addition, the presence of holocord syringohydromyelia extending from the cervicomedullary junction down to the T12 level of the spinal cord was noted. The conus medullaris and paravertebral soft tissues were normal. There was no evidence of focal disc herniation, spinal canal narrowing, cord compression, and neural foraminal compromise.

KUA was eventually discharged improved with the following medications: 1) ivabradine 5 mg/tablet, half-tablet BID; 2) carvedilol 6.25 mg/tablet, half-tablet OD; and 3) clonazepam 2 mg/tablet, half-tablet at bedtime, as needed for myoclonic jerks of the lower extremities. The final discharge diagnoses included: sepsis secondary to necrotizing fasciitis, left lower extremity, resolved; s/p debridement; s/p fasciotomy (6 sessions); t/c metabolic syndrome. KUA was compliant with all his medications but nonetheless continued to experience significant difficulty in transferring between bed and wheelchair since his discharge.

On October 28, 2018, KUA was readmitted for skin grafting under the Plastic and Reconstructive Surgery service. The procedure was unremarkable and KUA tolerated it well. KUA was discharged improved after two weeks and was advised to undergo extensive home-based physical therapy and rehabilitation, at least three sessions per week, as recommended by the Rehabilitation and Physical Medicine service.

Course in the home setting

Physical examination on first home visit (October 2018)

- *General survey*: awake, conversant, coherent, oriented to three spheres with good fund of knowledge, bedridden but can sit without support, morbidly obese
- *Vital signs*: BP = 120/80 mm Hg; CR = 76 beats per minute in sinus rhythm; RR = 20 cycles per minute; T = 36.7°C; O_2 sat = 98% at room air
- *HEENT*: with midline surgical scar in the occipital area; anicteric sclerae, pale palpebral conjunctivae, pupils 2 mm with equal brisk reaction to light; no nasoaural discharge; no tonsilopharyngeal congestion; no facial asymmetry; no anterior neck mass; no neck vein engorgement; no cervical lymphadenopathy
- *Chest & pulmonary system*: equal chest expansion; equal vocal and tactile fremitus; all lung fields resonant on percussion; good air entry; clear breath sounds, no crackles, no wheezes
- *Heart & cardiovascular system*: adynamic precordium; apex beat at 5th intercostal space, left midclavicular line; distinct S1 and S2, no S3 gallop, no murmurs
- *Abdomen & gastrointestinal system*: globular and non-distended, soft abdomen; no striae; normoactive bowel sounds; no tenderness, no organomegaly
- *Extremities*: capillary refill time less than 2 seconds; with full and equal pulses and good skin turgor; dystrophic and discolored nails noted in both upper and lower extremities; with unequal length of upper extremities; no varicosities noted; grade III pitting bipedal edema (i.e., left more than right) with erythema and warmth; with occasional jerking and twitching of the left leg; no cyanosis, no pallor; with limited range of motion and contractures in the upper and lower extremities; with note of multiple deep ulcers on the anterior, lateral, and posterior aspects of the left leg; no wound discharge noted

Neurological examination on first home visit (October 2018)

- *Mental status examination*: frontal: awake, alert, with coherent speech and good attention span, follows commands, and with good insight and judgment; parietal: (-) right-left disorientation, (-) agraphia, (-) acalculia, (-) astereognosis, (-) finger agnosia; temporal: intact immediate, recent, and remote memory, oriented to time, place, and person; occipital: can identify objects and colors
- *Cranial nerves*: intact
- *Superficial sensation*: with sensory deficits for touch, pain, and temperature on the left upper extremity in C5-C6 distribution
- *Deep tendon reflexes*: with no reflexes on right upper extremity; hyperactivity with clonus on the right lower extremity; left ankle jerk reflex was not tested because of the extent of wound bandage.
- *Manual motor testing*:

Muscles/motion assessed	Left	Right
Shoulder flexors	3+ / 5	0 / 5
Shoulder extensors	3+ / 5	0 / 5
Shoulder abductors	3+ / 5	0 / 5
Shoulder adductors	3+ / 5	0 / 5
Shoulder external rotators	3+ / 5	0 / 5
Shoulder internal rotators	3+ / 5	0 / 5
Elbow flexors	3+ / 5	0 / 5
Elbow extensors	3+ / 5	0 / 5
Forearm pronators	3- / 5	0 / 5
Forearm supinators	3- / 5	0 / 5
Wrist flexors	2 / 5	0 / 5
Wrist extensors	0 / 5	0 / 5
Wrist ulnar & radial deviation	0 / 5	0 / 5
Hip flexors	3 / 5	5 / 5
Hip extensors	3+ / 5	2 / 5
Hip abductors	3+ / 5	2 / 5
Hip adductors	3+ / 5	2 / 5
Hip external/internal rotators	3+ / 5	2 / 5
Knee extensors	3+ / 5	2 / 5
Knee flexors	3+ / 5	2 / 5
Ankle plantiflexors	3+ / 5	2 / 5
Ankle dorsiflexors	3+ / 5	2 / 5
Ankle eversion/inversion	3 / 5	2 / 5

Since his last hospitalization, KUA underwent regular home-based physical therapy with thrice

weekly sessions under the Rehabilitation and Physical Medicine service. He tolerated the PT management without any adverse events noted. KUA presented with improved cardiovascular endurance during exercises, as manifested by decreased fatigability and shorter rest periods. Standing tolerance was also significantly improved, but there was very slow progress in terms of transfers from bed to wheelchair and vice-versa with maximum assist. KUA was given frequent reminders to perform home exercises on days without PT sessions for optimal functional results. Other recommendations included application of orthoses for KUA's wrist-hand contractures in the left upper extremity and use of a joystick-controlled powered wheelchair for easier mobility. The incompletely healed skin graft site slowed down the rehabilitation progress.

KUA's mother was also taught proper bandaging to minimize development of bipedal edema. In addition, psychosocial support was continuous being given to both KUA and his mother who functioned as the primary care giver.

Pertinent physical examination on last home visit (July 19, 2019)

- *General survey*: awake, conversant, coherent, oriented to three spheres with good fund of knowledge, bedridden but can sit without support, morbidly obese
- *Vital signs*: BP = 130/80 mm Hg; CR = 98 beats per minute in sinus rhythm; RR = 20 cycles per minute; T = 36.5°C; O_2 sat = 95% at room air
- *Extremities*: (+) waiter's tip deformity on right upper extremity and contractures on both upper extremities; (+) surgical scar on left posterolateral thigh from skin graft harvest; (+) wounds with gauze covered with elastic bandages on left lower extremity; (+) elastic bandages on right lower extremities; (+) Grade 4 pitting bipedal edema with hyperpigmentation of the skin and scaly lesions
- *Rest of the systemic physical examination*: generally unremarkable; essentially normal

On the morning of August 2, 2019, KUA complained of sudden onset difficulty of breathing with associated decreased hearing. He was noted to gasp for air and suddenly lost consciousness. His extremities were noted to be cold and clammy, but KUA did not complain of chest discomfort. He was rushed to the nearest tertiary hospital via ambulance. At the emergency room, he was noted to have faint pulses and very weak palpatory blood pressure. He was intubated and hooked to a mechanical ventilator. However, he was described to have recurrent apneic spells, and cardiac rate was erratic despite maximal doses of inotropes. KUA eventually went into asystole, and despite aggressive resuscitation, he was pronounced dead within two hours from the time of admission.

Past medical history

KUA suffered from Erb's palsy, a birth complication that affected his right arm when he was being delivered due to shoulder dystocia. He was born full term and macrosomic via forceps-assisted delivery to a then 28-year old primigravid with untreated gestational diabetes mellitus (GDM). Childhood illnesses included measles, chickenpox, typhoid fever, pneumonia, and viral hepatitis. KUA allegedly received complete immunizations during infancy. No vaccination was given recently. There was no history of recent trauma or accidents.

In April 2010, KUA noted difficulty in opening his left hand and eventually underwent ulnar nerve transposition. However, there was persistence of the symptoms, and in August 2010, he was subsequently diagnosed with CM Type II. He underwent sub-occipital craniectomy for Chiari decompression in April 2011. Some time in 2011, he was confined again for cellulitis.

Personal and Social History:

KUA was a known 10-pack-year smoker and an occasional alcoholic beverage drinker, consuming two bottles of beer on a monthly basis. He denied using illicit or prohibited drugs. His diet was carbohydrate and protein rich; he consumed mostly rice meals and sugar-sweetened beverages regularly. KUA also drank a cup of coffee daily. KUA described himself to be completely sedentary due to his physical condition and limitations. He was completely dependent on a 24-hour caregiver for all his ADLs, including grooming and bathing. His caregiver often prepared his food; KUA was able to feed himself independently using his left arm prior to his most recent hospital admission and surgeries in 2018.

He resided in a two-storey family-owned house in an exclusive subdivision with his 61-year old mother and 18-year old half-sister. KUA described his community to be generally safe, peaceful, and clean. The family had adequate access to electricity and clean potable water. Because of his current physical condition, KUA could not use his own bedroom on the second floor of their house. Instead, he occupied the master bedroom at the first floor, which he shared with his mother and sister.

After passing the Physician Licensure Exam, KUA was employed as a full time faculty in his *alma mater* in 2013, with a rank of Assistant Professor. He pursued further post-graduate studies, however, his latest medical ordeal with necrotizing fasciitis prevented KUA from working; he had been on leave of absence from June 2018 until the time of his demise.

Family history

KUA had a blended family and lived with his mother and maternal half-sister (i.e., refer to Figure 1, the family genogram). KUA was an illegitimate child, and at the time of his demise, he belonged to a family at an adolescent stage (in terms of the family life cycle). Since his parents had been estranged since 1998, KUA had not developed any strong kinship with his father and his paternal half siblings. KUA gained psychosocial support from his maternal family, and until his death, KUA was highly dependent on his elderly mother, the main breadwinner and sole caregiver, for all his ADLs.

KUA's biological father is a retired military personnel. He presently resides with his common-law wife in a different country. On the other hand, KUA's biological mother is a retired employee. KUA's 18-year old sister with Down syndrome is home-schooled. His mother is a known hypertensive, and KUA is unaware of any familial illnesses on the side of his biological father, except that his father suffered from coronary artery disease and had undergone bypass grafting.

In terms of the illness trajectory, KUA and his family exhibited positive coping mechanisms for his permanent disability. KUA and his mother answered the family APGAR, giving scores of 10 and 8, respectively, and with an average of 9, indicating a highly functional family with good levels of satisfaction for familial relationships. This connoted a strong probability of coping well with life's stressors (i.e., refer to Figure 2, the family lifeline from 1994 to 2019), with the potential of regaining family homeostasis amidst medical crises or ordeals.

KUA scored 13, and his mother 14, on the Social, Cultural, Religious, Educational, Economic and Medical (SCREEM) Family Resource Survey (Table 1), indicating that the family had adequate resources,

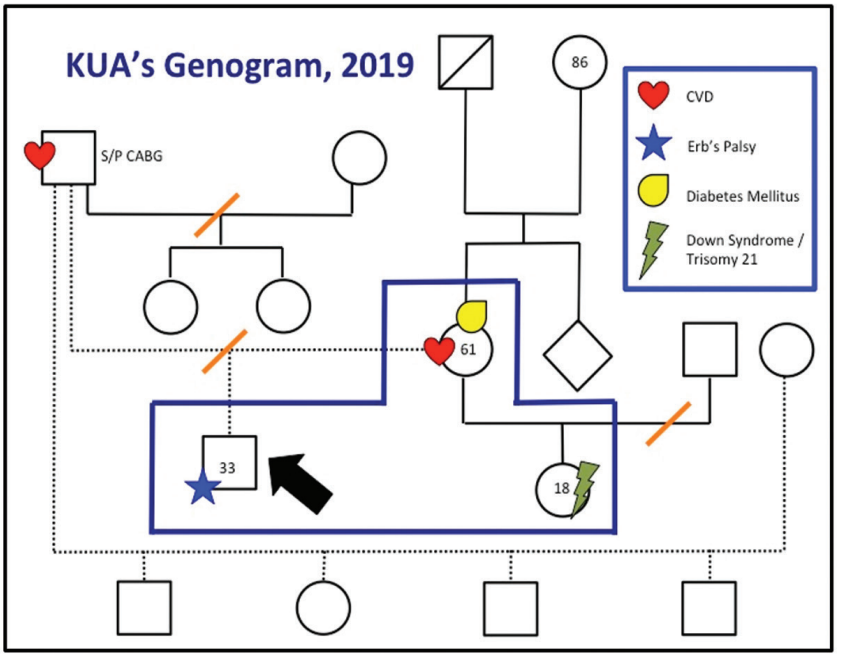

Figure 1. The family genogram of KUA

Age	Year	Life Event / Psychosocial Factors	Medical Condition / Diagnosis
9	1994	KUA met his paternal half siblings from his first family.	KUA grew up a highly functional individual despite having Erb's palsy.
13	1998	KUA's biological parents separated.	
14	1999	KUA's mother re-married and gave birth to his half-sister with Down's syndrome.	
15	2000	KUA had his first of several romantic relationships over the next years.	
17	2002	KUA met his paternal half siblings from his third family.	
21	2006	KUA earned the degree Bachelor of Science in Biology.	
25	2010	KUA earned the degree Doctor of Medicine. He was a scholar in medical school.	KUA underwent ulnar nerve transposition in the right upper extremity. Later on, KUA was diagnosed with Chiari malformation type II. KUA underwent sub-occipital craniectomy for Chiari decompression. KUA was then re-admitted for cellulitis. He gradually lost function of his extremities and eventually became paraplegic. He likewise exhibited signs of clinical depression, but he refused to seek Psychiatric consultation.
25	2011	KUA passed the PRC Physician Licensure Examination. KUA ended his last romantic relationship.	
27	2013	KUA was gainfully employed for the first time in the medical academe of private institution.	KUA coped with his clinical depression and was able to resume assisted but functional capacity.
32	2018	KUA was hospitalized and the prolonged medical ordeal forced him to go on leave of absence from his work.	KUA was diagnosed with NEC and underwent multiple surgeries, including a series of fasciotomy and skin grafting. He did home-based physical therapy and rehabilitation. He became immobile, unable to do ADLs and simple transfers. He again developed clinical depression.
33	2019	KUA was immobilized and became highly dependent on his mother for all his activities of daily living. The family experienced a lot of financial and emotional difficulties.	

Figure 2. The family lifeline of KUA

enabling them to adapt better in times of family crises, such as KUA's medical ordeal. Using the Modified Caregiver Strain Index (MCSI), KUA's mother scored 19 out of a highest possible score of 33, indicating a small possibility of caregiver fatigue. KUA's mother showed resilience amidst adversity, perhaps because she had taken care of her ailing father before he died, her geriatric mother in the province, her 18-year-old daughter with Down syndrome, and KUA who had now deteriorated significantly in terms of functional capacity.

Discussion

Chiari malformation is an anatomic anomaly of the craniocervical junction that involves the cerebellum, brainstem, and other related structures causing the downward displacement of the cerebellum, and sometimes also the lower medulla, into the spinal canal.[4] Hans Chiari classified the malformations into four groups in 1891: Chiari I: abnormally-shaped cerebellar tonsils are displaced below the foramen magnum; Chiari II (i.e., also known as Arnold-Chiari malformation): downward displacement of both cerebellar vermis and tonsils, associated with a birth defect called "spinal myelomeningocele" (i.e., incomplete formation of the spinal cord); Chiari III: rare and the most serious condition wherein the cerebellum and brainstem herniate through the encephalocele and spinal canal, respectively; and Chiari IV: the cerebellum is underdeveloped (cerebellar hypoplasia).[4] There are other conditions associated with Chiari malformations, such as hydrocephalus, syringomelia, tethered cord syndrome, and spinal curvature.[5-8] Chiari malformations can be diagnosed through magnetic resonance imaging (MRI), plain radiography, and computed tomography (CT). Surgery is the preferred treatment for advanced cases of Chiari malformation.

Table 1. The Family SCREEM of KUA

SCREEM	Resource	Pathology
Social	There was open communication among the family members of KUA, specifically with his mother and teenage half-sister. Prior to the development of NEC and his comorbidities, KUA spent quality time with his family. They would often go to malls, dine out in restaurants, do road trips to visit family in the province, and even target-pistol shooting. KUA belonged to a medical school fraternity. Despite being a person with disability (PWD), KUA maintained communications with his friends and colleagues through social media.	KUA did not develop an intimate relationship with his biological father who was often away due to work assignments. This also translated to irregular communications with his two sets of paternal half-siblings. KUA also dealt with living with his younger maternal half-sister with Down syndrome. KUA opined he did not really have a healthy relationship also with his sister, despite living together all her life. KUA had five unsuccessful romantic relationships, and he called off his wedding engagement when he developed clinical depression.
Cultural	KUA was recognized as a competent physician in his subdivision. Neighbors often did home consultations with KUA. KUA was a keen advocate of public health, and championed disease prevention and control in his community.	KUA did not belong to any ethnic group. There were no pathologic cultural factors evident at the time of assessment.
Religious	KUA and his family are practicing Roman Catholics. KUA's mother often used religious sayings and teachings whenever KUA felt depressed and anxious.	Because of his limited functional capacity, KUA was unable to hear Sunday mass on a weekly basis. However, he tried to go to Church during special Catholic holidays. KUA often questioned the goodness of the Lord whenever he felt depressed and anxious.
Economic	KUA was employed as Assistant Professor, full time in a medical school in the National Capital Region. With his savings, KUA was able to purchase his brand new van in 2015. KUA's mother worked as an employee. The combined financial resources of the two were sufficient to cover for their basic needs at home. She likewise had several land properties, which also provided added income to the family.	In October 2018, KUA had to file leave without pay from his current work, due to his medical condition (i.e., NEC) and immobility. This coincided with his mother's early retirement. The prolonged hospitalization and medical ordeal of KUA resulted in gradual depletion of their financial resources and savings in less than one year. Financial assistance sometimes came from relatives, friends, and colleagues.
Educational	KUA attended high school in an exclusive boys' school, college (BS Biology) in a state university, and medical school (Doctor of Medicine) in a private higher institution of education. Throughout his schooling, KUA was an academic / financial scholar. Because of his medical background, KUA understood perfectly his medical condition, including what potential complications might develop, as well as prognosis that could impact on his quality of life.	KUA's sister who had Down syndrome attended a special school and had regular home-based tutorial sessions. However, when KUA was hospitalized in 2018 and the family's resources gradually depleted, his sister had to abruptly stop schooling too. KUA's mother was a bit in denial as to the actual prognosis of her son's medical condition. She was optimistic KUA would still regain the ability to stand up and ambulate despite his very poor progress during home-based physical therapy sessions.
Medical	KUA enjoyed medical benefits, including free medicines and hospitalization, from his employer-institution. In addition, KUA also availed of medical privileges given to PWDs (i.e., 20% discount and 12% VAT discount).	The prolonged hospitalization and needed medical services of KUA entailed a lot of financial resources. Unfortunately, KUA's medical benefits were also suspended when he had to file for leave without pay. Because KUA was totally immobilized and dependent on a 24-hour caregiver for all his activities of daily living, KUA's elderly mother had to assume this role despite her small physique and frailty.

Necrotizing fasciitis is a rare and severe condition which involves the rapid spread of infection of the muscle fascia and the overlying subcutaneous tissues. It is considered as limb-debilitating and life-threatening. It occurs when necrosis develops in the deep fascial layers and consequently affects the superficial fascial planes. Polymicrobial (Type I) necrotizing infection is caused by mixed aerobic and anaerobic bacteria. An aerobic species is combined with Enterobacteriaceae (e.g., *Escherichia coli*, *Enterobacter, Klebsiella, Proteus*) and one or more facultative anaerobic streptococci other than group A *Streptoccocus*.[9-11] In contrast, monomicrobial (type II) necrotizing infection is often caused by Group A *Streptoccocus* or *Staphylococcus aureus*, which results in gangrenous myositis with toxic shock syndrome as a potential complication. Toxic shock syndrome may be due to the release of exotoxins A, B, and C.[9-11]

Clinical signs and symptoms of necrotizing fasciitis include edema, pain, fever, crepitus, erythema, and bullae, necrosis, or ecchymosis. Other possible clinical manifestations include fever, tachycardia, malaise, myalgia, diarrhea, anorexia, and systemic toxicity.[12] The diagnosis of necrotizing fasciitis can be made clinically, as in patients with soft tissue infection accompanied by systemic illnesses. Radiographic imaging and/or surgical exploration (i.e., debridement with tissue biopsy) may be performed to directly establish the diagnosis. Treatment and management of necrotizing fasciitis involves surgical debridement and broad-spectrum empiric antibiotic therapy against gram-positive, gram-negative, and anaerobic organisms.[12]

KUA also suffered from other comorbid conditions. Erb's palsy is considered to be one of the most common brachial plexus injuries involving the C5-C6 upper plexus (i.e., and C7 in 50% of cases). It is often a result of shoulder dystocia during forceps or breech delivery. Erb's palsy can precipitate paralysis of the abductors, external rotators, and extensors of the shoulder, as well as the flexors and supinators of the forearm, resulting in a waiter tip's deformity. Patients with Erb's palsy have absent biceps reflex, present palmar and Moro reflexes but no shoulder abduction.[13] Long term complications of Erb's palsy include decreased innervation, decreased strength and stamina, altered movement and biomechanics, muscle atrophy, impaired bone growth, joint dysfunction, osteoarthritis, limb length discrepancy, scapular winging, glenohumeral dysplasia, scoliosis, impaired balance and coordination, decreased bimanual dexterity, psychological changes, partial paralysis of the diaphragm, and Horner's syndrome.[14]

KUA also suffered from metabolic syndrome (MS), primarily because of his lack of physical activity, present body mass index and waist-hip circumference, and his immunocompromised state due to his recent two-month hospitalization. MS is characterized by hypertension, diabetes mellitus, dyslipidemia, obesity and hypercoagulable state.[15]

Though he was not officially diagnosed with clinical depression, KUA manifested depressive symptoms, such as suicidal ideation, lack of appetite, sleep abnormalities, and anhedonia.[16] Most of the symptoms were triggered after the craniectomy in 2011, which left KUA with significant motor and sensory deficits, resulting in paraplegia. The possibility of an adjustment disorder could not be totally ruled out.

A. Patient-centered health care

Since the last admission, KUA was diagnosed to have metabolic syndrome on the basis of his elevated blood pressure, impaired fasting glucose and abnormal oral glucose tolerance test, dyslipidemia, and morbid obesity. His maintenance medications were carvedilol, ivabradine, clonazepam and simvastatin. Several surgical procedures were done, including multiple debridements and fasciotomy. Skin grafting was also performed for the extensive exposed areas in the left lower extremity.

At home, the main goal was for the patient to regain functional capacity. Under the supervision of the Rehabilitation and Physical Medicine specialist, home-based physical and occupational therapy sessions were conducted thrice a week. A specific goal was to maintain and improve passive and active range of motion by employing active-assisted range of motion exercises for all joints of both the upper and lower extremities and by applying passive-assisted range of motion exercises with isometric exercises on all joints. The next goal was to assess static and dynamic balance abilities in order to determine the most appropriate ambulatory assistive device. The worst-case scenario would be the use of a wheelchair, and given that KUA's lower extremities had a score of 2/3+, the best type of wheelchair was one with an electronic joystick on the relatively more functional left side. An electronic joystick was preferred since

using the device would only entail flexion and extension of wrist. The third aim was to implement progressive resistance exercises to improve the muscle strength of the left upper and lower extremities and to maximize residual strength of the right upper and lower extremities. The final goal was to initiate the sensory retraining of the left upper extremity, such as visual monitoring, to prevent further injuries.

KUA underwent occupational therapy aimed to maximize independence, efficiency, and safety when participating in meaningful activities, such as 1) ADLs, which included self-care and ambulation, and 2) work-related activities, such as preparing and delivering lectures. Home visits were also essential to assess the KUA's living environment and to ascertain safety assessments. Patient counselling was also equally important to improve motivation to engage with others and perform independent tasks, despite physical limitations and constraints. The use of assistive devices was encouraged for him to be able to participate in daily activities, such as grooming, bathing, dressing, and toileting. Counselling was also an effective avenue to identify other psychosocial issues that KUA might be facing, including those that could trigger depression. Adaptive techniques were also introduced to facilitate independent daily activities that were individualized and adjusted to the existing resources of the patient. Caregiver education on assistance, together with performing exercises as prescribed by a physical therapist and an occupational therapist, was also encouraged to maximize remaining motor and sensory functions.

Lifestyle modification for KUA was also encouraged and encompassed a combination of diet, exercise, and behavioral modification. KUA was likewise directly advised to cut down on the consumption of carbonated drinks, including soda, to include possible significant weight reduction. This was on top of the recommendation for a low-salt, low-fat, low-purine diet, high-fiber diet. Cigarette-smoking cessation was also strongly encouraged. Exercises were aligned with the goals of the physical and occupational therapy sessions.

B. Family-focused health care

For the mother

Regular medical follow-up and good adherence with the maintenance drugs for diabetes mellitus and hypertension were prioritized, in terms of the health needs, for KUA's 61-year-old mother. From a wellness perspective, regular vaccination for geriatric patients was advised for KUA's mother, including annual quadrivalent influenza vaccine and immunization for pneumococcal diseases (i.e., both conjugate and polysaccharide vaccines).

Before the sudden demise of KUA, his mother was gradually exhibiting manifestations of caregiver fatigue syndrome despite her optimistic outlook in life. For a senior citizen to be the lone caregiver of two PWDs who were fully dependent on her for all their ADLs, it was a very stressful home environment that she endured on a daily basis. Perhaps, what was even more difficult for the mother was the unexpected death of KUA. The successive sad life events that were happening to their three-member family over that brief period definitely impacted on her psychological and emotional well-being. KUA's mother will benefit from individual counselling, since psychotherapy may be designed to reduce distress of the primary caregiver. The counselling intervention may potentially enhance the morale, self-esteem, coping, and the sense of control while alleviating anxiety and melancholy. Talking or emotional catharsis allows the caregiver to discuss her feelings, frustrations, and fears. Counselling sessions may help the caregiver gain insight that she is not really totally in control of the situation.[17] This intervention may also facilitate the grief and the bereavement process of KUA's mother.

For the Sister

KUA's sister suffers from Down syndrome and has other existing comorbidities, on top of congenital anomalies and physiologic changes related to puberty and early adulthood (i.e., irregular menses, etc.). She likewise requires regular medical consultation, which was interrupted since a significant amount of the family's resources was diverted to provide for KUA's medical needs. She also will benefit from adult immunization, such as the yearly quadrivalent influenza vaccine.

The sister became neglected because of KUA's medical ordeal. It is advisable for her to resume her home schooling, since the family gives so much premium on quality education. Likewise, she may also require counselling intervention because her mental capabilities may not fully comprehend the meaning of her brother's death. And, it may also be advantageous

if the sister undergoes debriefing sessions, for her to better vent her grief and possible repressed emotions from KUA's unexpected demise.

C. Community-oriented health care

A family in health crisis is often burdened by the economic impact of prolonged hospitalization and the necessary medical, surgical, and rehabilitative interventions. To a certain degree, many gainfully employed Filipinos rely on the financial assistance from the National Health Insurance Program through PhilHealth, which theoretically provides comprehensive packages of health services to all Filipinos.[19] Other sources of financial assistance must also be sought due to the limited PhilHealth benefits. These include monetary support from political leaders from various local and national government agencies, non-government organizations, and other institutions like the Philippine Charity Sweepstakes Office (PCSO).

For most chronically-ill and debilitated patients, an inter-disciplinary team approach is often required to ensure good quality of life. At times, referral to a Hospice and Palliative Medicine specialist may be prudent because ministering anticipatory care for an imminent death may also be pertinent for some families, including provision of psycho-emotional support.[19] To date, the PhilHealth recognizes palliative medicine as one of its essential package clusters under the Universal Health Care Act of 2019. On top of the PhilHealth benefits, with Republic Act 10754, PWDs are granted 20% discount on medical and other essential services, as well as exemption from the value added tax (VAT).[20] Advocacies that champion the rights of PWDs can also contribute to the welfare of this vulnerable population by providing awareness on social issues, such as inequities in employment and other forms discrimination against PWDs.

Conclusion

The biopsychosocial approach to care is essential in Family and Community Medicine practice, especially when dealing with a family in medical crisis, such as that of KUA's who presented with two rare medical conditions --- necrotizing fasciitis and CM Type II. The patient-centered care utilizes understanding of the interplay of biomedical and psychosocial factors to implement management that is tailor-fitted to the needs and values of KUA. The family-focused component utilizes family assessment to generate assumptions on how the family dynamics affect or facilitate the prescribed management of KUA's medical conditions. Lastly, the community-oriented dimension enables the primary care physician to use social determinants of health as a lens to understand how larger systems support or hinder the provision of care. With this patient-centered, family-focused, community-oriented (PFC) matrix, the Family and Community Medicine specialist can provide care for KUA and his family in a holistic manner by recognizing patient needs, creating an enabling family support environment, and helping KUA and his family navigate various community resources.[21]

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Primary health care in the age of advanced technology and modern medicine: Perspectives of future Filipino doctors

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Abstract

Introduction In a healthcare system that has been specialty-centric for decades, the Universal Health Care (UHC) Act would try to refocus on primary health care (PHC) to better navigate the entire healthcare delivery system of the country. This paper determined the perception of clinical clerks on the relevance of UHC and PHC on the practice of medicine in the Philippines.

Methods Clinical clerks rotating in Community Medicine were surveyed and focus group discussions were conducted to elicit the viewpoints of the students. Thematic analysis of the responses was subsequently performed.

Results Majority of the 247 student-respondents viewed UHC and primary health care (PHC) as relevant, however, some did not see the need to shift the focus of care from a specialty-centric orientation to that of a PHC approach. Medical students still dream of becoming specialists, and the idea of general medicine practice was not very popular among them. There were negative perceptions on essential healthcare at the community setting, given the inadequacy of medical facilities and technology, medications, and healthcare services in the locality.

Conclusion Sociopolitical factors remained important determinants of health, which often resulted in service delivery inequities, making access to health difficult for the marginalized and indigent. Given the efforts of the government to champion UHC amid the advances in modern medicine often localized in urban areas in the country, PHC was viewed to be relevant albeit not a priority for future Filipino doctors.

Key words: universal health care; primary health care; patient-centered, family-focused, community-oriented healthcare

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The establishment of a universal health care (UHC) system is a crucial part of successfully achieving the third sustainable development goal (SDG) promulgated by the United Nations in 2015.[1] Ideally, UHC should provide all people easy access to essential health services without them incurring financial hardship. The World Health Organization (WHO) continues to be a strong proponent of UHC, with emphasis on the role of primary health care (PHC) towards achieving global well-being and

improvement in quality of life.[2] This strategy is considered quintessential for countries that struggle to provide adequate and essential health care for their underserved and indigent populations, such as what has been seen in the Philippines for decades.

In 1995, the Philippine government moved towards implementing UHC by launching the National Health Insurance Program of the Philippines managed by the Philippine Health Insurance Corporation (PhilHealth). This government-owned corporation was meant to to provide all Filipinos with health insurance and alleviate the financial strain related to seeking health care.[3] As optimistic as it seemed, many Filipinos still found themselves out of reach of PhilHealth accredited facilities, while many others struggled to pay the out-of-pocket expenses for their health needs, such as medical supplies and medications.[4] In the following decades, the government strived to improve the country's health care system by reforming PhilHealth's insurance policies to increase coverage to more people and expanding benefit packages to cover a wider scope of illnesses. By 2010, PhilHealth reported coverage for 86% of the country's population, yet the system still suffered from implementation and management gaps that negatively affected the delivery of health services throughout the entire country.[5]

From late 2017 to early 2019, in further efforts to secure universal health coverage throughout the archipelago, the Philippine Senate worked with WHO and various stakeholders to draft and pass Republic Act 11223, also known as "The Universal Health Care (UHC) Act of 2019."[6] Using examples and experiences from other countries and regions with UHC, this act aims to reform the health care sector by improving the way health services are managed and delivered throughout the country's health care networks and automatically enrolling all Filipinos in the National Health Insurance Program. With this law, each Filipino, in principle, will be able to choose a primary care provider (PCP) who will offer free essential health services, treat the individual regarding health concerns, and coordinate care with other health facilities if his or her patient needs more extensive treatment.[7]

The shift of focus towards health promotion and preventive care, in contrast to curative care, realigns the Philippines with the 2018 Astana Declaration and the 1978 Alma-Ata Declaration, both of which envision PHC as the main strategy to attain "health for all" globally.[8] The WHO continues to assert that emphasis on primary care is the best strategy for dealing with the health issues currently faced throughout the world. Applying this approach to the Philippines can lead to better health outcomes by promoting efficient utilization of existing resources and assisting with navigation through the national health care delivery system. As the health care system in the Philippines continues to develop further, it becomes important to pay attention to the future doctors who will be serving the country under these new changes.

This paper assessed the perceptions of fourth-year medical students or clinical clerks regarding the relevance of UHC and PHC on the practice of medicine in the Philippines after their Community Medicine rotation.

Methods

This was a mixed method cross-sectional study involving fourth-year medical students enrolled as clinical clerks in a teaching hospital and academic medical center in school year 2018-2019 rotating for four weeks in Community Medicine in semi-rural areas in the Municipality of Taytay, Rizal. This study was approved by the institutional Ethics Review Committee prior to the implementation. Informed consent was obtained from the clinical clerks to participate in the study.

Semi-structured questionnaires (pilot tested for face and content validity) and focus group discussions (FGDs) were employed to elicit viewpoints of the study participants on UHC and PHC in the Philippine medical setting. The questionnaire allowed the respondents to reflect on their personal experiences during the Community Medicine rotation. Each clinical clerk was required to complete and submit his or her responses to the questionnaire at the end of the four-week Community Medicine engagement. Students participated in a three-hour FGD facilitated by doctor-faculty of the Department of Preventive and Community Medicine during the last week of their rotation, where they could voice opinions and thoughts on the country's current health care system.

The questionnaire responses underwent thematic analyses to look for recurring concepts and ideas that were frequently mentioned by the clinical clerks. Based on the content of their answers, each response was categorized into one or more themes. The total

numbers of responses per theme were computed to determine how frequently each topic was addressed.

Results

All study respondents were of adult age, with majority having Filipino backgrounds and lineage. The responses of 247 clinical clerks regarding the social significance of PHC and UHC in the age of advanced technology and modern medicine were collected and assessed. In general, the respondents opined that the state of PHC and UHC in the Philippines was problematic.

Recurring themes (Table 1) on the dismal condition of PHC and UHC in the Philippines that were found within the responses were: 1) lack of health education of the general public (mentioned 157 times); 2) improper distribution of health facilities and resources (mentioned 111 times); 3) financial constraints as an obstacle in seeking health care (mentioned 92 times); 4) insufficient government attention to the health care system; and 5) lack of interest to be a primary care provider. Feedback responses would often be placed into more than one category, especially when multiple ideas were expressed within a single response.

To expound on the opinions that were collected, verbatim responses from five clinical clerks were selected to demonstrate each of the recurring themes. The responses were included to better illustrate the general opinions that were commonly shared among the students.

Lack of health education of the general public

"The rotation was very interesting and eye opening to me because it showed me the true state of health care here in the Philippines and how a lot of Filipinos are still not knowledgeable with regard to a very common condition such as hypertension. I realized that it is not enough to treat the patient's condition because the same thing will just happen over and over again if the patient is not informed and does not understand the significance of the prescribed medications and even the non-pharmacologic advice given to them." – Clinical Clerk J.R. in 2019

Clinical Clerk J.R. expressed her surprise upon finding out that many Filipinos did not know much about the conditions that afflicted them or their family members. This sentiment was shared the most among respondents, mentioned in 157 of the 247 responses (63.6%). In this example, she reflected on her experiences after conducting a public health discussion on hypertension, one of the most widespread morbidities among Filipinos. Despite the high prevalence of hypertension and the abundance of information that may be obtained from the internet, many Filipinos did not fully understand the disease, resulting in both worry and indifference to the subject. Lack of correct information among the public (sometimes taken from the internet) also contributed to the spread of misinformation among families and within communities. As pointed out in this reflection, a low level of knowledge could potentially aggravate further health problems and contribute to the burden of the disease.

Inadequate distribution of health facilities and resources

"Rotating in these health centers made me realize how much Philippine health care has to go for universal well-being of the Filipinos. Medications not being enough, no sufficient diagnostic materials and equipment at hospitals, limited access to health care facilities, and so much more that I was not able to see

Table 1. Summary of responses and common themes elicited and recorded during the focus group discussions (FGDs).

Theme	Frequency (#) of responses mentioning theme	Percentage (%) of responses mentioning theme
• Lack of health education in the general public	157	63.6
• Improper distribution of health facilities and resources	111	44.9
• Financial constraints as an obstacle in seeking health care	92	37.2
• Insufficient government attention to the health care system	26	10.5
• Lack of interest to be a primary care provider	12	4.9

in that brief three-week stint in the community. What more in other provinces that are farther from the urban places?" – Clinical Clerk M.E. in 2019

As mentioned in this statement by Clinical Clerk M.E., there were major shortages in health facilities and equipment, especially in rural areas. Of the 247 responses, 111 clinical clerks (44.9%) mentioned this finding while engaging with the people. Important basic health instruments, such as diagnostic tools and hospital equipment, were unavailable in many primary care health facilities, infirmaries, and even some local hospitals. For many struggling Filipinos who could not afford to travel far distances, this meant compromising on quality of health and health services. This further deterred people from seeking health care locally since they felt it was a waste of time or that treatment would be either inadequate or simply out-of-reach. For those who consulted, oftentimes medications or vaccines would be in short supply or out-of-stock. Other clinical clerks mentioned the lack of health care providers (doctors, public health nurses, registered midwives, etc.) in some facilities. This was common in rural areas since many health professionals preferred to work in urbanized areas or abroad, due to higher standards of work and living in these places.

Financial constraints as obstacles to seeking health care

"Spending three weeks at the community gave me a peek at the real state of health of our country and fellowmen. Not all people have access to health centers and not all have the means to spend for consultations, much more on medications." – Clinical Clerk C.C. in 2018

Clinical Clerk C.C. shared a harsh fact of life for many Filipinos. Poverty-stricken and low-income households are a common scenario in the Philippines, and many families continue to struggle to simply provide for their daily needs. Health has never been the top priority for many of those who could barely make ends meet or who were in financial debt, even if their health condition deteriorated. Due to this, many Filipinos experienced difficulty in financing expenses for health, from transportation to consultations to even prescription medications. Among the 247 responses, 92 clinical clerks (37.2%) highlighted these financial hardships and how they negatively affected health outcomes. Many Filipinos were worried about getting sick because it was very often associated with a significant monetary hit. This would even become a larger issue if the disease was chronic and/or affected the main breadwinner of the household. Those who were able to save enough money for consultation and treatment would often still fall short in purchasing their prescription medications, which was one of the prevailing reasons for drug non-adherence and compliance.

Insufficient government attention to the health care system

"The rotation was an eye-opener. It made me realize that people really do put their trust in us. It also reminded me how we, as doctors, should advocate for better living conditions and increased government health funding." – Clinical Clerk L.D. in 2018

Another point that was mentioned occasionally pertained to government involvement in health care, since health care had been devolved to the local government units since the early 1990s. Clinical Clerk L.D. opined that doctors should participate in efforts to promote more funding from the government to improve the nation's health care system. A total of 26 of the 247 clinical clerks (10.5%) stated that they felt that there was an urgent and appropriate need for more government involvement and support the health needs of the country. Some clinical clerks referenced specifically to either local government or national government, while most referred to the government in general, without making any distinction. The sentiment arose more often after pointing out the difficulties that health care providers and clients mentioned in previous themes but placing more responsibility on government agencies. The government has been the subject of scrutiny among many Filipinos who follow the political scene. Amid the reports of corruption and mismanagements of funds, clinical clerks opined that there were a lot of suspicion and feeling of distrust of the government. Though PhilHealth was established, and legislative bills had been passed to provide better health care for all Filipinos, there remained an apparent lack in the standard of health care in the Philippines, and the clinical clerks questioned whether the government was putting in enough effort to really improve conditions.

Lack of interest to be a primary care provider

"I've always wanted to enter a surgical field, specifically in Neurosurgery; however, because of the experience and the knowledge that I have gained during this rotation, I'm now considering taking Family and Community Medicine, and can see that I can be a good Family and Community Medicine practitioner." – Clinical Clerk J.D. in 2018

At the end of the Community Medicine rotation, only 12 out of the 247 clinical clerks (4.9%) expressed their intention to pursue a career path related in some way to primary care and general medicine practice. In a country where doctor shortages have always been problematic especially in the geographically isolated and disadvantaged areas (GIDAs), any desire to alleviate the shortage is welcome and encouraged. Clinical Clerk J.D. expressed a possible shift in desire after seeing the health conditions of those living in the rural areas, from wanting to pursue a specialty in Clinical Neurosciences to a possible future in Public Health or Family and Community Medicine. Several students expressed interest in taking part in the Doctors to the Barrios (DTTB) program of the Department of Health, which deploys community-oriented doctors to GIDAs to provide better quality of care for the people living in the marginalized and underserved areas of the Philippines. A minority of respondents expressed willingness to serve as general medical practitioners in more remote areas of the Philippines. The rest of the respondents either made no definitive mention of their plans or expressed no desire to pursue primary care to the rural areas, stating some uncertainty in their ability to function optimally in areas with limited resources.

Focus Group Discussions

From the focus group discussions, most of the respondents viewed UHC and PHC as relevant and likely to be helpful for the country if implemented properly, especially in improving health outcomes in resource-limited communities like Taytay, Rizal. Although most students agreed that focusing on primary care was a good approach towards serving the entire country, some of these clinical clerks still did not feel it was necessary to make any large shift in the current specialty-centric orientation to that of PHC. When asked, most medical students still wanted to pursue some form of clinical specialization rather than general practice. The idea of following into fields such as Preventive, Family, and Community Medicine, Public Health, or Social Medicine was not very popular among the study participants. There were still negative perceptions on the status of essential health care at the community setting, given the inadequacy of medical facilities and technology, medications, and health care services in the locality. Some clinical clerks proposed that there were several sociopolitical factors that remained to be important determinants of health, often resulting in inequities in health care delivery and accessibility for many of the marginalized and indigent people of the communities.

Discussion

A good health system can significantly improve the health of the population by providing effective health services equitably. The Universal Health Care Act of 2019 aims to adopt a health care system that provides all Filipinos access to quality and cost-effective promotive, preventive, curative, rehabilitative and palliative health services without causing financial hardship, especially for the marginalized sector.

The feedback analysis of student responses reveals that today's clinical clerks generally agree that the current Philippine health care system is suboptimal and in need of improvement. There is a widespread dissatisfaction with the way health care is distributed and managed in many parts of the country, especially after experiencing frustrations first-hand while working in a rural community. It is evident to the students that despite efforts by the government to make health more available to the public, many medical facilities still lack necessary equipment needed to properly diagnose, treat, and manage patients. Despite the creation of PhilHealth and passage health legislation, many Filipinos feel that necessary health care is oftentimes unaffordable and/or unavailable.[10] With the number of sociopolitical issues that detract from providing better health care to Filipinos, many students are unsure or even doubtful about how much change will actually be accomplished from the passing of more laws towards universal coverage, even when students are aware of the theoretical benefits of implementing UHC in the Philippines, utilizing patient-centered, family-focused, community-oriented health care approach and strategies.

Furthermore, only a small number of these future physicians appears to be on-board with the idea of shifting more focus from specialized care to primary care, which is an important part of the strategy towards achieving "health for all." Even though most students can understand the benefits of increasing the availability and utilization of primary care physicians (PCP), only a few clinical clerks demonstrated interest to pursue a career in primary care. The lack of enthusiasm for primary care works against the goal of the UHC Act of 2019 to connect all Filipinos with a primary health care provider who can attend to patients' medical needs locally. This is a potential threat to the full implementation of the UHC Act of 2019 which aimed to shift the focus of health care from a hospital-centric approach (i.e., secondary and tertiary care) to that of primary care and primary health care (i.e., health promotion, disease prevention and control at the level of higher units of care to include families and communities) by 2025. This revealed a dilemma in terms of the basic medical curriculum in the country, where the main program outcome of the Doctor of Medicine degree was to produce generalists, rather than specialists, for the Philippine healthcare system.[9] In addition, there may be a need to revisit the existing clinical rotations of the fourth-year medical students to give more exposure to primary care cases in the out-patient and community clinics, over in-patient hospital work that focused on specialty management of secondary and tertiary levels of care.

Less than 1% of the general population would be admitted to a hospital facility and seen by specialists within any given month, whereas around 80% of a population would experience symptoms that could be evaluated and attended to by a primary care

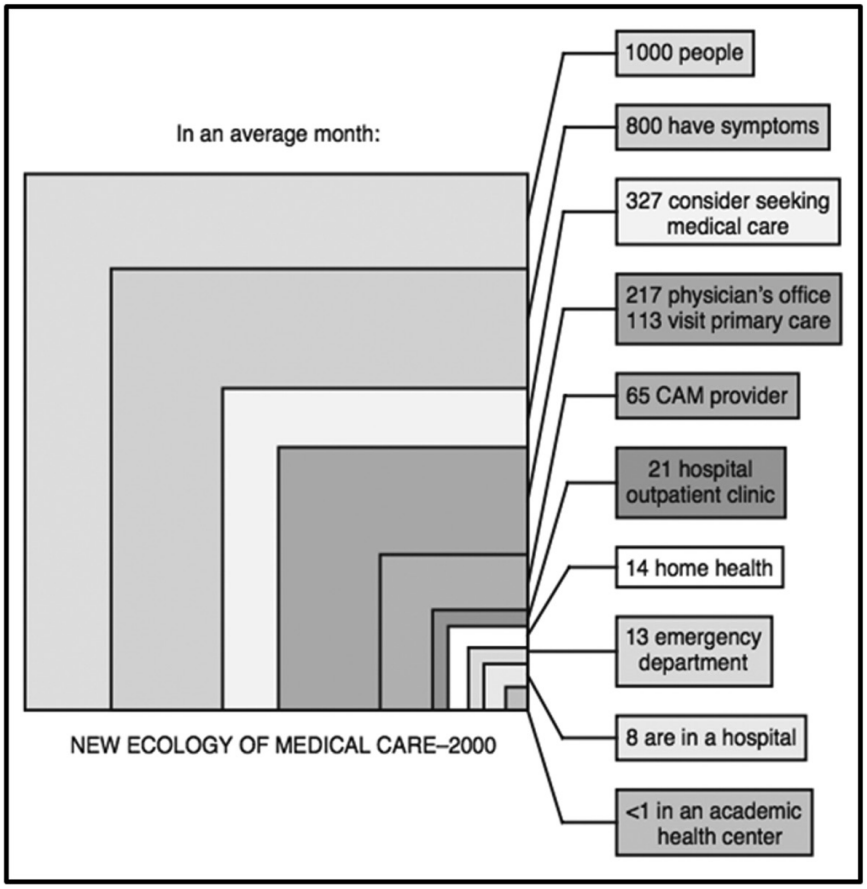

Figure 1. New Ecology of Medical Care, 2000. Number of persons experiencing illness during an average month per 1,000 people. (From Green LA, Fryer GE Jr., Yawn BO, et al. The ecology of medical care revisited. N Engl J Med 2001; 344: 2021-5.)

provider (Figure 1).[11] The aim of UHC is to provide enough PCPs who can meet the basic health needs of the majority of the population, ultimately leading to significant relief of disease burden through health promotion, prevention, and early detection. However, if the focus of doctors in the Philippines is still shifted towards specialization rather than primary care, most Filipinos will continue to struggle with finding feasible ways to address their personal health needs.

For the past decades, the Philippine Academy of Family Physicians has been campaigning for patient-centered, family-focused, community-oriented health care to medical students and trainees, hoping to emphasize the important roles that PCPs play, especially in a developing country. Within the health care delivery network, PCPs serve the majority of a population's health care needs, addressing the healthy, at-risk, and majority of the sick (Figure 2).[12]

In contrast to this model, the attitude of many Filipinos today is to seek consult from specialists for issues that the individuals deem as possibly urgent or distressing, while choosing to wait-out the less important health issues rather than consult with PCPs.[13] Similarly, many Filipinos are now using the internet to obtain health information, though there may be instances that the knowledge that they get may not entirely be accurate and true. Additionally, social and institutional influences gear today's medical students towards pursuing specialization, subtracting from the number of doctors who will serve as general physicians in the localities and populations in need.

These findings tend to suggest that achieving UHC within the Philippines will continue to be an uphill battle for some time. Unless stronger efforts are given to enforce the goals set by the Universal Health Care Act of 2019 and promote the necessity for more PCPs in the community setting, conditions are likely to stay the same. With this mindset, medical students are more likely to follow the status quo and continue along the trends that have been holding back the Philippine health system, effectively acting as setbacks in achieving universal health coverage.

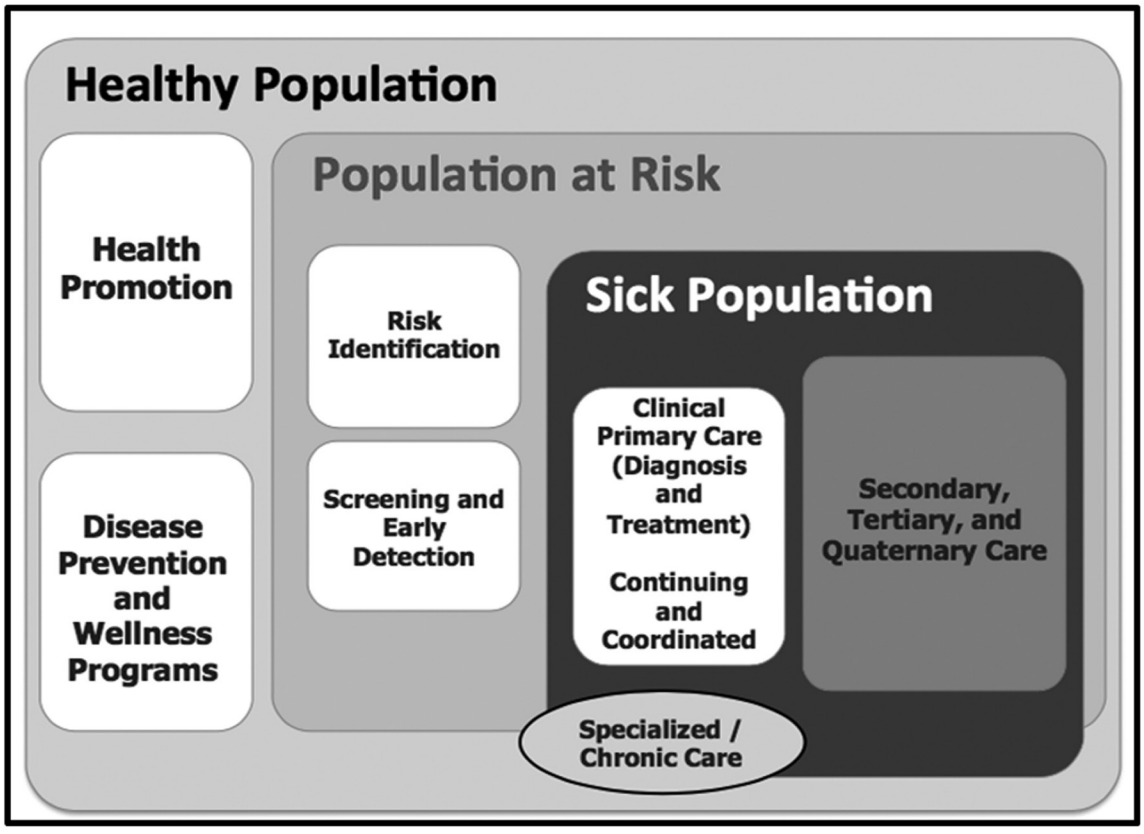

Figure 2. Spectrum of Services of Primary Care Providers. From the Universal Health Care Act lecture of Leilani S. Apostol-Nicodemus, MD, MScCMFM, DFM, FPAFP, National Director of the Philippine Academy of Family Physicians, 2019.

The future seen by many of today's clinical clerks is incongruent with the vision of UHC Act of 2019 that the government hopes to achieve. The condition of the health care system is still very far from the ideal picture of "health for all," and because of this, it is understandable that many clinical clerks are be apprehensive and doubtful about achieving 100% health coverage throughout the country, despite ongoing government efforts to push forward with their plans. With uncertainty towards the success of UHC and lack of interest towards PHC, most medical students will continue to pursue specialized medicine, rather than general practice, such as Family and Community Medicine and/or Public Health.

In this age of modern medicine often localized in urban regions, PHC in the grassroots and resource-limited community levels will need to overcome many sociopolitical barriers and perceptual attitudes surrounding the future of the Philippine health care system to achieve universal coverage for every Filipino in the coming years. Given the efforts of the government to promote UHC, PHC had been viewed to be relevant albeit not a priority for future Filipino doctors. Champions of patient-centered, family-focused, community-oriented health care must be born among today's Filipino medical students to truly realize the implementation of UHC throughout the country.

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Significance of hypocalcemia in predicting dengue severity in the pediatric population: A systematic review and meta-analysis

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Abstract

Introduction Dengue is one of the causes of morbidity and mortality among pediatric patients. Calcium has been shown to play a role in the myocardial function of the patient and is a potential cause of mortality among dengue patients. This study aimed to determine the accuracy of hypocalcemia in predicting the severity of dengue among pediatric patients.

Methods This is a systematic review and meta-analysis of published studies identified through an electronic literature search using PubMed/Medline, Cochrane Library, Herdin, Google Scholar, and hand search. Validity was assessed using the Cochrane risk of bias tool. Statistical analysis of the diagnostic test accuracy review was done using Review Manager 5.4.1 with the random effects model. Results showed sensitivity and specificity of hypocalcemia in severe dengue with a 95% confidence interval. The predictive values and likelihood ratios were also computed.

Results Four studies were analyzed. The mean serum total and ionized calcium levels of patients were decreased among the severe dengue group. Data showed that there is a 74% sensitivity (95% CI = 0.58, 0.84) and 75% specificity (95% CI = 0.67, 0.81) with a positive predictive value of 67% and a negative predictive value of 90.7%.

Conclusion This systematic review and meta-analysis showed that hypocalcemia may be a useful tool to predict severe dengue fever. However, further analysis is needed to strengthen the the diagnostic accuracy of hypocalcemia.

Key words: hypocalcemia, severe dengue, meta-analysis

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Dengue is very common in the Philippines especially during rainy season. It has been one of the morbidity cases seen in hospitals and can be a part of the mortality census. Mortality among pediatric patients can be prevented with adequate hydration and recognizing complications early in the course of the illness. There are different studies that focus on determining electrolyte imbalances seen during the course of the disease and calcium is the main interest of the researchers. Calcium has been shown to play a

role in the myocardial function of the patient and a low level is a potential cause of mortality.

Dengue is a mosquito-borne viral disease that is transmitted by female *Aedes aegypti* mosquitoes. It has rapidly spread in all regions in recent years. It is widespread throughout the tropics including the Philippines where there is a mixture of heavy rainfall and high relative humidity.[1] Dengue has four distinct serotypes which are DENV-1, DENV-2, DENV-3 and DENV-4. Recovery from the infection is believed to provide lifelong immunity against that serotype. Subsequent infections (secondary infection) by other serotypes increase the risk of developing severe dengue.

There is an estimate of 390 million dengue infections per year. The number of dengue cases reported has increased more than eight-fold over the last two decades from 505,430 cases in 2000 to 4.2 million in 2019. Dengue fever can range from a subclinical disease to severe flu-like symptoms. Some patients develop severe dengue with a number of complications like severe bleeding, organ impairment and/or plasma leakage. Severe dengue has a higher risk of death when not managed appropriately. As such, reported deaths from 2000 and 2015 increased from 960 to 4,032.[1]

The World Health Organization (WHO) classifies dengue into two major categories: dengue (with/without warning signs) and severe dengue.[1] Dengue should be suspected when a high grade fever is accompanied by any two of the following symptoms: severe headache, pain behind the eyes, muscle and joint pain, nausea, vomiting, swollen glands and rash. Severe dengue is diagnosed when the patient enters the "critical phase" and presents with signs of severe plasma leakage, fluid accumulation, respiratory distress, severe bleeding or organ impairment. Complications from severe dengue increase the risk of mortality. The dengue virus may be isolated from the blood during the first few days of infection and can be detected by testing for a virus-produced protein called NS1. Another test is the enzyme-linked immunosorbent assay (ELISA) that may confirm the presence of a recent or past in infection with the detection of IgM and IgG antibodies.

In severe dengue infection, there are several serum biochemical parameter changes that occur with the onset of plasma leakage such as decreased levels of calcium.[2] In some studies, hypocalcemia has been documented in dengue infection and is seen frequently among severe dengue patients.[3] Shivanthan and Rajapakse noted that the depletion of magnesium and calcium has been shown to enhance binding of dengue virus to monocyte macrophages and cells of T-cell and B-cell lineages.[3] Calcium is essential for the cytotoxic activity of dengue virus and this increased intracellular calcium leads to cell death. Calcium also has a role in the induction of dengue-specific T-helper cells; the dengue antigen increases the influx of calcium into the T-cells, hence leading to further cell death. Dahanayaka postulated that hypocalcemia in dengue fever could be due to influx of calcium and calcium replacement could enhance the dengue virus activity by increasing intracellular calcium ion concentration.[4]

Calcium plays a role in platelet aggregation and immune response in dengue infection.[5] Patients with hypocalcemia may present with hypotension, reduced myocardial function, electrocardiogram (ECG) abnormalities and heart failure which may worsen the patient's condition and lead to death. Since calcium plays a role in the functioning of myocardial tissue, derangements of calcium levels may directly contribute to myocarditis. Patients present with ECG changes like sinus bradycardia, tachycardia and T-wave inversion, and elevated creatine phosphokinase-MB (CPK-MB) levels.

In some studies, calcium levels were determined by testing either for the total calcium or ionized calcium. These studies revealed varied results with regard to the severity of dengue. Jayachandra stated that the calcium ion plays a critical role in normal cellular function and signaling, regulating diverse physiologic processes such as neuromuscular signaling, cardiac contractility, hormone secretion, and blood coagulation.[6]

Total serum calcium exists in three forms: 1) ionized, normally 50% of the total; 2) bound to plasma proteins such as albumin, usually 40% of the total; and 3) complexed to anions such as lactate and phosphate, usually 10% of the total. Ionized calcium, the physiologically active form of calcium found in the blood, is regulated by homeostasis. The total calcium level, therefore, is influenced directly by the serum albumin concentration. Free calcium is a more useful index than total calcium and provides a better indication of calcium status.

There are few literature documenting the role serum calcium levels in dengue. Some studies showed that dengue severity is correlated with the serum

ionized calcium levels. The general objective of this study is to determine the accuracy of hypocalcemia in predicting dengue severity among the pediatric age group. The specific objectives are to: a) determine the serum calcium levels of the dengue patients and b) compare the serum calcium levels of the pediatric patients diagnosed with non-severe dengue (dengue with and without warning signs) and severe dengue.

Methods

This study is a systematic review and meta-analysis of published studies that fulfill the inclusion criteria. Electronic literature search using PubMed/Medline, Cochrane Library, Herdin databases, Google Scholar and hand search was done using the following key words: severe dengue, hypocalcemia, low serum calcium level and children. Search was limited to descriptive studies on patients aged 0-18 years old, published until the time of study. Abstracts, single case reports and letters were not included in the analysis but were used as supporting literature. Bibliographies of studies and related articles were also scanned to identify additional trials and other relevant publications.

A study was included in this review if the following criteria were met: a) serum calcium levels of patients was tested and correlated with dengue fever; b) patients were aged 0-18 years; c) diagnosis and confirmation of dengue through Dengue NS1 and/or Dengue IgG, IgM and/or ELISA rt-PCR; d) severity of dengue of the patients was specified; and e) serum calcium levels of the patients were stated. A study was excluded in this review if any the following criteria were present: a) unavailability of full text; and b) patients received calcium supplement.

Once the studies were adequately screened, the authors independently appraised the validity and applicability based on the user's guides in Table 1. The studies for screening were also assessed for the risk of bias using the Cochrane risk of bias tool. Each criterion was scored as "low risk", "high risk" and "unknown risk" signifying potential for risk of bias in the respective category. The authors scored the studies independently and any disagreements were resolved with the aid of the third party.

Statistical analysis was done by recording the data into the Review Manager 5.4.1 program. A random effects model was used. The author was guided through the Cochrane diagnostic test accuracy review which provided information on how well the test distinguished patients with the disease from those without. The statistical analysis included the sensitivity of the test, which tells the proportion of those with severe dengue who have hypocalcemia, and the specificity of the test, which tells the proportion of those with non-severe dengue (dengue with or without warning signs) who have a normal calcium level. Additional computations specifically the manual computation of the sensitivity and specificity were done by making a 2 x 2 cross classification table of hypocalcemia and severe dengue. The results of the sensitivity and specificity of the included studies were plotted in the forest plot and receiver operating characteristic (ROC) curve. The positive (PPV) and negative predictive values (NPV), likelihood ratios (LR+, LR-) and diagnostic odds ratios were also computed.

Table 1. User's guides for appraising validity, results and applicability

1. Validity
   a. Was there an independent blind comparison with a reference standard?
   b. Did the patient sample include an appropriate spectrum of patients to whom the diagnostic test will be applied in clinical practice?
   c. Did the results of the test being evaluated influence the decision to perform the reference standard?
   d. Were the methods for performing the test described in sufficient detail to permit replication?

2. Results
   a. Are likelihood ratios for the test results presented or data necessary for their calculation provided?

3. Applicability
   a. Will the reproducibility of the test result and its interpretation be satisfactory in my setting?
   b. Are the results applicable to my patient?
   c. Will the results change my management?
   d. Will patients be better off as a result of the test?

Results

A total of 28 studies were identified in the initial search. Four studies were added with the hand search. After removing duplicates, 32 studies were screened. Five studies were excluded due to the inability to acquire the full text and 13 studies were excluded due to the irrelevance of the title and abstracts. The remaining 14 articles were then screened for eligibility based on the inclusion criteria and objectives of the study. Ten studies were excluded for incomplete data and risk for bias. In the 10 excluded studies, categorization of dengue was not specified, or no mean result of the ionized calcium was provided. The identification of studies was summarized in the PRISMA flow diagram (Figure 1). Four articles (Kumar 2017, Manjunath 2019, Nguyen 2004, Singh 2019) were included in the systematic review and meta-analysis and their study characteristics are shown in Table 2.[5,7-9]

Validity of included studies was assessed using the Cochrane risk of bias tool. All the included studies had low risk of bias on patient selection, index test, reference standard and flow and timing. However, one study showed unclear applicability in the patient

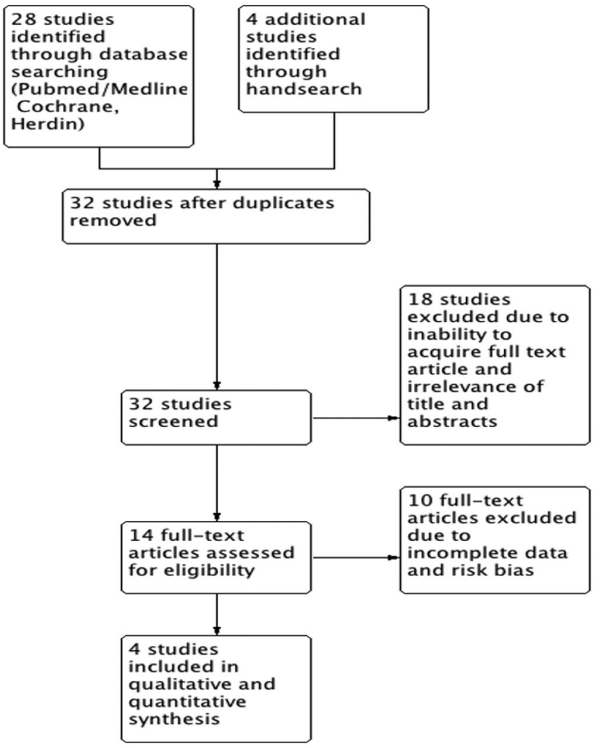

Figure 1. Study flow diagram

Table 2. Characteristics of included studies

Study	Methods	Participants	Diagnosis	Outcome
Kumar 2017	Cross sectional	306 children < 12 years with dengue fever; Jan 2013-Jun 2014	Patients categorized as dengue without and with warning signs and severe dengue; confirmed with Dengue NS1 or IgM.	Calcium level decreased among all severe dengue patients (mean = 7.3 ± 1.8), normal among non-severe dengue (mean = 8.8 ± 0.8), $p < 0.001$
Manjunath 2019	Case control	75 children 1-18 years with dengue fever; Oct 2014-Mar 2016	Patients categorized as dengue without and with warning signs and severe dengue; confirmed with Dengue NS1 antigen detection by ELISA or IgM ELISA.	Ionic calcium level decreased in 15/22 severe dengue patients (mean = 1.06; SD = 0.111), 27/53 non-severe dengue patients (mean = 1.11; SD 0.090); 7 severe dengue patients expired with a mean ionic calcium of 0.97 $p < 0.001$
Nguyen 2004	Cross sectional	107 infants < 12 months with dengue fever; Jan 1998-Mar 2002	Patients categorized as non-severe dengue (Grade I and II) and severe dengue (Grade III and IV); confirmed with Dengue IgM and IgG ELISA	Ionic calcium level decreased in 6/22 severe dengue patients (mean = 0.98)
Singh 2019	Cross sectional	100 children 1mo-18 years; Jan-Dec 2017	Patients categorized as dengue without and with warning signs and severe dengue; confirmed with Dengue NS1 antigen detection or IgM/IgG ELISA	Ionic calcium level decreased in 19/19 severe dengue patients (mean = 0.98 ± 0.05); 40/41 non-severe dengue patients (mean 1.05 ± 0.06)

selection and index test because the subjects only involved a specific age group at < 1 year old (Figures 2 & 3).

Results revealed hypocalcemia in both non-severe and severe dengue though majority was seen among the severe dengue group, especially those with fatal disease. The results are summarized in Table 3. Kumar and Singh had the highest sensitivity while Kumar and Nguyen had the highest specificity as shown in Figure 4.[7-9] The average sensitivity was 0.74 (95% CI = 0.58, 0.84) and specificity was 0.75 (95% CI = 0.67, 0.81). There is a 74% chance of hypocalcemia in a patient with severe dengue and a 75% chance that a patient with non-severe dengue will not have hypocalcemia, as shown in Figure 4. Kumar and Nguyen had the highest PPV while Kumar and Singh had the highest

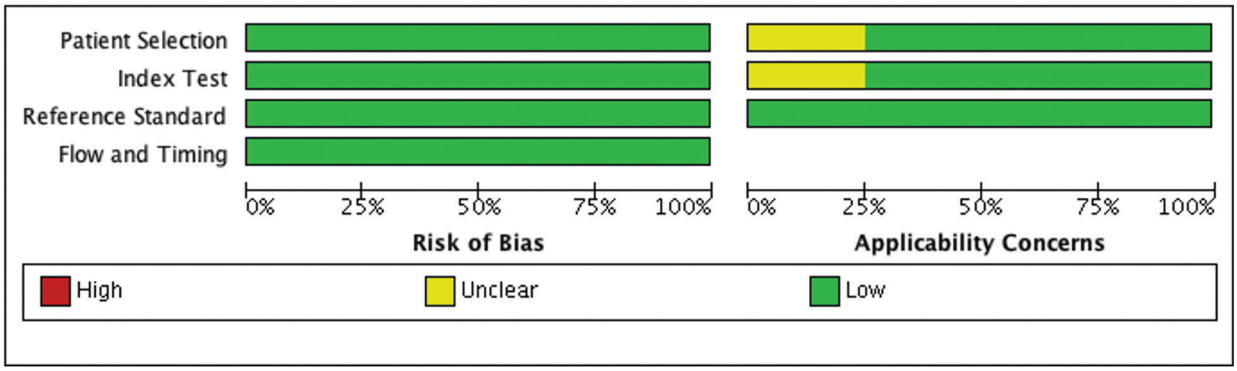

Figure 2. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies

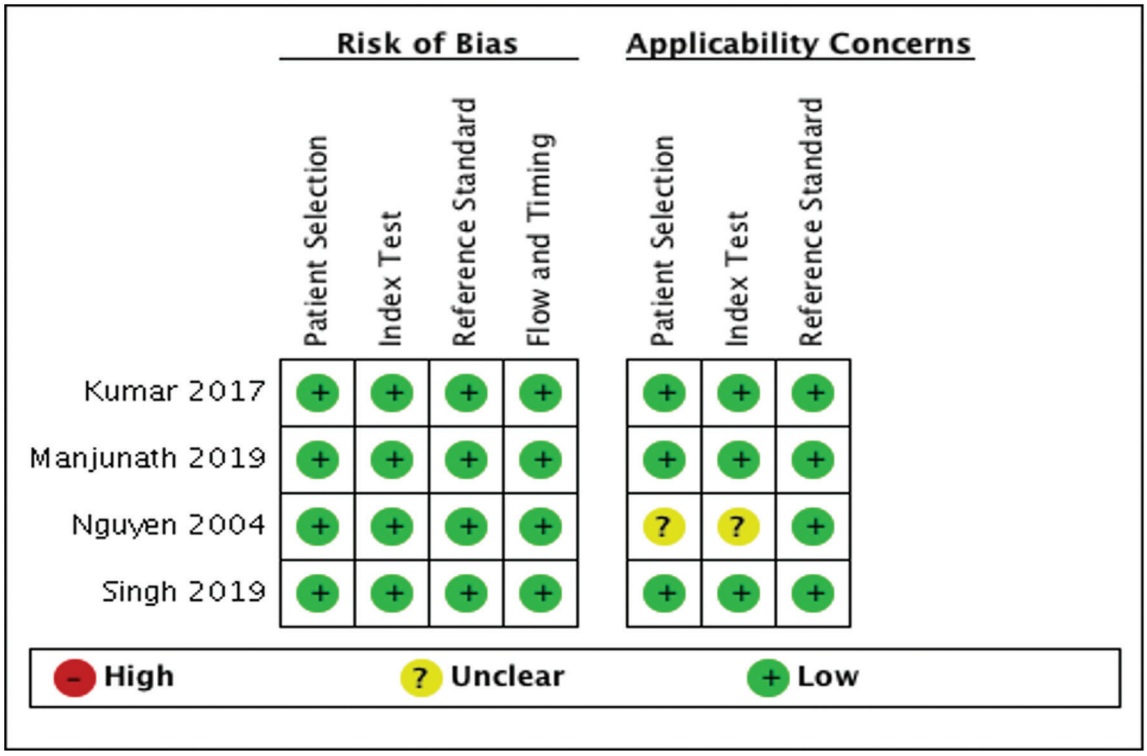

Figure 3. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study

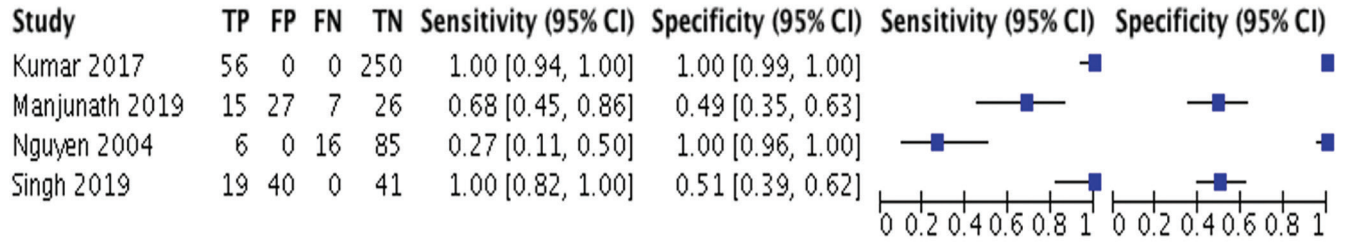

Figure 4. Forest plot of hypocalcemia in severe dengue

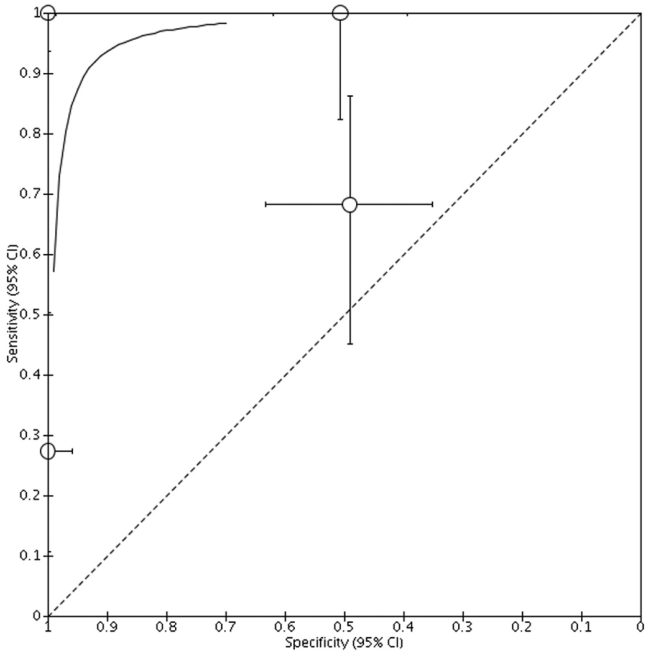

Figure 5. Summary ROC plot of hypocalcemia in severe dengue

NPV as seen in Table 4.[7-9] There is also a 67% predictive value of hypocalcemia for severe dengue. While the negative predictive value showed a 90.7% probability that when calcium levels are normal dengue will be non-severe. The summary ROC scatter plot (Figure 5) also shows greater variability in estimated sensitivity and specificity across studies. Although there was one outlier, the curve leaned to a higher sensitive and specific test.

Discussion

Based on the four included studies the average sensitivity is 0.74 and specificity is 0.75. There is a 74% chance of hypocalcemia among patients with severe dengue and a 75% chance of hypocalcemia among those with non-severe dengue. There is a 67% chance that a patient with hypocalcemia will have severe dengue and a 91% chance that a patient with no hypocalcemia will have non-severe dengue. From these percentages, the author cannot conclude that hypocalcemia is accurate in predicting a severe dengue. Thus, the author also looked into the summary receiver operator characteristic (sROC) curve. As the discriminatory power of a test increases, the sROC curve locates nearer to the top left-hand corner in ROC space towards the point where the sensitivity and specificity are both equal as seen in Figure 5.

Test accuracy may also vary according to the characteristics of the participants, setting, tests, reference standards and other methodological characteristics. This was assessed by investigating heterogeneity. The statistical power of a comparison depends on the number of studies, precision of the estimated within each study and will be lower where the characteristic is unevenly distributed across groups. In this case, such important heterogeneity or differences may be missed. This was one of the limitations of the study. The four included studies had undergone a validity appraisal, and all showed a low risk of bias. However, the review needs to include more studies to generate a more accurate result.

The included studies involved a good spectrum of the pediatric population, the serum total and ionized calcium levels were stated, and the diagnosis of dengue fever was confirmed by appropriate testing. Singh showed that the lowest mean ionized calcium (iCa) was found among severe dengue patients as compared to patients without warning signs.[9] This was similar to the findings of Habbu, Jayachandra, Azin, Manjunath, and Kumar.[5-7,10,11] A reason for

Table 3. Summary of non-severe and severe dengue patients with hypocalcemia

Study	Non-severe dengue		Severe dengue		Significance
	n*	Mean ± SD	n*	Mean ± SD	
Kumar 2017 (N = 306)	0/250	8.8 ± 0.8	56/56	7.3 ± 1.80	Hypocalcemia significant with severe dengue
Manjunath 2019 (N = 75)	Dengue without warning signs 6/12	1.096 ± 0.113	15/22	1.06 ± 0.11	Hypocalcemia correlates with the severity of dengue illness
	Dengue with warning signs 22/41	1.11 ± 0.090			
Nguyen 2004 (N = 107)	0/85	NA	6/22	0.98 ± 0.21	Not statistically significant
Singh 2019 (N = 100)	Dengue without warning signs 4/38	1.13 ± 0.10	19/19	0.98 ± 0.05	Hypocalcemia significant with severe dengue
	Dengue with warning signs 36/43	1.05 ± 0.06			

*n - number of patients who had hypocalcemia in each dengue category
Hypocalcemia defined serum ionized calcium levels < 1.1 mmol/L or total calcium levels < 7.5 mmol/L

Table 4. Predictive values and likelihood ratios of the included studies

Study	PPV	NPV	LR+	LR-	Prevalence
Kumar 2017	1	1	0	0	0.18
Manjunath 2019	0.36	0.79	1.34	0.65	0.29
Nguyen 2004	1	0.84	0	0.73	0.21
Singh 2019	0.32	1	2.03	0	0.19

PPV – positive predictive value, NPV – negative predictive value, LR+ - positive likelihood ratio, LR- - negative likelihood ratio

such finding as stated by Jayachandra is that calcium levels were lower with increasing severity of the dengue fever.[6] Several causes for low blood calcium levels have been suggested, including reduced Na^+-K^+ adenosine triphosphatase (ATPase) activity, reduced Ca^{2+}-ATPase activity, acquired parathyroid hormone deficiency, renal 1-alpha hydroxylase insufficiency, reduced dietary vitamin D intake, and reduced dietary calcium intake. Calcium appears to play a role in the induction of dengue specific T-helper cells. Dengue antigen has been shown to increase the influx of Ca^{2+} into T-cells. The proliferation of dengue-specific T-helper cells appears to be dependent on Ca^{2+} and is inhibited in the absence of Ca^{2+} and by calcium channel antagonist drugs. Despite these theories, the exact mechanism needs further investigation.

This review had limitations in terms of the inability to retrieve full text articles. These studies could have added more data to this review. Another limitation of this review is that there are few studies on pediatric patients, as majority of the studies involved adults. Lastly, the review analyses were limited only to the available data and to RevMan 5.4.1. Other analyses of diagnostic test accuracy like a hierarchical modelling can be done using other software like R or STATA or SAS but with a cost.

This review showed and summarized the significance of hypocalcemia in relation to severe dengue fever. There is a 75% sensitivity and specificity of hypocalcemia among severe dengue patients and has a 67% predictive value. However, it needs further analyses to strengthen the sensitivity and specificity of the diagnostic accuracy of hypocalcemia. This review suggests the potential benefit of determining hypocalcemia in predicting severe dengue as early recognition of patients at risk can contribute to decreasing mortality among dengue patients. However, studies as of this time of research are minimal thus the low statistical power of the review.

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Books and other monographs

Personal authors

Adams RD, Victor M. Principles of Neurology. New York: McGraw-Hill; 1981.

Chapter in a book

Corbett S. Systemic Response to Injury and Metabolic Support. In: Brunicardi FC (editor). Schwartz's Principles of Surgery. 10th ed. New York: McGraw-Hill; 2015: 13-50.

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