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23rd December 2003

Chairman, Select Committee to inquire
Into the handling of the Severe Acute Respiratory
Syndrome Outbreak by the Government and the
Hospital Authority
Legislative Council Building
8 Jackson Road
Central
Hong Kong

Dear Chairman,

Report to the Legco Select committee.

Thank you for inviting me to give a written submission to your questions in Appendix IV of your letters dated 15th and 16th December 2003. My report is based on the medical records of Mr. Liu Jianlun, my email communications with members of my department and the recollection of my phone calls to Dr. Margaret Chan, the ex-Director of Health.

AREA OF STUDY

(i) **Academic exchange with the Mainland about the situation of atypical pneumonia in Guangdong particularly during the period from late 2002 to early 2003**

Question 1

a. Yes, I did ask Dr. Y Guan and Dr. BJ Zheng to visit Guangzhou in early February 2003.

b. The background is as follows: Between Feb. 7 and 10, there were increasing reports in TV, online news and newspapers of Hong Kong and Mainland about unusual outbreaks of atypical pneumonia in the Guangdong province. The outbreaks were said to be associated with mortality and infection of hospital staff. I, as the head of microbiology and chair professor of infectious disease of HKU, was very concerned about the situation in Guangzhou and whether it was linked with a novel strain of influenza virus. After discussion with Dr. Guan Yi on Feb. 10,

we called a meeting at our Department. Four persons attended the meeting, including myself, Prof. M. Peiris, Dr. Guan, and Dr. B Zheng. During the meeting, Dr Guan expressed the concern that the atypical pneumonia happening in Guangdong region might be linked with H5N1 influenza virus, just like what had happened in Hong Kong in 1997. He proposed to initiate a more in depth field investigation to ascertain the infectious agents responsible for the outbreak.

c. The consensus of the meeting was that Dr. Guan and Dr. Zheng should try to contact the authorities in Guangzhou to facilitate the investigation, and if possible collect samples from the patients in Guangzhou. Dr. Guan and Dr. Zheng visited Guangzhou on Feb. 11, 2003.

Question 2

a. During that visit, Dr. Guan and Dr. Zheng met Prof. N.S. Zhong, head of the respiratory research centre at the First Affiliated Hospital, Guangzhou Medical College. He was in charge of the management of atypical pneumonia cases at his hospital. They stayed one night during the visit.

Question 3

a. During their visit, Prof. N.S. Zhong told Dr. Guan and Dr. Zheng that the atypical pneumonia outbreak might be caused by flu-like viral infection because all routine laboratory examinations for infectious agents were negative.

b. Prof. Zhong suggested a collaboration with The University of Hong Kong. He agreed to provide specimens from patients with atypical pneumonia for viral isolation and identification.

c. Dr Guan and Dr Zheng brought some nasopharyngeal aspirate specimens from these patients back to our department. All specimens were inoculated into chicken embryo and cell lines. After 3 to 5 days, four human H3N2 influenza viruses were isolated. One sample was positive for adenovirus and another one was positive for metapneumovirus by PCR tests. The later two findings could not be confirmed by culture. However, no other specific infectious agents were identified. All these information and investigation results were reported to me by the team members. Subsequent trips were made by Dr. Guan and Dr. Zheng to Guangzhou for the collection of more samples from patients.

Question 4

a. I phoned up Dr. Margaret Chan., the Director of Health on the morning of the 12th February 2003. This was done in view of a possible emergence of an epidemic flu; either caused by a genetically shifted or drifted human flu, or another bird flu H5N1.

b. Dr. Margaret Chan asked me to keep her updated on our investigations. During my subsequent phone conversations with Dr. Margaret Chan, I conveyed to her the information mentioned in my answer to Question 3 above. In addition, I have made a detail analysis of the situation in Guangzhou during the phone call on the morning of 12th February and on the 16th February 2003(when the initial microbiological test results were available). I conveyed the following points during the conversations:

(1)There is an impression of a large outbreak of acute community acquired pneumonia in Guangzhou and the Guangdong province which is severe enough to warrant hospitalisation. We have no information from the Mainland side on their surveillance data about this clinical entity in the previous years. The mortality of 5 in 305 is significant if the patients are mainly young immunocompetent adults, again we do not have the detail data for analysis. What is noteworthy is that over 100 of the cases are hospital staff which are generally young healthy individuals.

(2) The definition of typical and atypical pneumonia is difficult if there are no details on the clinical syndromes, the microbiological analysis and the therapeutic response to Penicillin group of antibiotics.

(3) In general, patients with typical pneumonia have a very acute onset with fever, chills, pleuritic chest pain, tachypnea and cough with rusty sputum. The infection is mainly caused by Streptococcus pneumoniae, Haemophilus influenzae or Staphylococcus aureus. Peripheral blood counts usually reveal neutrophilia. They respond very well to the beta-lactams (Penicillin group of antibiotics). Therefore these organisms are unlikely to be the cause of a major outbreak in a setting where antibiotics are liberally prescribed.

(4) Patients with atypical pneumonia usually have a less acute onset with preceding upper respiratory tract symptoms. The cough is often non-productive. The findings on clinical examination are disproportional to the chest radiographic changes. The infection is mainly

caused by Mycoplasma pneumoniae, Chlamydia pneumoniae/psittaci, Coxiella burnetti, Legionella pneumophila or less commonly various respiratory viruses. Peripheral blood can show either normal or increased white blood cells. They do not respond to treatment with Penicillin (note that Mycoplasma do not have a cell wall and the others are intracellular pathogens). All 4 bacterial agents are unlikely to cause a major community acquired outbreak with a high mortality and a high frequency of transmission to hospital staff because they respond very well to treatment by macrolides, tetracyclines and fluoroquinolones. Most of these infections by these agents can be diagnosed by serological testing.

(5) Thus the most likely explanation for the present situation is an outbreak of acute community viral pneumonia with spillage into the hospital staff when infection control measures are not enforced. Adult viral pneumonia is usually caused by

a. Influenza A and B viruses

b. Adenovirus

(6) Because of the lack of genetic variation, frequent exposure during childhood and protection by cross-reacting antibody; adenovirus can cause sporadic viral pneumonia in adults but very rarely a major outbreak except in a very enclosed setting such as military recruits or other institutions. However influenza A and B are also atypical in that the patients in Guangzhou did not seem to respond very well to anti-influenza agents.

(7) However during the winter period, influenza is still the top agent to be considered. In this regard, there is a possibility that the present outbreak in Guangzhou is due to an antigenically shifted or drifted human Influenza virus or an avian influenza A H5N1.

(8). My opinion are :

a. Without surveillance data on community acquired pneumonia in Hong Kong, it is difficult to formulate a detail control policy or to reassure the public .

b. Hospital infection control measures (droplet precautions) must be enforced.

Question 5

NOT applicable

AREA OF STUDY

(ii) The handling of the case of [redacted], who was admitted to Kwong Wah Hospital on 22 February 2003.

Question 1

a. I was aware of [redacted]'s admission to Kwong Wah Hospital on the morning of 24th February through a phone call from Dr. Andrew Yip, the chief of service of surgery of KWH, who asked for an expert opinion in my area of clinical microbiology and infectious diseases.

b. As I was just recovering from my sickness at that time, I asked my secretary to inform my colleague, Dr. PL Ho, associate professor of my department to see Professor Liu for me.

c. After Dr. Ho saw the case, he discussed with me his findings over the phone. He was going along the line of infections caused by Chlamydia and adenovirus.

d. My suggestion to him was that we should be open minded about other known or novel virus infections, and that ribavirin, a more broad spectrum antiviral agent should be given.

e. After I fully recovered, I went to KWH myself to assess the clinical condition of [redacted] on the 28th February.

f. My role was to find the cause of [redacted] illness (and later that of his brother-in-law) and suggest empirical treatment options for his critical condition.

g. The exact procedures of clinical consultation were performed according to the descriptions in our publications as enclosed in attachment I.

Question 2

a. When I examined [redacted] on 28th February, 2003, he was suffering from progressive respiratory failure due to interstitial pneumonia which necessitated the use of a ventilator. All the clinical information were obtained from the patient's records written by Dr. Watt and his team.

b. The infection control measures that I had taken were that of droplet precautions for community acquired pneumonia. That included the wearing of a mask, a gown, gloves and

performing hand washing before and after examining [redacted]. These were done in accordance with the CDC guideline for influenza. See attachment II.

Question 3

a. As all the results of the microbiological tests done at my department for Professor Liu were unremarkable, and his condition was considered too sick for an open lung biopsy; our clinical diagnosis was severe acute community acquired pneumonia caused by a virus of undetermined origin.

Question 4

a. Since then I have followed and discussed the conditions of [redacted], and later that of his brother-in-law, Mr. [redacted], with the doctors of KWH including Dr. Watt CL, Dr. So SO and Dr. Yee KS. As the condition of [redacted] was rapidly deteriorating, I suggested the use of steroid therapy since he did not respond to the use of intravenous immunoglobulin.

Question 5

a. I noticed that the case of [redacted] was already reported by the team of Dr. Watt to the infection control task force of the HAHO and regional office of DH. My subsequent discussion with Dr. Margaret Chan was mainly centred on the lack of any positive laboratory findings and the empirical use of antiviral and steroid for his very critical condition. I could not recall the exact date of this conversation.

Yours sincerely,

Professor K.Y. Yuen
Chair of Infectious Diseases
And Head of Department

Attachment I

Journal of Infection (1992) 25, 29–37

An evaluation of inpatient consultations conducted by clinical microbiologists in a teaching hospital

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Summary

A systematic procedure for conducting consultations by clinical microbiologists requested by their clinical colleagues is described. The method was evaluated over a period of 17 months and involved sequential consultations related to 229 patients with known or probable infections. An attempt was made to elucidate the contributions of the clinical microbiologists in achieving a better understanding of the problems experienced in this particular setting and which in turn led to improved management of patients. It is hoped that this paper may provide a practical working framework for clinical microbiologists in the care of patients suffering from infection.

Introduction

The role of laboratory-based clinical microbiologists in the medical service has been repeatedly questioned and considered by some as ill-defined and ostensibly dispensable.[1] On the other hand, their indirect contribution to the care of patients such as by liaising with various specialties, providing laboratory resources in the investigation of microbial diseases and investigating hospital and community outbreaks of infection has been more readily accepted in the health care system.[2] Such achievements, however, are difficult to quantify. We attempt in this paper to delineate the role and contributions of clinical microbiologists in conducting consultations at the request of their clinical colleagues. Furthermore, we show how clinical microbiologists by their proficiency in microbiology and by bringing the resources of the laboratory to the bedside can significantly improve the care of patients.

Method

During the period of January 1989 to May 1990, all written requests to clinical microbiologists for consultations from clinicians in various specialties in Queen Mary Hospital, Hong Kong (a teaching hospital with 1350 beds) were included in this study. The demographic data, recorded diagnosis and suspected infection were entered on an agreed standard consultation form used for all inter-specialty consultations. The specialties concerned consisted of internal medicine (medical), surgery (surgical), orthopaedics, radiotherapy (R/T), obstetrics and gynaecology (O&G), paediatrics and dermatology. Consultations by telephone without the need for seeing the patients in the ward were excluded.

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The clinical consultative procedure

(1) *Computer review*

After receiving the consultation form, a search of all the results of the patients' previous microbiological tests ordered since admission was made on our mainframe computer by use of the hospital number given to each inpatient. A chronological print-out containing the type of clinical specimens, their laboratory accession numbers, dates of requests and reported results was obtained.

(2) *Bench update*

For those specimens with results pending, the clinical microbiologist would derive from the relevant bench, by means of the laboratory accession numbers, the best available information before going to see the patient in the ward.

(3) *Ward visit and chart review*

A thorough review of the patient's medical record was followed by taking a further history and conducting a physical examination in order to ascertain the presence and/or the location of any infective focus. The various antimicrobial agents used, positive cultures from normally sterile body fluids and other relevant investigative findings such as new radiographic changes were entered on the temperature chart chronologically.

(4) *Recommendations on management*

By analysing all the available clinical and microbiological findings, a working diagnosis and appropriate recommendations were then written in the patient's record.

(5) *Provision of further test*

When further clinical specimens were needed for rapid diagnostic tests, the clinical microbiologist would collect and transport the specimen himself. Such specimens included needle aspirates of skin lesions, semiquantitative samples of surgical wounds[3] and punch biopsies in addition to routine clinical specimens. Rapid diagnostic tests were performed when indicated by the clinical situation. Reports and further recommendations were discussed by telephone with the clinician-in-charge.

(6) *Clinical surveillance*

Patients were observed until they improved or died. Further amendments to clinical management were made in the light of new clinical and microbiological findings.

Data processing

The demographic data of each patient including age, sex and the specialty of referral were recorded.

The specific problems that clinicians requested the clinical microbiologist to address were categorised under the following headings.

(1) Cause of persistent fever despite multiple antimicrobial therapy.

(2) Treatment of infections due to 'difficult' microbes such as fungi, mycobacteria, rare bacteria and parasites.
(3) Treatment of infections caused by multiple resistant bacteria.
(4) Suggested alternative antimicrobial regimes because of drug allergy or toxicity, difficulty in venous access, impaired liver and renal function.
(5) Miscellaneous problems which included the differentiation of bacterial colonisation from infection; infection in special anatomical sites such as ocular or intracranial regions; peculiar skin rashes; interpretation of serological findings; requests for special tests; management of fulminant sepsis.

The contributions of clinical microbiologists in the management of patients were categorised under the following headings.

(1) Finding additional clinical clues on physical examination and history taking that contributed to revised diagnoses.
(2) Collecting new clinical specimens for examination or ordering additional routine tests.
(3) Rapid diagnostic tests that give preliminary information. These included direct staining of specimens (Gram, Ziehl-Neilson, Gomori Silver; Indian ink); antigen detection (such as by latex agglutination tests for *Cryptococcus neoformans* and *Clostridium difficile* and by counter-immuno-electrophoresis for common encapsulated bacteria).
(4) Addition of other antimicrobial agents; altering dose or route of administration of currently administered antimicrobial agents.
(5) Stopping treatment with unnecessary antimicrobial agents.
(6) Suggested modifications of therapy (such as the removal of catheters, the need for surgical drainage, vaccination and use of immunoglobulins).
(7) Therapeutic drug monitoring (immunoassay, bioassay, serum bactericidal tests.)
(8) Additional antimicrobial susceptibility test (disc diffusion tests; broth dilution MIC, MBC; antifungal and antimycobacterial susceptibility tests).
(9) Alerting laboratory staff to unsuspected pathogens, misidentification and incorrect susceptibility test results.
(10) Miscellaneous (referral to ophthalmologist, otorhinopharyngologist; initiation of investigation of suspected nosocomial outbreaks).

Commonly identified infections that required the opinion of clinical microbiologists, the most common new diagnoses reached after consultation and the final outcome of patients were also categorised. Those with defervescence of fever and/or improved symptoms were categorised as improved. Those without symptoms (especially those for whom consultations were requested for alternative oral drug regimes or interpretation of serological findings) were categorised as indeterminate.

The number of rapid diagnostic tests and direct susceptibility tests that contributed to an earlier new diagnosis or change of antimicrobial therapy within 24 h were also noted. All the findings are shown in Tables I to IV.

Results

In all, 229 consultations were conducted during the period of 17 months that the study lasted. Most requests came from the orthopaedic (53 %) and the medical (30 %) units. The remaining 17 % were from the surgical, R/T, O&G, paediatric and dermatology units. The ages of the patients ranged from 2 to 91 years. The mean age was 50·6 years. The male to female ratio was 1·27:1.

A wide range of problems was encountered (Table I). The most common was persistent fever despite multiple antimicrobial therapy (55 %). This was followed by therapeutic problems such as recommendation of an appropriate antimicrobial regime for treating patients infected by 'difficult' micro-organisms (14 %) or multiple resistant bacteria (13 %). Another common therapeutic problem was the need for alternative antimicrobial regimes for patients with difficult venous access or who had developed allergy or toxicity to certain drugs.

The contributions by clinical microbiologists in the management of these problems are summarised in Table II. The most prominent was related to antimicrobial chemotherapy. In 95·2 % patients, a change of antimicrobial agent(s), a different dosage and/or another route of administration were suggested. In 76·4 % cases, antimicrobial agents were considered to be either unnecessary or covering an incorrect range of pathogens in that particular clinical setting or replaceable with equally effective but less expensive alternatives. The number of antimicrobial agents used before the consultation was, on average, 2·9 agents per patient. The range varied from zero to 11 antibiotics per patient. Therapeutic drug monitoring was considered to be necessary in 63·3 % cases and additional antimicrobial susceptibility tests were performed in 41 % cases in order to optimise treatment. Other therapeutic measures such as removal of infected vascular catheters and surgical drainage were recommended in 17 % cases.

With respect to contributions in the diagnosis of infection, additional clinical specimens for routine or special tests were collected in 52·4 % cases. Rapid diagnostic tests were done for 41 patients (17·9 %). Of these, 28 tests gave positive preliminary results which affected the choice of antimicrobial agents. Additional clinical clues were found in 19 patients (8·3 %). Most of these clues were either skin or optic fundal lesions. They included drug-induced rashes, ecthyma gangrenosum, scrub typus rash, fluffy cotton-ball fundal lesions in systemic candidiasis and subcutaneous cysts in cysticercosis. If it had not been for the consultative procedure, six instances of misidentification and incorrect results of susceptibility tests would not have been subsequently detected (Table III). Strains of *Pseudomonas pseudomallei*, *Cryptococcus neoformans* and *Penicillium marneffei* had been misidentified as *Pseudomonas* species, commensal yeasts and contaminants from sputum specimens respectively. An outbreak of *Candida tropicalis* peritonitis in dialysis patients was investigated and the source attributed to the use of blood warmers for warming peritoneal dialysis fluid.

The spectrum of diseases seen in consultations was quite diverse as shown in Table IV. Among those consultations in respect of patients with already recognised infections, infection of prosthetic devices (39 %) was the most often

Table I *Problems arising in clinical consultations**

		Orthopaedic	Medical	General surgery, R/T, O&G, Paediatrics	Subtotal number (%)
(1)	Persistent fever despite multiple antimicrobial therapy	67	54	30	151 (55)
(2)	Difficult microbial infections: fungal, mycobacterial, parasitic or other unusual isolates	19	17	3	39 (14)
(3)	Multiply resistant bacteria	24	9	2	35 (13)
(4)	Alternative anti-microbial regime in view of drug allergy, toxicity or difficulties with venous access	21	1	0	22 (8)
(5)	Miscellaneous†	5	18	4	27 (10)

* Several problems may be present in one patient.

† Differentiation of colonisation from infection, ocular infection, intracranial abscess, unusual skin rashes, interpretation of serological results, request for additional tests, fulminant sepsis.

Table II *Contributions by the clinical microbiologists in the management of patients*

		Number (%) $n = 229$
(1)	Additional clues on history and physical examination	15 (6·6)
(2)	Taking additional clinical specimens/ordering new test(s)	120 (52·4)
(3)	Rapid diagnostic tests to give preliminary information	41 (17·9)
(4)	Change of antimicrobial agent/altering dose or route of administration	218 (95·2)
(5)	Stopping use of unnecessary antimicrobial agents	175 (76·4)
(6)	Suggesting other therapy*	39 (17·0)
(7)	Therapeutic drug monitoring†	145 (63·3)
(8)	Additional antimicrobial susceptibility tests	94 (41·0)
(9)	Alerting laboratory to unsuspected pathogen, misidentification and incorrect susceptibility test results	6 (2·6)
(10)	Miscellaneous‡	23 (10·0)

* Suggesting the removal of vascular catheters, vaccination and use of immunoglobulins.

† Includes serum concentrations of aminoglycosides, vancomycin and co-trimoxazole or serum bactericidal titre.

‡ Referral to ophthalmologist, dermatologist, otorhinopharyngologist; initiation of investigation of nosocomial outbreak and isolation procedures; further organ imaging.

Table III *Incorrect laboratory reports which were corrected after consultations*

Sex/age	Initial reports	Reasons for consultation	Corrections after consultations
(1) M/35 years, fever, neutropenia.	*Xanthomonas maltophilia* from septic spots; susceptible to carbenicillin and piperacillin.	Persistent fever while treated with piperacillin and amikacin.	Repeated susceptibility test showed resistance; co-trimoxazole recommended with defervescence.
(2) M/1 week, neonatal sepsis.	Gram-positive cocci in chains in blood culture; phoned report: resistant to penicillin in direct susceptibility test.	Query on the need to use vancomycin instead of penicillin and gentamicin.	Wrong susceptibility test due to the use of inoculum from blood culture broths with added penicillinase. Confirmed *Streptococcus milleri* infection which responded to the original treatment.
(3) M/24 years, pneumonia.	Aminoglycoside-resistant *Pseudomonas* species in sputum.	Failed treatment with piperacillin.	Typical wrinkled colonies on original plates found on the fourth day and confirmed to be *Pseudomonas pseudomallei*; Co-trimoxazole and Ceftazidime were recommended with good response.
(4) M/31 years, pneumonia and skin pustules.	Aminoglycoside-resistant *Pseudomonas* species from both sputum and pustules.	Failed treatment with carbenicillin.	As above.
(5) F/38 years, systemic lupus erythematosis with pneumonia and a thigh abscess.	Only commensals isolated from sputum.	Failed treatment with intravenous cloxacillin and ceftazidime.	*Penicillium marneffei* recovered from the original cultures was ignored as a contaminant. The same fungus was recovered from the thigh aspirate.
(6) M/45 years, pulmonary tuberculosis being treated.	Only commensals isolated from sputum.	Persistent fever and shadows in chest X-ray despite standard anti-tuberculous therapy.	Scanty growth of yeast mixed with oral bacterial commensals was ignored as normal oral flora. Further identification revealed *Cryptococcus neoformans*. Fever responded to fluconazole.

Table IV *Diseases seen in consultations*

	Orthopaedic	Medical	General surgical, O&G, R/T, paediatric, dermatology	Subtotal number (%)
(A) Known infections				
(1) Infected prosthesis	55	0	2	57 (39·0)
(2) Sepsis and neutropenia	2	17	4	23 (15·8)
(3) Intraabdominal sepsis and total parenteral nutrition	0	0	19	19 (13·0)
(4) Endocarditis	2	15	1	18 (12·3)
(5) Others*	14	11	4	29 (19·9)
(B) New diagnoses made by the clinical microbiologist				
(1) Vascular catheter associated infections	7	14	10	31 (34·8)
(2) Drug fever ± rash or leucopenia	16	4	2	22 (24·7)
(3) Hidden collection of pus†	4	6	3	13 (14·6)
(4) Others‡	18	3	2	23 (25·8)

* Extrapulmonary mycobacterial infections, disseminated fungal infections, chronic osteomyelitis, tetanus, fulminant pneumonia, cavernous sinus thrombosis, mastoiditis, endophthalmitis, CAPD peritonitis, disseminated herpes simplex, meningitis.

† Thoracic empyema, Brodie's abscess, ischiorectal abscess.

‡ Extrapulmonary mycobacterial infections, disseminated fungal infections, other antimicrobial-induced toxicity, urinary tract infections, bronchopulmonary infections, surgical wound infections, typhoid fever, scrub typhus, ecthyma gangrenosum, pressure sore-associated osteomyelitis, pseudomembranous enterocolitis, sinusitis, endophthalmitis.

found and was mainly in the orthopaedic unit. This was followed in frequency by sepsis in neutropenic patients (15·8 %) and endocarditis (12·3 %) among patients in the medical unit. Surgical patients with intra-abdominal sepsis and receiving total parenteral nutrition constituted 13 % recorded infections.

Among the 89 new diagnoses made by the clinical microbiologist, most were vascular catheter-associated infections (34·8 %) which were distributed throughout all specialties. Drug-induced fever with/without skin rashes or leucopenia came second (24·7 %) and was found mostly in orthopaedic patients. Hidden collections of pus were detected in 13 patients (14·6 %).

As regards the spectrum of pathogens isolated from blood, normally sterile body fluid, tissue and other deep specimens in these 229 patients, methicillin-resistant *Staphylococcus aureus* (19·7 %) was the most important pathogen. This was followed by *Pseudomonas* species and other non-fermenters (11·1 %) which were often resistant to multiple antibiotics. *Mycobacterium tuberculosis*, *Mycobacterium marinum* and various fungi ranked third. One strain each of *Anaerobiospirillium succiniciproducens*[4] and penicillin-resistant *Streptococcus*

pneumoniae[5] was isolated and confirmed by the Public Health Laboratory Service. There was one sample of peritoneal fluid positive for *Trichosporon beigelii* and which gave a falsely positive cryptococcal latex agglutination test.[6] *Pseudomonas pseudomallei* and *P. marneffei* were also among the unusual isolates.

Most patients (70·3%) improved while 27 patients (11·8%) died. The outcome of the remaining patients (17·9%) was indeterminable.

Discussion

Few, if any, studies have tried to provide an entire picture of how clinical microbiologists, in co-operation with colleagues in various medical specialties, can function in the management of patients with infection. A relatively systematic approach to consultations was adopted in this study. The results were then analysed by categorising the common clinical problems, the contributions offered by the clinical microbiologists in diagnosis and therapy, the various infections recorded in the consultations and the pathogens isolated.

The study was limited to the collection of data from one particular teaching hospital. Nevertheless, the findings did provide some insight into this particular aspect of our service as clinical microbiologists. Investigation of the cause of persistent fever after multiple antimicrobial therapy was the most important reason why clinicians from various specialties asked for the help of a clinical microbiologist (Table I). This was followed by the therapeutic problems that arise in managing infections due to 'difficult' micro-organisms such as mycobacteria or fungi, organisms which were unfamiliar to many clinicans and especially to our general surgical and orthopaedic colleagues. Moreover, the armamentarium of antimicrobial therapy has expanded to such an extent that the choice of antimicrobial agents for combating multiply resistant bacteria or in difficult clinical situations is confusing to many clinicians. Thus, it is clear from Table II that one of the most prominent contributions of clinical microbiologists stemmed from their knowledge of antimicrobial therapy. Besides help in the choice of antimicrobial agents used, therapeutic drug monitoring and additional susceptibility testing were other services that were frequently offered.

Most clinicians had treated their patients with many antibiotics with little, if any, response before they consulted the clinical microbiologist. One of our important roles was to stop treatment with drugs that were not indicated (76·4%). This was important in order to avoid drug toxicity, unnecessary expense and the emergence of resistance.[7]

The use of rapid diagnostic tests (17·9%) and the collection of additional specimens for routine or special tests (52·4%) were considered necessary in many cases. These often led quickly to specific diagnoses and change of antimicrobial agents. The most fruitful part of the clinical examination was related to the examination of the skin and optic fundi where unexpected and important signs had been missed.

As regards the diseases seen in consultation, infections of prosthetic devices and sepsis in neutropenic patients were among the most frequent. This was not unexpected due to the more specialised services in a teaching hospital. Intra-abdominal sepsis and endocarditis were particularly difficult conditions to

treat and required the advice of clinical microbiologists. The provision of anaerobic bacteriological services, MIC, MBC and serum bactericidal tests were used in the management of these patients.

Among the new diagnoses made by the clinical microbiologists, hospital-acquired vascular catheter infections and drug-induced allergic manifestations were the most important. These were related to the frequent use of intravenous therapy in sick patients and prolonged antimicrobial treatment in patients with infected prosthetic implants. Consequently, requests for more than half of the consultations came from the orthopaedic unit.

As regards the pathogens involved in these 229 patients, hospital-acquired bacteria such as methicillin-resistant *S. aureus* and non-fermenting organisms created the biggest problems. This was due to the resistance of these organisms to multiple antibiotics and the need for more toxic, expensive and less familiar drugs. Fungal and mycobacterial infections were also important in the setting of a teaching hospital with a large population of immuno-suppressed patients. Even so, micro-organisms such as *M. marinum*, *P. marneffei* and *P. pseudomallei* gave rise to problems specific to our locality. There were instances when a pathogen was not isolated and the clinical microbiologist had difficulty in deciding whether empirical treatment was indicated despite the lack of positive laboratory findings. In five cases, empirical therapy was subsequently found to have been unnecessary when the diagnosis later proved to be 'malignant' fever (three cases), active systemic lupus erythematosis (one case) and polyarteritis nodosa (one case).

Conducting clinical consultations was not restricted entirely to the contribution of clinical microbiologists to the management of patients. The consultative procedure was also of value in that the clinical information collected during consultations could alert the laboratory to unsuspected pathogens, misidentification of organisms and sometimes wrong results of susceptibility tests. It also played an important part in the quality assurance of laboratory tests.

It was difficult, if not impossible, to relate the outcome of these patients directly to the effort spent on them. Nevertheless, we hope that this study may highlight some of the contributions made by clinical microbiologists to the care of patients as a result of inpatient consultations.

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Attachment II

Influenza

Recommendations for the Prevention of Nosocomial Influenza

I. Staff Education and Infection Surveillance

A. Staff Education

Educate personnel about the epidemiology, modes of transmission, and means of preventing the spread of influenza.(659-661,719,720) *CATEGORY IA*

B. Surveillance

1. Establish mechanism(s) by which the appropriate hospital personnel are promptly alerted of any increase in influenza activity in the local community. *CATEGORY IB*

2. Arrange for laboratory tests to be available to clinicians, for use when clinically indicated, to promptly confirm the diagnosis of influenza and other acute viral respiratory illnesses, especially during November-April.(620-625) *CATEGORY IB*

II. Modifying Host Risk to Infection

A. Vaccination

1. Patients

Offer vaccine to outpatients and inpatients at high risk of complications from influenza, beginning in September and continuing until influenza activity has begun to decline.(628,631,648,721-723) Patients at high risk of complications from influenza include those > or = 65 years of age; in long-term-care units; with chronic disorders of the pulmonary or cardiovascular systems, diabetes mellitus, renal dysfunction, hemoglobinopathies, or immunosuppression; and children 6 months-18 years of age who are receiving long-term aspirin therapy.(628) In addition, consider patients with musculo-skeletal disorders that impede adequate respiration to be at risk of complications from influenza. *CATEGORY IA*

2. Personnel

Vaccinate health-care workers before the influenza season each year, preferably between mid-October and mid-November. Until influenza activity declines, continue to make vaccine available to newly hired personnel and to those who initially refuse vaccination. If vaccine supply is limited, give highest priority to staff caring for patients at greatest risk of severe complications from influenza infection, as listed in Section II-A-1 above.(628) *CATEGORY IB*

B. Use of Antiviral Agents (See Section IV below, Control of Influenza Outbreaks)

III. Interruption of (Person-to-Person) Transmission

A. Keep a patient for whom influenza is suspected or diagnosed in a private room, or in a room with other patients with proven influenza, unless there are medical contraindications to doing so. *CATEGORY IB*

B. As much as feasible, maintain negative air pressure in rooms of patients for whom influenza is suspected or diagnosed, or place together persons with influenza-like illness in a hospital area with an independent air-supply and exhaust system.(614,615,724) *CATEGORY II*

C. Institute masking of individuals (except those immune to the infecting strain) who enter the room of a patient with influenza.(614,615,724) *CATEGORY IB*

D. As much as possible during periods of influenza activity in the community, have the hospital's employee health service evaluate patient-care staff who have symptoms of febrile upper respiratory tract infection suggestive of influenza for possible removal from duties that involve direct patient contact. Use more stringent guidelines for staff working in certain patient-care areas, eg, ICUs, nurseries, and units with severely immunosuppressed patients.(649,725) *CATEGORY II*

E. When community and/or nosocomial outbreaks occur, especially if they are characterized by high attack rates and severe illness:

1. Restrict hospital visitors who have a febrile respiratory illness. *CATEGORY IB*

2. Curtail or eliminate elective medical and surgical admissions as necessary. *CATEGORY IB*

3. Restrict cardiovascular and pulmonary surgery to only emergency cases. *CATEGORY IB*

IV. Control of Influenza Outbreaks

A. Determining the Outbreak Strain

Early in the outbreak, obtain nasopharyngeal-swab or nasal-wash specimens from patients with recent-onset symptoms suggestive of influenza for influenza virus culture or antigen detection. *CATEGORY IB*

B. Vaccination of Patients and Personnel

Administer current influenza vaccine to unvaccinated patients and staff, especially if the outbreak occurs early in the influenza season.(610,628) *CATEGORY IB*

C. Amantadine or Rimantadine Administration

1. When a nosocomial outbreak of influenza A is suspected or recognized:

a. Administer amantadine or rimantadine for prophylaxis to all uninfected patients in the involved unit for whom it is not contraindicated. Do not delay administration of amantadine or rimantadine unless the results of diagnostic tests to identify the infecting strain(s) can be obtained within 12 to 24 hours after specimen collection.(634,642) *CATEGORY IB*

b. Administer amantadine or rimantadine for prophylaxis to unvaccinated staff members for whom it is not medically contraindicated, and who are in the involved unit or taking care of high-risk patients.(642) *CATEGORY II*

2. Discontinue amantadine or rimantadine if laboratory tests confirm or strongly suggest that influenza type A is not the cause of the outbreak.(632) *CATEGORY IA*

3. If the cause of the outbreak is confirmed or believed to be influenza type A AND vaccine has been administered only recently to susceptible patients and personnel, continue amantadine or rimantadine prophylaxis until 2 weeks after the vaccination.(726) *CATEGORY IB*

4. To the extent possible, do not allow contact between those at high risk of complications from influenza and patients or staff who are taking amantadine or rimantadine for treatment of acute respiratory illness; prevent contact during and for two days after the latter discontinue treatment.(633,643-647) *CATEGORY IB*

Influenza

PART I. Issues on Prevention of Nosocmial Pneumonia, 1994

I. Epidemiology

Pneumonia in patients with influenza may be due to the influenza virus itself, secondary bacterial infection, or a combination of both.(599-601) Influenza-associated pneumonia can occur in any person, but is more common in the very young or old and in persons in any age group with immunosuppression or certain chronic medical conditions such as severe underlying heart or lung disease.(576,602-604)

Influenza typically occurs annually in the winter between December and April; peak activity in a community usually lasts from 6 to 8 weeks during this period.(605,606) During influenza epidemics in the community, nosocomial outbreaks can occur and are often characterized by abrupt onset and rapid transmission.(607,609) Most reported institutional outbreaks of influenza have occurred in nursing homes; however, hospital outbreaks have been reported on pediatric and chronic-care wards, as well as on medical and neonatal intensive care units.(557,610-613)

Influenza is believed to be spread from person to person by direct deposition of virus-laden large droplets onto the mucosal surfaces of the upper respiratory tract of an individual during close contact with an infected person, as well as by droplet nuclei or small-particle aerosols.(614-617) The extent to which transmission may occur by virus-contaminated hands or fomites is unknown; however, it is not the primary mode of spread.(618)

The most important reservoirs of influenza virus are infected persons, and the period of greatest communicability is during the first 3 days of illness; however, the virus can be shed before onset of symptoms, and up to 7 or more days after illness onset.(451,557,605)

II. Diagnosis

Influenza is clinically indistinguishable from other febrile respiratory illnesses, but during outbreaks with laboratory-confirmed cases, a presumptive diagnosis of the infection can be made in cases with similar manifestations.(619) In the past, diagnosis of influenza was made by virus isolation from nasopharyngeal secretions or by serologic conversion, but recently developed rapid diagnostic tests that are similar to culture in sensitivity and specificity allow early diagnosis and treatment of cases and provide a basis for prompt initiation of antiviral prophylaxis as part of outbreak control.(620-625)

III. Prevention and Control of Influenza

Vaccination of persons at high risk for complications of influenza is currently the most effective measure for reducing the impact of influenza, and should be done before the influenza season each year. High-risk persons include those > or = 65 years of age; those in long-term-care units; those with chronic disorders of the pulmonary or cardiovascular systems, those with diabetes mellitus, renal dysfunction, hemoglobinopathies, or immunosuppression; and children 6 months-18 years of age who are receiving long-term aspirin therapy. Patients with musculo-skeletal disorders that impede adequate respiration may also be at high risk of developing complications of influenza. When high vaccination rates are achieved in closed or semi-closed settings, the risk of outbreaks is reduced because of induction of herd immunity.(629,630)

When an institutional outbreak is caused by influenza type A, antiviral agents may be used both for treatment of ill persons and as prophylaxis for others.(642) Two related antiviral agents, amantadine hydrochloride and rimantadine hydrochloride, are effective against influenza type A, but not influenza type B, virus.(544,632-634) These agents can be used to prevent influenza type A (1) as short-term prophylaxis after late vaccination of high-risk persons; (2) as prophylaxis for persons for whom vaccination is contraindicated; (3) as prophylaxis for immunocompromised persons who may not produce protective levels of antibody in response to vaccination; (4) as prophylaxis for unvaccinated healthcare workers who provide care to high-risk patients, either for the duration of influenza activity in the community or until immunity develops after vaccination; and (5) when vaccine strains do not closely match the epidemic virus strain.(642)

Amantadine has been available in the United States for many years; rimantadine has been approved for use since 1993. Both drugs protect against all naturally-occurring strains of type A influenza virus; thus, antigenic changes in the virus that may reduce vaccine efficacy do not alter the effectiveness of amantadine or rimantadine. Both drugs are 70-90% effective in preventing illness if taken before exposure to influenza A virus.(632,635) In addition, they can reduce the severity and duration of illness due to influenza type A when administered within 24-48 hours after onset of symptoms.(636,637) These drugs can limit nosocomial spread of influenza type A if they are administered to all or most patients when influenza type A illnesses begin in a facility.(610,638,639)

Compared to rimantadine, amantadine has been associated with a higher incidence of adverse central nervous system (CNS) reactions such as mild and transitory nervousness, insomnia, impaired concentration, mood changes, and light-headedness. These symptoms have been reported in 5%-10% of healthy young adults receiving 200 mg of amantadine per day.(544,632) In the elderly, CNS side effects may be more severe; in addition, dizziness and ataxia are more common in this age group.(640,641) Dose reductions of both amantadine and rimantadine are recommended for certain patient groups, such as persons > or = 65 years of age and/or those who have renal insufficiency. The drug package insert for amantadine or rimantadine contains important information regarding administration of either drug. Guidelines for the use of these drugs and considerations for the selection of amantadine or rimantadine have been developed by the Advisory Committee for Immunization Practices.(642)

Emergence of amantadine- and rimantadine-resistant strains of influenza A virus has been observed in persons who have received these drugs for treatment of the infection.(643,644) Because of the potential risk of transmission of resistant viral strains to contacts of persons receiving amantadine or rimantadine for treatment,(644,645) to the extent possible, infected persons taking either drug should avoid contact with others during treatment and for 2 days after discontinuing treatment.(645,646) This is particularly important if the contacts are uninfected high-risk persons.(645,647)

Vaccination of high-risk patients and of hospital personnel before the influenza season is the primary focus of efforts to prevent and control nosocomial influenza.(628,631,648) The decision to use amantadine or rimantadine as an adjunct to vaccination in the prevention and control of nosocomial influenza is based in part on results of virologic and epidemiologic surveillance in the hospital and the community. When outbreaks of influenza type A occur in a hospital, and antiviral prophylaxis of high-risk persons and/or treatment of cases is undertaken, administration of amantadine or rimantadine is begun as early in the outbreak as possible to reduce transmission.(610,631,642,647)

Measures other than vaccination and chemoprophylaxis have been recommended for control of nosocomial influenza outbreaks. Because influenza can be transmitted during contact with an infected person, contact-isolation precautions, placing a patient symptomatic with influenza in a private room, cohorting og patients with nfluenza-like illness, and masking upon entering a room with person with suspected or proven influenza have been recommended.(224) Handwashing, gloving, and gowing by health-care workers during the patient's symptomatic period have also been recommended, but the exact role of these measures in preventing influenza transmission remains to be elucidated.(224,609,649) Although influenza can be transmitted via the airborne route, the efficacy of placing infected persons in room with negative pressure in relation to their immediate environment has not been assessed. In addition, this measure may be impractical during institutional outbreaks that occur in the midst of a community epidemic of influenza because many newly admitted patients and healthcare workers may be infected with the virus; thus, the hospital would face the lofistical problem of accommodating all ill persons in rooms with special ventilation. Although controlled studies are not available to measure their effectiveness, the following additional measures have been recommended for consideration, particularly dring severe outbreaks: (1) curtailment or elimination of elective admissions, both medical and surgical; (2) restriction of cardiobascular and pulmonary sugery; (3) restriction of hospital visitors, especially those the acute respitaroty illnesses; and (4) work restriction for healthcare workers with acute respiratory illness.(649)