Ann Natl Acad Med Sci (India), **45(1)**: 1-6, 2009

Primary Neonatal Anorectoplasty without Colostomy for High Anorectal Malformations including Pouch Colons

S.Chooramani Gopal
Department of Pediatric Surgery, Institute of Medical Sciences,
Banaras Hindu University, Varanasi – 221 005

Abstract

As a tribute to Col. Sangham Lal, an outstanding Surgeon of international and national repute, we chose to evaluate "Primary Neonatal Anorectoplasty without Colostomy for High Anorectal Malformations including Pouch Colons" as single stage procedure with special reference to modified technique of Posterior Sagital Anorectoplasty (PSARP) developed and promoted by the author at the Department of Pediatric Surgery, Institute of Medical Sciences, Banaras Hindu University since 1996 (1,2), as against the gold standard protocol of three stage management. Out of a total of 1036 newborns admitted with ARM since January 1996 till July 2007, 907 (87.5%) were high ARM including 87 Pouch Colons and 129 (12.5%) low ARMs. Only 24 babies had colostomy. The remaining 883 had primary single stage operation: SCG Modified PSARP – 466; Abdomino Perineal Pull through (APP) – 263; PSARP combined with APP – 23 Anterior Sagital Anorectoplasty (ASRP) for intermediate anomalies – 131. The results were analyzed and compared with previously performed 458 three staged procedures for mortality, morbidity, continence and cost.

Correspondence: Dr. S. Chooramani Gopal, FAMS, Vice-chancellor, Chhatrapati Shahuji Maharaj Medical University, Shameena Road, Chowk, Lucknow-223006. Mob: 9336926879. E-mail: chooramani@yahoo.com. Col. Sangham Lal Oration 2006-07. Delivered at the Annual Conference of the National Academy of Medical Sciences (NAMSCON, Amritsar), 2007.

The neonatal single stage procedure mortality was (4.5%) compared to 13.5% colostomy mortality in staged procedure. Good continence (80%) was achieved in Neonatal single stage group compared to (45%) in staged group. The mortality rate was particularly low among the babies who underwent single stage modified PSARP (3.1%) as compared to APP (10.2%). Based on our large experience we strongly recommend primary modified PSARP or single stage APP for all high anorectal malformations. Colostomy must be avoided to achieve better continence due to physiological reasons.

Keywords: primary PSARP, single stage anorectoplasty, colostomy, high ARM in newborns

Introduction

Anorectal malformations (ARM) are the most common surgical anomalies encountered in the newborns in our country (3) particularly so in our hospital catering to relatively poor belt of eastern UP, Bihar, Jharkhand & Chattisgarh. The anomaly is easily identified and for surgical management is classified into high, intermediate or low type depending upon the extent of anorectal agenesis. The high ARM (including Intermediate & Pouch Colon) are more frequent (85%) than low type (15%). For high ARMs over last 150 years, the gold standard protocol of management has been: I- preliminary neonatal colostomy, II- anorectoplasty (abdomino perineal –APP / posterior sagital - PSARP / anterior sagital - ASARP), and III – Colostomy closure. Our experience with staged procedures has been very dissatisfying: high colostomy mortality and colostomy morbidity, poor colostomy care, diarrhea, colostomy prolapse, chronic anemia, repeated UTI, coupled with problems of travelling, repeated hospitalization, high risk of anesthesia and high cost of surgery. Our study further revealed that only 40% of babies of High ARM could complete the three staged procedures. And at the end, the result of achieving good continence (good Kelly's score) was seen only in 45% cases, 3 years after colostomy closure. Clearly, staged approach was far from satisfactory. Hence at our Institution the author modified the technique of Pena's PSARP (4) and promoted it for primary PSARP without colostomy for management of high ARM, in which the anorectal pouch was less than 3 cm. above the perineum. In

other (> 3 cm.) cases single stage APP was done.

Material and Methods

Losing large number of babies of staged procedure in ARM while waiting for definitive pull through, forced us to innovate in favour of single stage neonatal anorectoplasty. The author modified in 1996 Pena's PSARP, the crux being: (a) recto-vesical fistula, carefully dissected extra luminally and extramurally without opening the AR pouch (b) the AR pouch is not tapered (c) the AR pouch after mobilization first secured at the new anal site to superficial muscle complex and with few stitches to skin (d) the pouch is opened only when whole wound is stitched. The mecorium is sucked actively – to prevent spillage and wound infection.

Our initial experience of the procedure was very encouraging. Its results were presented at the Annual meeting of India Association of Pediatric Surgeons, Bombay, 1997. We have been following ever since single stage operations in ARM, using our modified technique of PSARP in most of high ARMs. Since January 1996 to July 2007, 1036 newborns with ARMs were admitted out of which 907 were diagnosed to have high anomalies (including 87 Pouch Colons). Only 129 were of low type. These 907 babies formed the subject material of single stage anorectoplasty, 661 being males (72.8%) and 246 (27.2%) females.

Observations

Out of 907 high ARM babies 24, (2.6%) were found too sick for pull through operations, hence had colostomy. Modified Primary PSARP was done in 466 cases, abdominoperineal pull through APP was done in 263 cases and in 23 cases PSARP was combined with APP. ASARP was done for intermediate lesions in 131 newborns.

Mortality

Out of 883 cases of single stage anorectoplasty 40 babies died (4.5%) during post-op period whereas in the staged group of 763 high ARMs, 103 (13.5%) patients died prior to getting second stage operation. Also it was revealed that the mortality of primary modified PSARP was only 3.1% and that of primary APP was 10.2%, thereby proving that primary modified PSARP is safer. All the three stages of operation could be completed only in 458 out of 763 ARMs cases admitted from January 1989 to January 1996. Thus nearly 40% of patients (39.9%) either succumbed to disease and its complication or reconciled with the pathology.

Morbidity

Table 1 shows the rate of various complications encountered between staged and primary single staged procedures. The incidence of all complications was observed to be far lower in single stage procedures as compared to staged. The blood requirement during surgery was very low in single stage procedures.

Continence

As assessed by Kelly's clinical method (5), continence was remarkably better in single stage group where 80% achieved good score as compared to 45% in staged procedure.

The misery of patients and cost of treatment was very high in staged procedures.

Table 1

Complications of anorectoplasty; Primary vs Staged procedures.
Period 1989 to July 2007

Complications	Staged 458 (%)	Primary 883 (%)
Significant bleeding	(26.42)	(9.39)
Bladder base injury	(1.96)	(0.82)
Prostatic uretheral injury	(3.71)	(1.63)
Faecal leak	—	(0.41)
Anal stenosis	(4.14)	(2.45)
Mucosal prolapse	(4.58)	(0.82)
Wound infection	(19.87)	(1.43)
Ureter injury	—	(0.20)
Neurogenic bladder	(1.75)	(0.20)
Chronic anaemia	(35.59)	—

Discussion

Primary anorectoplasty for ARMs was performed as early as 1948 by Rhoads and Randall (6), and by Noris and Brayton (7) in 1949, but were given up because of high mortality and infection. Aluwihare (8), Goon (9), Moore (10), Craig (11) and Narasimhan *et al* (12) tried to revive single stage anorectoplasty. However the results

showed high incidence of wound infection. Hence the single stage operation did not become very popular. We feel that extra luminal extra mural ligation/transaction of recto-uretheral/ recto-vesical, fistula and not opening the rectal pouch till whole wound is closed minimizes the risk of infection and wound dehiscence and also decreases morbidity and mortality. The achievement of better continence in our studies supports the theory of Dobbing *et al* (13) and of Wiesel and Hubel (14) which states that there is activity driven race for space allotment in the cerebral cortex immediately after birth for normal somato-sensory brain neocortical neuro-circuitory development in the first 7 days after birth. Placing the anorectum in perineum in first week of birth thus helps in achieving better continence. We feel that tapering the anorectum as advised by Pena may also compromise with anorectal function. Therefore our technique of modified PSARP seems to work better.

Conclusion

Colostomy in the management anorectal malformations should be avoided. Modified single stage PSARP is the operation of choice for majority of high and intermediate ARMs. When the agenesis of anorectum is more than 3 cm or there is pouch colon or common cloaca abdomino perinial, single stage operation should be done. *Primary neonatal anorectoplasty achieves far better results.*

Acknowledgement

The data presented here is a joint effort of all the teachers of the department of Pediatric Surgery, IMS, BHU, Varanasi. The author is highly grateful to Prof. A.N.Gangopadhyay, Prof. D.K.Gupta, Dr. S.P.Sharma, Dr. Vijeyndra Kumar, Dr. R.B.Singh and Senior Residents Dr. Vijay Upadhayay, Dr. Zaheer and Dr. Anand Pandey who have all contributed to management of these cases.

References

1. Chooramani Gopal S (2000). Single stage PSARP in Neonates. In: Textbook of Neonatal Surgery. DK Gupta (editor), Modern Publishers, 249-253.
2. Gangopadhyay AN, Chooramani Gopal S, Sharma S, *et al* (2005). Management of anorectal malformations in Varanasi, India: a long term review of single and three stage procedures. *Ped Surg*

Int 10.1007/s00383-005-1567-6 (published online).

3. Chatterjee SK (1993). A surgeon's experience. In Anorectal Malformations. New York, Oxford University Press.
4. Pena A (1988). Surgical management of anorectal malformations: a unified concept. *Pediat Surg Int* **3**: 82-93.
5. Kelly JH (1972). The clinical and radiological assessment of anal continence in childhood. *Aus NZ J Surg* **42**: 62-63
6. Rhoads & Randall (1948). A simultaneous abdominal and perineal approach in operations for imperforate anus with atresia of the rectum and rectosigmoid. *Ann Surg*. **127**: 552.
7. Noris & Brayton (1949). Imperforate anus: A case series and preliminary report of one stage abdomino – perineal operation. *Surg Gynaecol Obstet*. **88**:623.
8. Aluwihare APR (1990). Primary perineal rectovaginoplasty for supralevator imperforate anus in female neonates. *J Pediatr Surg*. **25**: 278-281.
9. Goon HK (1990). Repair of anorectal anomalies in the neonatal period *Pediatr Surg Int* **5**: 246-249.
10. Moore TC (1990). Advantages of performing the sagital anoplasty operation for imperforate anus at birth. *J Pediatr Surg*. **25**:276-277.
11. Albanese CT, Jennings RW, Lopoo JB, *et al* (1999). One stage correction of high imperforate anus in the male neonate. *J. Pediatr Surg*. **34**:834-836.
12. Mishra BN, Narasimhan KL, Chowdhary SK, Samujh R, Rao KLN (2000). Neonatal PSARP versus stages PSARP: a comparative analysis. *J Indian Assoc Ped. Surg*. **5**: 10-13.
13. Doobing J, Sands J (1973). Quantitative development of growth and development of the human brain. *Arch Dis Child* **48**:757.
14. Wiesel TN, Hubel DH (1981). Comparison of the effects of unilateral and bilateral eye closure on cortical unit response in kittens. *J Neurophysiol*. **28**: 1029-1040.

Ann Natl Acad Med Sci (India), **45(1)**: 7-16, 2009

Quality of Indian Doctors : A Matter for Concern?

SP Kaushik
Former Professor and Head, Department of Surgical Gastroenterology,
Sanjay Gandhi P.G.I., Lucknow

Abstract

Data from human development report, U.N. development program, updated in 2005, indicates that, out of 177 countries assessed, the Human Development Index ranking for India is 127. This reflects poorly on country's health and social statistics. Our health care system revolves around the quality and capabilities of medical manpower available to us. Unless the society, the academicians, and the government can ensure that only the best talented students would get the opportunity to enter medical courses, and are trained by the best available faculty, under the best possible support systems and environment, it would not be possible to break the shackles of mediocrity and expect better health care delivery as well as performance. Therefore, there is an urgent need today of combining our efforts and for corroborative working.

Keywords: human development index, medical education, academic hierarchy, brain drain

Introduction

The Human Development Index (Health status, education and poverty) ranking for India is 127 out of 177 countries assessed in the world (data from human development report, U.N. development program, updated in 2005). This reflects poorly on country's

Correspondence: Dr. SP Kaushik, F.R.C.S.(Edin), Ph.D.(Lon), F.A.M.S. Former Professor and Head, Department of Surgical Gastroenterology, Sanjay Gandhi P.G.I., Lucknow & President, Indian Association of Surgical Gastroenterology. Residence: H.No. 132, Sector 6, Panchkula - 134109. Tel: (0172) 2570971. E-mail - spkaushik@hotmail.com. Glaxo Oration 2006-07. Delivered at the Annual Conference of the National Academy of Medical Sciences (NAMSCON, Amritsar), 2007.

health and social statistics. The medical education system in India is one of the largest in the world. In the year 2005, there were a minimum of 258 medical colleges in India, producing 27676 doctors each year. Since a sizable numbers of our doctors leave the country to settle abroad and migrate to western world, the quality of Indian medical education and the physicians it produces indeed therefore has worldwide impact and ramifications (1).

In addition to the above there is a general impression in peoples' minds that performance capabilities of an average Indian doctor today have declined and are not commensurate with the expectations of the society. The quality status with the exception of very few, does not match the high moral, ethical and professional standards set out for this group of personnel. The service orientation has largely been replaced by greed and the sole objective appears to be to make large amounts of money in the shortest possible time period.

Disappointingly the Alma Ata declaration of "Health for all by year 2000" has also remained an unfulfilled dream for all of us. Inability to achieve the set goal has further eroded peoples' trust, not only in the functioning of the administrators and the political leadership but also in the competence of medical manpower.

Dutta (2) while commenting upon the 'National health policy: approach of the Government and Indian medical association', has outlined many things but his package did not include quality control of medical manpower. Bajaj (3) has emphasized the need for maintaining National standards in medical education and supported the idea of a matrix for establishing quality of medical education as proposed by the past president of ECFMG. In my experience as medical educationist of over four decades, I have strongly felt that quality control of medical personnel remains a core issue in the development of health care services in any country and particularly so in India, and is not solely dependent on education alone.

The basic pre requisite for quality control is honesty and sincerity of purpose by all concerned. In a society which is so openly corrupt as ours, it may well be out of place to write about quality controls. None the less, the need for quality controls cannot be overlooked any more, if progress has to be made. Medical profession is no longer a vocation, because it is also the part of the same society which harbours individuals and organizations with total moral and ethical degradation. For things to improve there has to be an upgradation in holding moral values in

all compartments of the society. The society at large, its leadership and medical administrators have to rise above their own selfish interests so as to help the ailing medical fraternity to get out of the present rot and serve the nation better.

Admissions to M.B.B.S. and Postgraduate Courses

In order to enter a medical college and /or an institute, a student after 10 + 02 and having attained the age of seventeen years, is required to appear and pass a premedical test, held at national as well as state level.

The ingenious Indian mind is always at work with certain percentage of back door entries being made invariably by foul means. The vernacular press is full of such happenings every year near the time of entrance tests held by different states and organisations. This results in a number of students with substandard merit, successfully getting admission to medical courses.

The remedy lies in making these competitive examinations as clean and transparent as possible, in order to allow only meritorious students to clear these tests, both at M.B.B.S. and postgraduate level. For the want of space and the risk of deviation from my central theme, I would like to leave this aspect here and not go into the details of foul means and practices used for this purpose, except to emphasize the point that the dilution of merit begins by such entrants.

A greater setback to the merit pool at the entry point is the practice of mandatory reservation of seats for various categories of candidates belonging to certain casts and religions. There may well be compelling socio-political reasons for such reservations of seats even in vital professional courses, but the society must consider this issue rather dispassionately and in details if the quality of care is to be ensured.

Since the percentage marks for clearing the examinations are lower for the reserved category students, the pool of selected candidates consists of two streams, one with high merit and other with low merit, clubbed together. This mixture of heterogeneous categories results in significant merit dilution and lowering of standards. It is almost impossible for teachers and the taught to improve the low merit over the years and bring the low merit group at par with high merit students. In order to create an equilibrium and uniformity in the two groups, the over all merit as a whole suffers. Since the objective had been to improve merit further, this amounts to be a major start point

failure and reflects badly on the final quality of the finished product. The society therefore has no other option but to finally and firmly decide now whether to continue with the practice of reservation of seats in professional courses in the present form, particularly when the product has to play such a vital and important role in alleviation of human suffering and is directly responsible for saving lives.

On the other hand, if reservations have to stay, the system ought to be modified in such a manner that the gap between the two merit groups is reduced to the minimum. This could easily be managed by bringing the cut off marks of both the reserved as well as the open category candidates at par with each other, so that they are able to compete with each other on a one-to-one basis. In order to make it possible for reserved category students to secure high merit marks equal to open category candidates, their support systems ought to be upgraded so that they are able to perform better. The state may provide complete financial, social and material wealth support *i.e.* money, furnished houses and fulfillment of day to day requirements of all the prospective reserved category candidates and their families but make them perform in the competitive examinations at par with rest of the students, in order to uniformalise the merit.

Alternatively reservations should only be provided once in life time at step one for any such candidate, in order to ensure that there would not be any dilution of merit at the higher levels of specialization. This hard choice has to be made if professionalism has to survive in this country.

The Faculty Selections, Promotions and the Phenomenon of Brain Drain

The faculty is the show piece of an Institution. They are the torch bearers and play a pivotal role in shaping the best quality of finished product. Unfortunately, it is a well known fact that no faculty selection is fair in our country. Merit is either not a criterion at all, or at best a secondary consideration. Money power, connections and patronage always seem to get a better priority over selection of deserving candidates. Inbreeding, automatic promotion schemes, not taking lateral entries at higher levels of faculty positions, domination of a select group of candidates from a particular geographical area and reservations lead to the selection of not necessarily the best candidates. Such manipulations are done in a manner that merit becomes a primary casualty.

The class of faculty which therefore comes up is in sharp contrast second rate with inadequate proficiency and capabilities of training and teaching medical graduates, the so called future of India.

On the other hand, these selections and / or promotions have a tremendous demoralizing effect on the meritorious faculty/ candidates, who are otherwise a hard working, sincere and honest lot trying to improve their contributions for the betterment of the society. The left out faculty thus not only lose all their desire for coordinated team approach but they also give up any firm commitment to work.

Total violation of the concept of academic hierarchy i.e. lecturers , assistant professors, and professors, with or without headship of the department, has also created an atmosphere in many institutions of free autonomy of working and has made most of these departments a battlefield for one upmanship, rather than a happy and healthy place of work. It would be an eye opener to see how many teachers partake fully and sincerely in academic teaching activity regularly, keep their time schedules and assignments. It is the selection of faculty on other considerations which remains a major cause of discontent amongst the rest of the members. The negativity of mindset further inflicts and potentiates 'no work' culture and at the same time kills new input of fresh ideas from the otherwise talented faculty.

Migration abroad, the so called brain drain of qualified professionals from India's premier institutions and other places, is also the direct result of this mounting frustration amongst the meritorious doctors, who find that they neither get their deserving placements, promotions, infrastructure support and required facilities to work as per their capabilities and merit, nor do they get the opportunity and exposure to innovate and/or experiment with the latest technological advances. No wonder then they look for better pastures off the Indian shores. This in turn further dilutes the performance capabilities of left over faculty. The sad part of the picture is that even the meritorious students now are seeking admissions in foreign universities and thus adding to the loss.

The end result is a compromised pool of students and a compromised pool of teachers. It should not be difficult to for any one to imagine the quality of out going product when both the faculty as well as the students do not have the best available merit and work ethos. Fair and impartial selections and promotions of meritorious faculty alone , based on best performance record and to provide them with the best possible infrastructure

support and equipment is the way to improve the overall situation and ensure best quality of care delivered by these professionals.

The Training Programme

A significant number of medical institutions in the country even today do not have a structured training program for undergraduate as well as postgraduate students (4). If a program does exist on paper, its implementation and or upgradation has often legged behind. I am in agreement with Dave (5) that the entire medical educational system in India perhaps requires revision in light of our own health care needs. In a survey of surgical residency program, training, teaching and evaluation in general surgery, based on opinion polls in five medical colleges in northern India, Gupta *et al.* (6) have also concluded that the main emphasis remains on theory alone and the program lacks opportunities for students to acquire open and laparoscopic surgical skills, learning of research methodology, sense of critical appraisal, ethics and so many other important aspects.

Surprisingly some of the institutions do not even have a well defined course curriculum available in details. The curriculum planning and course design is a vital force in providing good teaching and learning for the students and must take care of all its constituents. Unfortunately some of the curriculum only mention the administrative schedule and do not include any syllabus. Violations of set procedures of starting a new superspeciality course and deviations from defined curriculum have been frequently seen. Short cuts are made in meeting many of the pre course essentials. The requirement of creation of an independent superspeciality department in existence for three years before starting a postdoctoral degree program, constitution of board of study, interaction with national associations/ bodies and the recommendations of MCI and peers in the speciality field are some such examples which have not been followed by some of the Institutions and have gone unnoticed or unchallenged in recent times.

The unfavourable ratio of teachers and taught is yet another deficiency which is commonly present. The number of teachers is often not adequate as per MCI norms. For the medical council inspections, teachers have often been hired or borrowed on short term contracts and they disappear soon after approval and/or recognition is received.

Clinical Proficiency, Patient Care, Research and Ethical Standards

The standards of patient care expected by the society from the medical fraternity are indeed and ought to be

very high. Any neglect is intolerable, often highlighted in vernacular press and even taken up by consumer courts. However, at times like these one forgets the common proverbial saying that 'you reap what you sow.'

The diluted merit of the teachers and taught, the unhealthy work culture and environment naturally influences and affects adversely the quality of patient care program, as well as the research potential of the faculty.

The main thrust areas in medical research are laboratory based, experimental (including animal studies) and problem oriented clinical research pertaining to patient related data collection and analysis. In a country like ours majority of medical institutions have relatively lagged behind in laboratory and experimental research, particularly in clinical disciplines. The main emphasis is usually on clinical research. Unfortunately even in this area one has failed to make any great mark in international and national arena. Although, the number of scientific papers published may well be in thousands per year, but very few of them attain a significant Citation Index and /or have a high Impact Factor. This is largely the result of poor record keeping (7), lack of appropriate data collection, proper and honest audit of one's results (8) and the prevalent practice of plagiarism. All these factors influence the quality improvement of publications and indicate the poor quality status of the man doing such research.

The ethical conduct and control of medical manpower is also a consideration of vital importance (9). The extension of boundaries of the malpractice arena has engulfed all moral, financial and legal limits. The commonly prevalent malpractices include patient snatching, undercutting (as there are no uniform fee structures), kick backs and reward systems, toutism, advertising, making false indications for admissions and interventions, cooking up data, making tall claims and running down other colleagues *etc.*

The medical curriculum till date does not include ethics as part of teaching subjects. By and large no ethical monitoring of personal conduct of an individual seems to exist. A large number of medical colleges and postgraduate institutions do not even have a properly constituted and functional ethical committee and if one does exist, its activity is often confined to research projects monitoring and reviews. Further the authority to implement an adverse decision on any so- called violation of ethical limits by a single or group of individuals does not really lie with the committee.

The Infrastructure Support

A compromised manpower *i.e.*, students with suboptimal merit and faculty which has a poor research potential, ethical standards and work ethos could hardly be expected to have an excellent grade of performance. There is further worsening of this situation, when one realizes that even the best of our public medical institutions are unable to provide a good infrastructure support. The equipment is usually old, outdated and not necessarily in good functional state. The new equipment is not easy to procure because of cumbersome government procedures, red tapism and financial constrains. The nonfunctional machinery is neither repaired nor updated or replaced for want of expertise, good workshop facilities and budgetary difficulties. The resultant deficiency further erodes the capability of medical manpower to learn, practice and innovate new methodology in order to deliver adequate and better patient care.

The Reject Pool

The author has always felt greatly concerned about the quality value of those medical graduates who get an MBBS degree from substandard private or public medical colleges in India or from abroad. A fairly large number of these doctors do not progress any further in order to improve their qualifications. This group along with those who are unable to make it to postgraduate courses by an open competition, inspite of having made repeated attempts, constitute the so called 'reject pool'.

The size of this 'pool' is indeed quite large. This MBBS manpower often or usually gets distributed to middle or small set ups in rural and urban areas and work unsupervised as general duty / resident medical officers for years before finally settling down on their own in general practice.

No one has ever bothered to monitor the quality of experience gathered by this group in their formative years. This experience plays a vital role in making of a good or bad doctor for life. All the experience gained by them is by their own effort, since the training is totally unstructured and there is absolute lack of guidance or help available to them for picking up correct methods and knowledge in order to deliver good medicare in later years. The healthcare potential and performance capabilities of this manpower would therefore always remain compromised and well below average.

The Regulatory Controls

In order to verify the capabilities of a medical person to be able to deliver quality care after graduation and /or postgraduation, many countries in the world have strict controls (10). Regular participation in continuing medical education programs, compulsory audit of one's results, record keeping , ethical monitoring and periodic recertification by competent authorities are some of these measures(11,12). The Indian government is yet to implement any such measures and regulatory controls which would ensure the best possible training and quality of experience gathering to these young graduates and postgraduates.

The Finished Product

As evident from the above narration, the qualified Indian doctor today is well below average and lacks in capabilities. He, therefore, has no confidence and the basic professional expertise expected from a medical graduate par excellent. The health care he is thus able to provide is at best of mediocre and of substandard quality. As a surgeon, trainer and a teacher of over forty years duration, I find that the large majority of these individuals with the exception of very few who get the chance of working in large institutions or corporate hospitals, are not able to perform difficult and major procedures on their own or have a very high rate of procedure related complications (13). The management outcome is often poor and eventually limits further their practice thus making them to perform only simple and safe surgery. This automatically down- grades the type of surgical care offered by them and thus results in under utilization of surgical expertise *vis-à-vis* their role in alleviation of human suffering as per their potential and expected level of talent.

Conclusions

The write up is not meant to be a negative report but a factual narration of the ground realities. Our health care system revolves around the quality and capabilities of medical man power available to us. Unless the society, the academicians, and the government can ensure that only the best talented students would get the opportunity to enter medical courses, and are trained by the best available faculty, under the best possible support systems and environment, it would not be possible to break the shackles of mediocrity and expect better health care delivery as well as performance. Therefore, there is an urgent need today of combining our efforts and for corroborative working.

The author does not mean any gender bias by using the word 'man power', 'he' or 'him'. Please read this as either a male or female doctor.

References

1. Supe A and Burdick WP (2006). Challenges and issues in medical education in India. *Academic medicine*. **81**, 1076-1080.
2. Dutta PK (1979). National health policy: approach of the government and the IMA. *J. Ind. Med. Assoc.* **72**: 129-131.
3. Bajaj JS (2006). National standards for medical education. *Ann. Nat. Acad. Med. Sc. (India)* **42**, 85-168.
4. Kaushik SP (2002). Surgical training in India. *Nat. Med. Jour. Ind.* **15**: 282-283.
5. Dave PK (2005). The relevance of medical education for overall health care. *Ann. Nat. Acad. Med. Sc. (India)* **41**: 77-81.
6. Gupta A, Kumar S, Kumar Shailendra, Mishra MC, Kumar Sandeep (2006). Surgical residency program: Training, teaching, and evaluation in general surgery – A peer opinion poll in five medical colleges in northern India. *Ind. J. Surg.* **68**: 310 – 315.
7. Kaushik SP (2007). Data management in GI surgery. Under publication in the book 'Text book of GI surgery'.
8. Kaushik SP (2000). Surgical Audit: A must for speciality development in India. *J. Trop. Gastro.* **21**: 41-42.
9. Kaushik SP (2002). Ethics in surgical practice: An Indian viewpoint. *Nat. Med. Jour. Ind.* **15**: 34-35.
10. Independent external quality control of medical services rendered by private health care providers. http://dec2.bumc.bu.edu/Russianlegalhealthreform/project documents.n940. IG1b.com pdf
11. Schilling J, Cranovsky R and Straub R (2001). Quality programmes, accredition and certification in Switzerland. *Int. J. of Quality in Health care*. **13**: 157-161.
12. Lynch DC, Surdyk PM, Eiser AR (2004). Assessing professionalism: a review of the literature. *Med.Teach.* **26**: 366-73.
13. Kaushik SP (2007). Social implications of surgical complications. Under publication.

Ann Natl Acad Med Sci (India), **45(1)**: 17-28, 2009

Nutritional Profile of Patients with Compensated Alcoholic Liver Disease (ALD)- Cirrhosis

Amit Bery, Dinesh Gupta*, Navjot Bajwa**,*
*Deepinder K Chhina***, Rajoo S Chhina*****
Departments of *Medicine, ** Biochemistry,
*** Microbiology and ****Gastroenterology,
Dayanand Medical College and Hospital, Ludhiana

Abstract

Nutritional profile in fifty patients of alcoholic liver disease (ALD) with compensated cirrhosis was studied for its relationship to amount and duration of alcohol intake. Anthropometric, clinical signs of nutritional deficiencies, dietary assessment, heamatological and biochemical parameters were used for nutritional assessment. Clinical signs of nutritional deficiencies were found in all subjects. The mean values of body mass index (BMI), triceps skin fold thickness (TFT) and midarm circumference (MAC) were found to be decreased as compared to normal subjects. Vitamins B_{12} and serum folate levels were decreased in 12% and 44% cases respectively. Serum magnesium, serum phosphorus and serum zinc levels were also lower than that found in normal population (in 46%, 38% and 42% cases respectively). Total calorie intake was found to be significantly decreased in these subjects. Nutritional deficiencies were more pronounced in patients with increased amount and duration of alcohol intake. Thus, nutritional deficiencies are present in compensated ALD-cirrhotics and correlate with amount and duration of alcohol intake.

Keywords: Alcoholic liver disease, cirrhosis, nutritional profile.

Correspondence: Dr. Rajoo Singh Chhina, 18- Shakti Vihar, Haibowal Road, Ludhiana-141001. Phone: 9815545318; Fax: 0161-2302620; Email: drrajoosingh@rediffmail.com

Introduction

Alcoholism is a common form of drug abuse in India, especially in Punjab (1). The diet of alcoholic cirrhotic patient is usually inadequate and frequently grossly deficient in nutrients (2). Nutritional intake in patients taking only alcohol cannot compensate for the nutritional needs completely (3). The prevalence of malnutrition closely correlates with severity of liver disease (4). The alcoholic cirrhotic patients are often found to have deficiency of calories, vitamins and minerals (5). Anthropometrically these patients are also found to be malnourished (6).

The various methods to assess the nutritional status in alcoholic cirrhotic patients include history, physical examination, laboratory parameters, anthropometry and specialized methods like bioelectrical impendence analysis, energy expenditure, 24 hours urinary creatinine, creatinine height index and 24 hours urinary proteins excretion (7). Anthropometry has now been accepted as a standard method for evaluating nutritional status of cirrhotics with or without ascites, edema or both (8). Malnutrition in alcoholics has been classified as primary or secondary. Primary malnutrition refers to the failure of alcoholic patients to consume a nutritionally balanced diet due to appetite suppressant effect of alcohol, the preference of chronic alcoholics to spend their limited financial resources on ethanol and to the fact that with exception of beer, most alcoholic beverages are nearly devoid of essential vitamins and minerals (9). Secondary malnutrition is due to effects of chronic ethanol ingestion on utilization of nutrients. Chronic alcoholism also affects intestinal absorption and hepatobiliary metabolism of a variety of nutrients (10). In view of these, it is important to assess the nutritional status of patients with alcoholic liver disease, to institute a suitable and timely intervention to improve survival as well as quality of life.

Methods

Fifty patients with compensated alcoholic liver disease-cirrhosis coming to outpatient clinic of Medicine and Gastroenterology department of Dayanand Medical College & Hospital, Ludhiana were enrolled. Inclusion criteria were:

1. History of significant amount of alcohol intake that is 80 gm/day for ten years or 160 gm/day for 5 years with

a. Ultrasound of abdomen suggestive of cirrhosis i.e. showing coarse echotexture of liver, irregular

margins or presence of collaterals or

b. Upper gastrointestinal endoscopy (UGIE) showing oesophageal/ fundal varices.

2. Absence of other aetiology of cirrhosis (i.e viral, autoimmune etc).

Exclusion criteria were:

1. Patients with positive viral serology i.e. Anti-HCV or HBsAg.
2. Patients having decompensation in form of gastrointestinal bleed, ascites, hepatic encephalopathy and high Child-Pugh score (score>7).
3. Patients having comorbid conditions in form of renal failure (serum creatinine > 2 mg/dL), diabetes mellitus, malignancy or other chronic infections.

The patients with jaundice were included and all patients were advised to abstain from alcohol at the time of study.

The methods used to assess nutritional status in cirrhotics included measurement of anthropometric indices (weight, height, body mass index (BMD), triceps skin fold thickness (TFT) measured using Heperden skin fold caliper and midarm circumference (MAC)). Clinical signs of nutritional deficiencies were noted. 24-hour dietary intake was recorded. Hematological parameters (hemoglobin, peripheral blood film) and biochemical parameters (total proteins, serum albumin, vitamin B_{12}, serum folate, serum magnesium, serum calcium, serum phosphorus, serum zinc, serum iron, serum sodium and serum potassium) were obtained for all the patients. Institutional ethical committee approval was taken for this study.

Statistical Methods

The data were expressed as mean or median and/or range as appropriate. The quantitative variables were compared using student's t-test and qualitative variable using the chi square test.

Results

Fifty subjects were assessed by means of anthropometric, biochemical, heamatological and dietary intake recall method. All subjects were male and mean age was 47.46 ± 1.41 years (range 27-67 years). All these patients had irregular liver margins and coarse echotexture on ultrasound examination. All the patients were in Child Pugh Class A (score=6). Twenty-three (46%) of patients had esophageal varices on endoscopy.

The mean weight of subjects was 64.40±1.29 kg while height was

173.16±1.55 cms. The Body Mass Index (BMI) was 21.86±0.60 kg/m^2. The midarm circumference (MAC) was 22.04±0.55 cm and the triceps skin fold thickness (TFT) was 6.74 ± 0.36 mm (Table 1).

The haemoglobin was 11.54±0.30 g/dl and was below the normal reference range in 22 subjects (44%) (Table 1). The most common type of anemia was found to be dimorphic anemia (n=12, 24% subjects) followed by microcytic hypochromic anemia.

The total serum proteins were 6.68±0.09 g/dl and it was below the reference range in 38% cases (n=19). Serum albumin was decreased in 50% cases (n=25). Vitamin B_{12} levels were decreased in 12% (n=6) and serum folate was decreased in 44% (n=22) cases as compared to the normal reference range. Serum zinc was decreased in 42% cases (n=21), serum magnesium was decreased in 46% cases (n=23), serum iron was decreased in 22% cases (n=11), serum calcium was decreased in 14% cases (n=7) and serum phosphorus was decreased in 38% cases (n=19). Serum sodium and potassium were decreased in 26% cases (n=13). The values were significantly decreased for vitamin B_{12}, serum magnesium, serum calcium, serum iron, serum sodium and serum potassium (Table 1). The 24-hour dietary recall method was used to quantify the intake of various nutrients (calories, protein, carbohydrate and fats). The total calories intake was 2045.92±72.23 Kcal/day (Table 1). The protein intake was low in 18% (n=9) cases, carbohydrate intake was low in 80% (n=40) and fat intake was low only in 2% (n=1) of the cases.

Nutritional deficiencies and amount of alcohol intake

The subjects in our study took amount of alcohol ranging from 100g/day to 320g/day. The mean value of this range i.e. 210g/day was taken to study the effect of amount of alcohol intake on nutritional status. The patients were divided into two groups :

Group A consisted of 24 subjects with amount of alcohol intake < 210 g/day, and

Group B consisted of 26 subjects with amount of alcohol intake > 210 g/day.

The mean and standard deviation of all parameters were computed for each group (Table 2). Results of both the groups were compared. Significant decrease (p-value<0.01) in BMI, MAC, TFT, minerals (serum zinc, serum magnesium, serum phosphorus), calories and protein intake parameters was seen in patients with increased amount of alcohol intake. Nutritional

TABLE 1

Mean Values of Anthropometric, Hematological, Biochemical And Nutritional Parameters In Compensated ALD Cirrhotic Patients

A) Anthropometric parameters	**Mean ± SD**
Weight (kg)	64.40 ± 1.29
Height (cm)	173.16 ± 1.55
Body mass index (BMI) (Kg/m^2)	21.86 ± 0.60
Midarm circumference (MAC) (cm)	22.04 ± 0.55
Triceps skin fold thickness (TFT)(mm)	6.74 ± 0.36
B) Hematological parameters (normal values)	
Hemoglobin (12.2-17.2 gm/dl)	11.5 ± 0.30
MCV (82.2-97.4 cubic µm)	97.38 ± 2.35
INR (<1.6)	1.65 ± 0.05
C)Biochemical parameters (normal values)	
RBS (70-140 mg/dL)	114.08 ± 3.87
Total Protein (6.6-8.7 gm/dl)	6.68 ± 0.09
Serum albumin (3.5-5.0 gm/dL)	3.34 ± 0.08
Vitamin B_{12} (187-1059 pg/ml)	454.48 ± 44.73
Serum Folate levels (>5.31 ng/ml)	12.18 ± 1.95
Serum Zinc (80-140 µg/dl)	83.46 ± 4.12
Serum Magnesium (1.7-2.5 mg/dl)	1.94 ± 0.14
Serum Calcium (8.6-10.2 mg/dl)	8.94 ± 0.11
Serum Phosphorus (2.7-4.5 mg/dl)	2.92 ± 0.16
Serum Iron (45-158 µg/dl)	80.52 ± 5.11
Serum Sodium (136-148 mmol/L)	137-92 ± 0.80
Serum Potassium (3.6-5.0 mmol/L)	3.76 ± 0.08
D) Nutritional parameters	
Total calorie intake (Kcal/day)	2045.92 ± 72.23
Protein intake (gm/day)	69.29 ± 2.08
Carbohydrate intake (gm/day)	292.90 ± 11.6
Fat intake (gm/day)	44.50 ± 2.62

TABLE 2
Nutritional Parameter Relation with Amount of Alcohol Intake

Parameter	Mean ± S.D in group A	Mean ± S.D. in group B	p-value
Age (years)	41.54 ± 1.80	52.92 ± 1.49	> 0.10 NS
Body Weight (kg)	67.31 ± 1.83	61.72 ± 1.69	> 0.10 NS
Height (cms)	172.04 ± 2.55	174.19 ± 1.86	> 0.10 NS
BMI (kg/m^2)	22.94 ± 0.68	20.86 ± 0.94	< 0.01 S
MAC (cm)	24.38 ± 0.65	19.89 ± 0.64	< 0.01 S
TFT(mm)	7.70 ± 0.59	5.85 ± 0.36	< 0.01 S
Hb (gm/dl)	12.67 ± 0.28	10.48 ± 0.42	> 0.10 NS
MCV (cubic µm)	96.83 ± 4.46	97.88 ± 1.95	> 0.10 NS
INR ratio	1.62 ± 0.09	1.69 ± 0.07	> 0.10 NS
RBS (mg/dl)	108.13 ± 4.25	119.58 ± 6.22	> 0.10 NS
Total Protein (gm/dl)	6.87 ± 0.14	6.50 ± 0.11	> 0.10 NS
S. Albumin (gm/dl)	3.48 ± 0.11	3.22 ± 0.11	> 0.10 NS
Vit B_{12} Level (pg/ml)	499.08 ± 73.54	413.31 ± 5.61	> 0.10 NS
Folate Levels (ng/ml)	14.60 ± 3.26	9.95 ± 2.20	> 0.10 NS
S. Zinc (µg/dl)	91.79 ± 5.87	75.77 ± 5.46	< 0.01 S
S. Magnesium (mg/dl)	2.20 ± 0.18	1.70 ± 0.20	< 0.01 S
S. Calcium (mg/dl)	9.11 ± 0.15	8.78 ± 0.15	> 0.10 NS
S. Phosphorus (mg/dl)	3.51 ± 0.19	2.37 ± 0.21	< 0.01 S
S. Iron (µg/dl)	93.17 ± 7.32	68.85 ± 6.44	> 0.10 NS
S. Sodium (mmol/l)	138.17 ± 1.17	137.69 ± 1.11	> 0.10 NS
S. Potassium (mmol/l)	3.82 ± 0.11	3.71 ± 1.12	> 0.10 NS
Calorie intake (Kcal/day)	2325.88 ± 114.83	1787.50 ± 53.87	< 0.01 S
Protein (gm/day)	77.90 ± 3.03	61.54 ± 1.84	< 0.01 S
Carbohydrate (gm/day)	291.42 ± 16.13	294.27 ± 15.76	> 0.10 NS
Fats (gm/day)	48.13 ± 3.03	55.31 ± 14.70	> 0.10 NS

Group A = patients with amount of alcohol intake < 210 gm/day

Group B = patients with amount of alcohol intake > 210 gm/day

NS= Non Significant

S= Significant

deficiencies were more severe and mean of all parameters were less in patients of group B with exception of height, MCV (Mean corpuscular volume), INR and carbohydrate intake, which were comparable to group A values. Amount of fat intake was more in group B patients than in group A patients. On reviewing dietary history, it was found that there was excessive consumption of dairy products and non-vegetarian fried food in group B patients.

Nutritional deficiencies and duration of alcohol intake

The duration of alcohol intake in our patients ranged from 8-22 years. The mean value of this range i.e 15 years was taken to study the effect of duration of alcohol on nutritional status. The patients were divided into two groups :

Group I consisted of 21 subjects with duration of alcohol intake < 15 years and

Group II consisted of 29 subjects with duration of alcohol intake > 15 years.

The mean and standard deviation of all parameters were computed for each group (Table 3). The results of both the groups were compared. Significant decrease (p-value<0.01) in BMI, MAC, TFT, minerals (serum zinc, serum magnesium, serum phosphorus), calories, proteins and carbohydrate intake parameters was seen in patients with increased duration of alcohol intake.

Discussion

Alcoholism is a common problem in Punjab. The prevalence of malnutrition in patients with alcoholic liver disease and cirrhosis varies widely, depending upon the nature of study population and the method of nutritional assessment used. A number of studies have suggested the beneficial effect of nutritional therapy in malnourished patients with cirrhosis (11-14). Nutritional status improvement in chronic liver disease has been shown to decrease morbidity and mortality in chronic liver disease (15,16). Therefore, appropriate measures should be taken to avoid, promptly recognize and treat nutritional deficiencies, which are present in ALD-cirrhotics. In our study, emphasis was laid on these selective important nutritional measurements, which have been universally recommended to determine nutritional status of human subjects.

The mean BMI (21.86 ± 0.60 kg/m^2) in present study was within normal range (18.5-24.99 kg/m^2) as recommended by World Health Organization (WHO) [17]. Narayanan LS *et al* (18), while studying 30

TABLE 3
Nutritional Parameters Relation with Duration of Alcohol Intake

Parameter	Mean ± S.D. in group I	Mean ± S.D. in group II	p-value
Age (years)	38.10 ± 0.93	54.24 ± 1.27	> 0.10 NS
Body Weight (kg)	66.94 ± 2.04	62.56 ± 1.61	> 0.10 NS
Height (cms)	172.10 ± 2.85	173.93 ± 1.74	> 0.10 NS
BMI (kg/m^2)	23.45 ± 1.14	20.70 ± 0.55	< 0.01 S
MAC (cm)	24.48 ± 0.71	20.28 ± 0.63	< 0.01 S
TFT (mm)	7.75 ± 0.58	6.00 ± 0.42	< 0.01 S
Hb (g/dl)	12.69 ± 0.34	10.70 ± 0.38	> 0.10 NS
MCV (cubic μm)	96.90 ± 4.98	97.72 ± 1.94	> 0.10 NS
INR ratio	1.60 ± 0.10	1.70 ± 0.06	> 0.10 NS
RBS (mg/dl)	113.62 ± 4.60	114.41 ± 5.86	> 0.10 NS
Total Protein (gm/dl)	6.81 ± 0.16	6.58 ± 0.10	> 0.10 NS
S. Albumin (gm/dl)	3.34 ± 0.10	3.34 ± 0.12	> 0.10 NS
Vit B_{12} Level (pg/ml)	451.43 ± 64.64	456.69 ± 56.63	> 0.10 NS
Folate Levels (ng/ml)	16.12 ± 3.58	9.32 ± 2.03	> 0.10 NS
S. Zinc (μg/dl)	95.48 ± 6.02	74.76 ± 5.10	< 0.01 S
S. Magnesium (mg/dl)	2.70 ± 0.21	1.61 ± 0.16	< 0.01 S
S. Calcium (mg/dl)	8.97 ± 0.24	8.91 ± 0.07	> 0.10 NS
S. Phosphorus (mg/dl)	3.60 ± 0.19	2.42 ± 0.20	< 0.01 S
S. Iron (μg/dl)	101.52 ± 7.31	65.31 ± 5.61	> 0.10 NS
S. Sodium (mmol/l)	138 ± 1.07	137.86 ± 1.15	> 0.10 NS
S. Potassium (mmol/l)	3.77 ± 0.14	3.76 ± 0.11	> 0.10 NS
Amt. of alcohol (gm/day)	175.71 ± 12.36	300 ± 16.90	> 0.10 NS
Calorie intake (Kcal/day)	2312.95 ± 124.00	1852.55 ± 67.89	< 0.01 S
Protein (gm/day)	77.83 ± 3.30	63.28 ± 2.04	< 0.01 S
Carbohydrate (gm/day)	313.87 ± 20.78	277.74 ± 11.53	< 0.01 S
Fats (gm/day)	48.10 ± 3.11	41.90 ± 3.89	> 0.10 NS

Group I = duration of alcohol intake < 15 years
Group II= duration of alcohol intake > 15 years
NS= Non Significant
S = Significant

hospitalized ALD-cirrhotic patients, made the same observation. BMI was decreased in subjects with increased amount and duration of alcohol intake, which was similar to the finding of Santolaria F *et al* (19). The midarm circumference (MAC) was 22.04±0.55 cm, which was less when compared with that of Punjabi Healthy adult male reference values of 24.01±2.07 cm (20). The TFT of present study group was significantly less when compared with that of Punjabi Healthy adult male reference values of 11.79±2.12 mm (21). The mean TFT values were found below the fifty percentile of WHO values given for normal healthy adult male for that particular age group (17).

The most common type of anemia in the present study was dimorphic anemia. In comparison to this, the most common type of anemia in alcoholics as studied by Linderbaum J *et al* (22) was megaloblastic anemia. The cause of difference in present study could be the poor dietary intake, increased phosphate, decreased vitamin C intake and increased incidence of worm infestation in Indian population (23). The mean hemoglobin value was less in subjects with increased amount and duration of alcohol in present study. The international normalized ratio was also more in patients with increased amount and duration of alcohol intake suggesting role of amount and duration of alcohol intake in causing more severe disease.

The mean total serum proteins and albumin were below normal range in the present study. Sarin *et al* (24) obtained similar results in moderate to severe alcoholic cirrhotic patients in Indian population. The values of these parameters were less in patients with increased amount and duration of alcohol. Vitamin B_{12} was decreased only in 12% cases. Serum folate levels were decreased in 44% cases. Among minerals, significant decrease of serum magnesium, serum phosphorus and serum zinc was seen in subjects (46%, 38% and 42% cases respectively). The study in western countries on alcoholics had also shown significantly decreased levels of serum zinc level (30-60% alcoholics without liver disease and 70% of alcoholic cirrhotic patients) (19). Serum calcium levels were decreased in 14% cases and serum iron levels were decreased in 22% cases. All these minerals were found to have inverse correlation with amount of alcohol intake and their mean values were less in patients with increased amount and duration of alcohol intake.

The mean total calorie intake was significantly decreased as compared with intake of normal healthy Indian adult male as recommended by ICMR (Indian Council of Medical Research).

Sarin *et al* (24) found similar results in moderate to severe ALD patients. It was found that the total caloric intake decreased as amount and duration of alcohol increased. The mean carbohydrate intake was also found to be significantly decreased in present study with mean value of 292.90 ± 11.6g/day. The ICMR recommendation for carbohydrate intake in normal healthy adult male is 375 g/day. The decrease in carbohydrate intake was more severe as amount and duration of alcohol increased. The mean protein intake was in normal range when compared with ICMR standard (normal recommended intake = 60 gm/day). Therefore, patients in the present study were on adequate protein diet. However, the mean protein intake in present study decreased, as amount and duration of alcohol increased. The fat intake in the present study was in the higher range than recommended by ICMR for healthy Indian adult males (normal recommendation is 20 g/day). Sarin *et al* (24) found the same results in patients with moderate to severe ALD-cirrhotic patients. Our study showed that nutritional deficiencies were present even in compensated ALD-cirrhotics. Anthropometery was found to be the single most reliable and cheapest method of determining nutritional status in ALD-cirrhotic patients. Fat intake in ALD-cirrhotics did not correspond with total serum protein or serum albumin levels. Nutritional deficiencies were more pronounced in patients with increased amount and duration of alcohol intake.

The comparison of alcoholic cirrhotics with a similar group of non-alcoholic cirrhotic patients might have been more informative but we included only patients with alcoholic liver disease in our study.

Conclusion

Nutritional deficiencies are present even in compensated ALD-cirrhotics. Nutritional deficiencies of vitamins, minerals and carbohydrates are more severe in patients with increased amount and duration of alcohol intake. Thus, nutritional intervention strategy is also needed even in compensated ALD-cirrhotic patients.

References

1. Dhawan S, Duseja A, Chawla Y, Dilawari JB (1994). Etiology and presentation of cirrhosis in North India. *Ind J Gastroenterology* **13:** A81.
2. Esteban Mezey (1980). Alcoholic liver disease. Role of alcohol and

malnutrition. *Am J Clin Nutrition* **33:** 2709-18.

3. Arthur J Patek (1979). Alcohol, malnutrition and alcoholic cirrhosis. *Am J Clin Nutrition* **32:** 1304-12.

4. Nielson K, Mondrup J, Martinsen L, Stilling B and Wikman B (1993). Nutritional assessment and adequacy of dietary intake in hospitalized patients with alcoholic liver cirrhosis. *Br J Nutrition* **69:** 665-79.

5. Allan D, Thomsen and Sisir K Majumdar (1981). Ethanol and nutrient absorption and utilization. *Clinics in Gastroenterology* 263-92.

6. Peter HRG (1983). Alcohol, Nutrition and malabsorption. *Clinics in Gastroenterology* 563-73.

7. Harrison JE, Mcneil KG (1994). Nutritional assessment. *Blood Purif* **12:** 68-72.

8. Crawford DH, Shepherd RW, Halliday JW, Cooksley GW, Golding SD, Cheng WS, et al (1994). Body composition in non-alcoholic cirrhosis. The effect of disease aetiology and severity on nutritional compartments. *Gastroenterology* **106:** 1611-17.

9. Lieber CS (1979). Alcohol-Nutrition interactions. *J Med Soc N J* **76(5):** 379-80.

10. Muller MJ (1995). Malnutrition in cirrhosis. *Journal of hepatology* **23:** 31-35.

11. Cabre E, Gonzalez Huix F, Abad Lacruz A, Esteve M, Acero D, Fernandez- Banares F, et al (1990). Effect of total enteral nutrition on the short-term outcome of severely malnourished cirrhotics. A randomized clinical trial. *Gastroenterology* **98:** 715-20.

12. Bunout D, Aicardi V, Hirsch S, Petermann M, Kelly M, Silva G, et al (1989). Nutritional support in hospitalized patients with ALD. *Eur J Clinical Nutrition* **43:** 615-21.

13. Diehl AM, Boitnott JK, Herlong HF, Potter JJ, Van Duyn MA, Chandler E, et al (1985). Effect of parenteral amino acid supplementation in alcoholic hepatitis. *Hepatology* Jan-Feb **5(1):** 57-63.

14. Simon DS and Galambos JT (1987). Peripheral hyperalimentation in alcoholic hepatitis. *Gastroenterology* **92:** 1777.

15. Mezey E, Caballeria J, Mitchell MC, Pares A, Herlong HF, Rodes J (1991). Effect of parenteral aminoacid supplementation on short term and long-term outcome in severe alcoholic hepatitis.

Randomized controlled trial. *Hepatology* Dec **14(6):** 1090-6.

16. Kulig G (2000): Nutritional treatment in decompensated liver cirrhosis. *Przeg L bek* **57(6):** 346-48.

17. World Health Organisation [WHO] (1995). Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *WHO Technical Report Series No. 854.* Geneva.

18. Narayanan LS, Chawla Y, Bhalla AK, Sharma M, Dilawari JB (1999).Assessment of malnutrition in alcoholic cirrhotics and non-alcoholic cirrhotics. *Tropical Gastroenterology* **20:** 120-22.

19. A V Santolaria F, Parez-Manzano JL, Milena A, Gonzalez-Reimers E, Gomez Rodriguez MA, Martinez-Riera A, et al (2000). Nutritional assessment in alcoholic patients. Its relationship with alcohol intake, feeding habits, organic complication and social problems. *Drug and alcohol dependence* **59(3):** 295-304.

20. Ajit Pal Singh, Pushpa Singal and SP Singh (2005). Arm Muscle and fat components in adolescent boys of Punjab.*Anthropologist* **7(3):** 161-163.

21. Sidhu LS, Sodhi HS and Bhatnagar DP (1975). Anthropometric changes from adulthood to old age. *Ind J Physical Anthropology and human genetics* **1:** 119-27.

22. Lindenbaum J and Mary J Roman (1980). Nutritional Anemia in alcoholism. *Am J Clin Nutrition* **33:** 2727-35.

23. Patwardhan VN (1961). Nutrition in India. *Ind J Med Sci* 261-292.

24. Sarin SK, Dhingra N, Bansal A, Malhotra S, Gupta RC (1997). Dietary and nutritional abnormalities in alcoholic liver disease – A comparison with chronic alcoholics without liver disease. *Am J Gastroenterology* **92:** 773-83.

Ann Natl Acad Med Sci (India), **45(1)**: 29-43, 2009

Management of Pneumonia in Immunosuppressed States : Malignancies & HIV Infection

Pankaj Malhotra and Navneet Singh*
Departments of *Internal Medicine and Pulmonary Medicine,
Post Graduate Institute of Medical Education and Research (PGIMER),
Chandigarh.

Abstract

The lungs are a common site of infection in patients with cancer and HIV infection. The presentation and management of pneumonia is influenced by factors related to the disease as well as those related to the host. The type of malignancy (solid organ vs. haematological), its status (controlled vs. uncontrolled) and its treatment (administration of chemotherapy and/or radiotherapy) are some of the important malignancy related factors. Host factors include age of the patient, performance status, functional status of body organs and past history of infection. Considering all the above factors, a net risk assessment (NRA) is made in a given patient for determining the overall state of immunosuppression and hence choosing the best form and duration of treatment. In human immunodeficiency virus (HIV) infected individuals, CAP has a 6-25 fold higher incidence. HIV infected patients have higher rates of bacteremia, infection with opportunistic bacterial and non-bacterial pathogens, unusual radiographic abnormalities, complicated parapneumonic pleural effusions/empyema and recurrence. Optimization of anti retroviral therapy, administration of polyvalent pneumococcal vaccine and co-

Correspondence:Dr. Pankaj Malhotra M.D., Associate Professor, Clinical Haematology, Department of Internal Medicine, Post Graduate Institute of Medical Education and Research (PGIMER), Sector 12, Chandigarh, India – 160012. Phone: +91–172–2756680. E-mail: malhotrapankaj@hotmail.com. Proceedings of the NAMS-PGI Symposium on 'Community Acquired Pneumonia', held in Chandigarh, 2007.

trimoxazole prophylaxis are other adjunctive measures that may be considered for reducing the morbidity and mortality associated with CAP in the setting of HIV infection.

Key Words: Pneumonia, malignancy, net risk assessment, human immunodeficiency virus, *Streptococcus pneumoniae*

Management of Pneumonia In Malignancies

Introduction

The lungs are common site of infections in patients with cancer and HIV infection. Hence, understanding the principles of management of pneumonia in these patients would lead to decrease in morbidity and mortality. However, the management issues are complex. The management issues may be related to malignancy per se or pertain to the factors related to patient (Table 1).

Factors Related To Malignancy

Type of Malignancy

Out of most malignancies, haematological malignancies and sarcomas are usually considered aggressive cancers that need aggressive treatment (1). The immune defects are also more common in these types of cancers.

Table 1: Risk-factors for pneumonia in patients with underlying malignancies

1. Quantitative defects in neutrophils (Neutropenia)
2. Qualitative defect in neutrophils (Functional abnormalities)
3. Defects in cellular immunity (disease or drugs)
4. Defects in humoral immunity (disease or drugs)
5. Disruption of physical barriers e.g. central venous lines, urinary catheters
6. Use and misuse of antibiotics, antifungals and antivirals drugs
7. Environmental factors
8. Overcrowded wards, inpatient and outpatient management
9. Co-morbidities e.g. Diabetes, Coronary heart disease, past tuberculosis etc.

Cancer is controlled or uncontrolled

Generally, the outcome of bronchopneumonia in a patient whose cancer is under control is better than in a patient whose cancer is uncontrolled.

Patient on Chemotherapy and or Radiotherapy

Pneumonia has a worse outcome if it develops during the time when patient is receiving chemotherapy. This is because the body is immune-suppressed during the time of chemotherapy (2). Most chemotherapies lead to decrease in white cell count as their side effect. Neutrophils are the primary defence against microorganisms in the body. The risk of infection becomes greater when absolute neutrophil count is below 500/ mm^3 and greatest if the ANC is less than 100/mm^3. The risk of infection also depends on the duration of neutropenia. In the initial period, the risk of bacterial infections is high, however, as the duration of neutropenia become prolonged, the risk of fungal infections also increases. A rapid decline in neutrophil again is an additional risk. Chemotherapy can also lead to functional defect in the neutrophils (Table 1).

Repeated courses of chemotherapy lead to decrease in the immunoglobulin levels (especially the IgG and IgA) that remain depressed for a considerable period of time depending upon the type of chemotherapy used.

Radiotherapy also leads to predisposition of body to infection. The factors related to radiotherapy are dose and duration of radiation.

Factors Related To Patient

Type of pneumonia and its management also depends upon the factors that are related to patient. These factors are age of the patient, performance status of patient, functional status of body organs and past history of infection. Older patients are more prone for complications following pneumonia if they have any underlying malignancy. Similarly if the performance status of the patient is low, there are lower chances of successful outcome of treatment. Co-morbidities in patients with cancer are considered additional risk factors that add complexities to the management. These co-morbidities may be presence of diabetes, coronary heart disease, hypertension, parkinsonism, neuropathy etc. Past history of recurrent infections also predisposes the patient for future risk of infections. Recurrent chest infections lead to structural lung damage and bronchiectasis.

Net Risk Assessment

Considering all the above factors, a net risk assessment (NRA) is made in a given patient for choosing the best form of treatment and duration of treatment. Net risk assessment takes into account all the variables in a given patient (related to cancer or related to patient himself) and helps in making treatment decision (tables 1 and 2).

Investigations

The investigations are directed towards making a diagnosis of pneumonia and its management (Table 2) (3). Besides taking into account the usual parameters for admission of patient with pneumonia, the other factors that help in immediate decision making consists of whether the malignancy is controlled or uncontrolled, whether patient is on chemotherapy and if yes when did he receive his last dose of chemotherapy. In uncontrolled cancer, the chances of success of treatment are low (vide supra). The importance of knowing the first day of chemotherapy is to assess for neutropenia which is perhaps the most important parameter in deciding about the choice of antibiotics and admission of patient into the hospital. Absolute neutrophil count of below 500/ mm^3 poses the greatest risk to the patient and one has to consider possibility of fungal pneumonia early in the course of treatment if patient is not responding to broad spectrum antibiotics. The other tests for diagnosis of pneumonia have already been highlighted in different presentations.

Treatment

The general guidelines for treatment of bronchopneumonia apply here. However, as has already been

Table 2: Pulmonary infiltrates on radiological investigations in cancer patients

Parenchymal
Acute Bacterial Pneumonias
Subacute/Chronic (Tuberculosis, Fungal, Neoplasm)
Interstitial
Acute Pulmonary Oedema, Diffuse alveolar haemorrhage, Viral Pneumonias, Mycoplasma Pneumonia, Pneumocystis jirovecii
Subacute/Chronic (Tuberculosis, Nocardia)

highlighted, unusual organisms do occur in patients with underlying malignancies and one has to be aware of that while deciding treatment. In neutropenic patients, gram positive organisms are the main culprit especially if patient has central lines *in situ*. The spectrum of gram positive to gram negative organisms infections is ever changing and one has to consider the local flora and type of infections occurring in their hospital environment before deciding empiric antibiotics (4). If neutropenia is prolonged and severe, fungal infections especially the Aspergillus species are common cause for fungal pneumonia. Zygomycosis is another emerging cause of pneumonia especially in patients who are on prophylactic antifungal therapy with voriconazole. In these patients, amphotericin B is the treatment of choice.

Patients with impaired cell immunity due to lymphoproliferative disorders or due to high-dose corticosteroid therapy have different spectrum of infections as compared to patients who have only neutropenia. Patients with impaired cellular immunity are more prone for infections with Nocardia, Pneumocystis jirovecii, Legionella and tuberculosis and viral infections with cytomegalovirus, influenza, respiratory syncytial virus etc. Co-trimoxazole is given for the treatment of Nocardia and Pneumocystis pneumonia. Gancyclovir is the treatment of choice for CMV pneumonia.

Patients with impaired humoral immunity (post splenectomy, multiple myeloma, chronic lymphocytic leukaemia etc.) are susceptible to infections caused by encapsulated organisms such as *S. pneumoniae* and *H. Influenza*. Penicillins are the drug of choice in this group of patients.

More often than not several immune defects exist together in a given patient and treatment decision covering all these aspects has to be taken in an emergency situation. However, a detailed assessment after stabilisation of patient and de-escalation of therapy can be done based on above-mentioned parameters.

Finally non-infectious causes of pneumonia have to be considered in patients with malignancies. Pulmonary haemorrhage can occur because of coagulopathy or thrombocytopenia. Many of the chemotherapeutic drugs such as busulphan, melphalan etc. can cause pulmonary infiltrates mimicking pneumonia. Radiation injury after several weeks may produce radiation induced pneumonitis. Lastly infiltration by neoplasm into the lung parenchyma itself can mimic pneumonia.

Some of the special treatment consideration in patients with malignancies consists of post obstructive pneumonia because of lung neoplasm or metastasis. Patients with brain tumours can have loss of gag reflex leading to aspiration pneumonia. Radiation can lead to loss of ciliary function further predisposing the patient to aspiration pneumonia.

Prevention

Patients with malignancies are in a state of immunosuppression as already stated. Taking good care of personal hygiene, drinking boiled water in our country, eating cooked food and avoiding contacts with persons having infections are some of the measure that can be taken at patient level. The role of prophylactic antibiotics, antifungals and antivirals in these patients generates considerable discussion and controversies (5). Primary prophylaxis with antibiotics, antifungals and antivirals is considered when patient is at a high-risk of getting these infections. Secondary prophylaxis consists of when patient already had an episode of infection and prophylaxis is given for prevention of future risk of infections. Briefly both primary and secondary prophylaxis can be considered in high- risk situations such as patients undergoing high-dose chemotherapy and stem cell transplant. In all other situations, physicians have to follow a balanced approach in deciding about the prophylaxis in the best interest of the patient.

Community Acquired Pneumonia In Patients With HIV Infection

Epidemiology

Community acquired pneumonia (CAP) is a common cause of morbidity in individuals infected with the human immunodeficiency virus (HIV). Incidence of CAP in HIV infected individuals is 6-25 fold higher than those not infected (6). CAP is frequently the first clinical manifestation of HIV infection. Despite the use of extensive testing, no organism may be identified in as many as one third-two third of cases of HIV-related CAP (7).

Among patients in whom lower respiratory tract symptoms predominate, the common etiological agents include: *S. pneumoniae* (28%), *Mycobacterium tuberculosis* (26%), *Klebsiella pneumoniae* (27%), *Pneumocystis jirovecii* (15%). On the other hand, those in whom upper respiratory tract symptoms predominate, *S. aureus* (15%), coagulase negative staphylococci (11%), streptococci (11%) and *Moraxella catarrhalis* (12%) are commonly responsible (8).

The incidence and the severity of bacterial lower respiratory tract infections (LRTIs), including the CAP increase in HIV infected patients as the CD4 lymphocyte count declines (Table 3).

Diagnosis

There are certain differences in the clinical presentation of bacterial CAP in HIV positive and negative individuals (9). HIV infected patients tend to have:

- Higher frequency of bacteremia
- Higher rate of unusual radiographic abnormalities
- Higher rate of parapneumonic pleural effusions (PPE) including a significantly higher rate of complicated PPEs and empyema. *S. aureus* is the most common microorganism isolated from pleural fluid and blood cultures (10).
- Higher incidence of opportunistic bacteria

Table 3: Common etiological agents for LRTIs at different levels of CD4 count

CD4 Count	Level of immune suppression	Common infectious agents
>500 cells/μL	Very mild impairment	Encapsulated bacteria
		M. tuberculosis
200-499 cells/μL	Mild impairment	Encapsulated bacteria
		M. tuberculosis
<200 cells/μL	Moderate impairment	Bacteria
		M. tuberculosis
		Pneumocystis jirovecii
<100 cells/μL	Severe impairment	Bacteria
		M. tuberculosis
		Pneumocystis jirovecii
		Non tubercular mycobacteria
		Fungi
		Cytomegalovirus (CMV)

Risk factors for hospitalization due to CAP (11) include:

- Prophylaxis with fluconazole in the recent past – reduced risk
- Prophylaxis with co-trimoxazole (protective) in the recent past – reduced risk
- Breathing chemical irritants in the recent past – increased risk
- Hospitalized for pneumonia in the preceding six months – increased risk
- Tobacco smoking: HIV-infected smokers are twice as likely to be hospitalized with CAP as non-smokers. The increased risk exists in a dose-dependent manner and is independent of the administration of HAART and antimicrobial prophylaxis (12).

Investigations include total and differential white cell count, sputum Gram stain and culture and blood culture. Further evaluation is generally warranted in case of clinical and/or radiological deterioration or absence of clinical improvement and this holds true even if = 1 bacteria as etiological pathogen(s) have been identified. The additional investigations that may be helpful under such circumstances include detection of *Legionella pneumophila* antigen in urine, IgM and IgG serology for *M pneumoniae* and *C pneumoniae*, high resolution computed tomography (HRCT) scan, bronchoscopy and bronchoalveolar lavage (BAL) with/without bronchoscopic lung biopsy (BLB). Depending upon the level of CD_4 count and clinical scenario, one may need to carry out a work up aimed at diagnosing Pneumocystis pneumonia (PCP), pulmonary tuberculosis (PTB) or non tubercular mycobacterial (NTM) disease as well as other oppoprtunistic infections since the latter may coexist with bacterial CAP (13).

Induced sputum, when compared with BAL/BLB as gold standards, has a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of approximately 60%, 40%, 80%, 20% and 56% respectively for the diagnosis of bacterial CAP in the HIV infected at a cut-off value of 10^6 colony forming units (CFU) per mL in quantitative cultures (14).

In comparison to plain chest radiographs (CXR), HRCT scans of the thorax can demonstrate parenchymal lesions that are not visualized on CXR and the discrepancy can be as high as 82%. Among patients in whom a microbiological diagnosis was established later, a correct diagnosis of bacterial CAP could be made in 84% of cases after a HRCT scan (15). A CT scan

can also identify mediastinal and pleural abnormalities that may not be apparent on CXR. Imaging findings of bacterial CAP in HIV infected individuals are similar to those in immunocompetent patients. The most common pattern is again that of single/ multifocal consolidation (16). Classically lobar consolidation has been related to infection by *Streptococcus pneumoniae*. A lobular pattern characterized by the presence of centrilobular nodules, tree-in-bud abnormalities and patchy consolidation has been described as "bronchopneumonia" and the common bacteria that have been related to such a presentation include *Staphylococcus* spp., *Streptococcus* spp., *Pseudomonas* spp., *Klebsiella* spp. and *Haemophilus* spp. (Table 4).

In a prospective study on the profile of pulmonary infections in 300 newly diagnosed HAART- naive HIV patients at this institute, pulmonary symptoms and abnormal chest radiographs were observed in 33 (11%) and 44 (14.6%) patients respectively (Table 5) (17). PTB and tubercular

Table 4: Important radiological findings of common pulmonary infections in HIV infected individuals

Infection	CD4 Count	Symptom duration	Parenchymal abnormalities	Lymph-adenopathy	Pleural Effusion
Bacterial	None	≤ 7 days	Focal consolidation	Rare	Common
PCP	<200 cells/μL	≅ 30 days	Bilateral, symmetrical interstitial; GGO on CT	Absent	Absent
MTB	None	> 7 days	CD4 >200: cavitation CD4 <200: consolidation	CD4 >200: common	Rare
NTM	<100 cells/μL	Variable (> 7 days)	Patchy consolidation; Bronchiectasis + nodules	Common	Rare
Fungal	<100 cells/μL	Variable (> 7 days)	Reticular and nodular opacities	Common	Common
CMV	<100 cells/μL	Variable (> 7 days)	GGO, consolidation, nodules	Rare	Rare

PCP = Pneumocystis pneumonia, MTB = Mycobacterium tuberculosis, NTM = Non tubercular mycobacteria, CMV = Cytomegalovirus, GGO = Ground glass opacification

Table 5: Profile of pulmonary infections in HIV infected patients observed at the PGIMER, Chandigarh

	Number (%)
Pulmonary Symptoms	**33**
• Cough	27 (81.8)
• Dyspnea	14 (42.4)
• Sputum	11 (33.3)
Abnormal CXR findings	**44**
• Consolidation	12 (27.3)
• Pleural effusion	8 (18.2)
• Hilar adenopathy	7 (15.9)
• Miliary nodules	5 (11.4)
Patient Groups	**Mean (SD) CD4 Count**
• Asymptomatic	245.1 ± 125.9 cells/μL
• Tuberculosis	117.1 ± 104.5 cells/μL
• Bacterial pneumonia	51.0 ± 40.3 cells/μL
• PCP	66.9 ± 33.9 cells/μL
• Cryptococcal infection	36.5 ± 25.6 cells/μL

CXR = Chest X Ray (chest radiograph), SD = Standard Deviation,
PCP = *Pneumocystis jirovecii* pneumonia

pleural effusion were diagnosed in 19 and 6 patients respectively. Sputum and BAL/BLB staining yielded the presence of acid fast bacilli (AFB) in 10 (52.6%) and 5 (26.3%) patients with PTB. The diagnosis of PCP was made in 87.5% patients on the basis of BAL/BLB. The mean CD4 count differed significantly ($p<0.001$) between asymptomatic patients and those with different pulmonary infections (Table 5).

Treatment

The principles of treatment remain the same as for HIV-uninfected patients. Generally the most common pathogens especially pneumococcus should be targeted. The preferred choice of antibacterial agents consists

of a combination of a β-lactam [extended-spectrum cephalosporin (ceftriaxone or cefotaxime)] with a macrolide [azithromycin, clarithromycin]. As an alternative to macrolides, a fluoroquinolone with anti-pneumococcal activity like levofloxacin, moxifloxacin or gemifloxacin may be used. However, this should be done only if pulmonary tuberculosis is not a diagnostic consideration. Wherever possible, the agents used should be selected on the basis of available sensitivity results. For individuals with a CD4 count <100 cells/μL, prior history of *P. aeruginosa* infection or neutropenia, consider broader coverage for Gram negative bacilli including *Pseudomonas* spp. Clinical improvement is expected in 48-72 hours after initiation of appropriate therapy. As mentioned earlier, in case of worsening symptoms/signs/radiology or no clinical improvement, further evaluation is required and pending additional diagnostic testing, one should consider addition of broader spectrum antimicrobials.

One of the most important aspects of treatment of CAP in the setting of HIV infection is prevention of recurrence and this can be achieved in the following ways:

- **Optimization of ART**: This remains the key to reducing secondary infections and the morbidity as well as mortality related to them in HIV infected individuals. Improvement in immune function can resolve or lessen the severity of certain infections.
- **23-valent pneumococcal vaccine**: It is indicated for adults and adolescents with a CD4 count of more than 200 cells/μL, if not given in the preceding five years.
- **Prophylactic antibiotics**: Frequent and serious bacterial LRTIs and CAP are considered by some to be an indication for the use of prophylactic antibiotics. Use of co-trimoxazole is associated with a reduction in the incidence of bacterial infections also. However, concerns regarding promotion of drug resistance remain unanswered, as of now.

Outcome

HIV-infected patients with CAP are more likely to present with severe symptoms but they tend to respond similarly to non infected patients and have similar short term mortality rates as the latter (18). In a case-control study, HIV patients admitted for CAP had longer hospital length of stay (LOS) and higher in-hospital and one year

mortality rates in comparison to matched controls (19). However, in another case-control study involving patients with a mean CD4 count of less than 200/μL, no differences were observed in the time to clinical stability, hospital LOS or mortality (20). Furthermore, in a prospective study of patients with a mean CD4 count of 153/μL, the in-hospital mortality was lower in those with HIV infection (15.7% vs. 26.7%) (21).

A staging system for predicting mortality in HIV-associated CAP has been developed. It is based on presence/absence of neurologic symptoms, respiratory rate and serum creatinine. This staging system has five categories and the mortality rates increase from 2.3% for patients falling in the first category (least sick) to 40.5% for those in the last category (sickest). The overall accuracy of this system is approximately 85% (22). Additional predictors for mortality include presence of CD4 cell count <100/μL and presence of pleural effusion or cavitation on CXR (23).

Despite similar short-term mortality rates, CAP in HIV infected patients may be associated with high rates of recurrence. The latter is true for both common and uncommon/opportunistic bacterial pathogens (9). Moreover, long term mortality is higher in HIV infected patients with CAP in comparison to non HIV infected. This has been attributed to the fact that occurrence of CAP leads to enhanced local and systemic replication of HIV and thus an acceleration in the progression of HIV disease. Infact, bacterial CAP especially if it is recurrent or severe, is itself a marker of severe degree of immune suppression.

Conclusions

Lungs are the commonest site of infections in patients with cancer and HIV infection. While managing pneumonia in these patients, one has to have the high index of suspicion, consider the overall state of immunosuppression and make net risk assessment. Lastly one should not forget the non-infectious cause of pneumonia in these patients. In HIV infected individuals, bacterial LRTIs including CAP are the most frequent respiratory diseases. The presentation, management and short-term outcome is similar to non infected patients if appropriate and prompt treatment is initiated. Higher recurrence rates and lower long term survival may be altered with optimal HAART.

References

1. Varma S, Malhotra P (2003). Infections in Acute Leukemia. In Progress in Haematologic Oncology. Ed. Lalit Kumar. The Advanced Research Foundation New York, New York. pp 61-74.
2. Joos L, Tamm M (2005). Breakdown of Pulmonary Host Defense in the Immunocompromised Host. *Proc Am Thorac Soc* **2**: 445–448.
3. Waite S, Jeudy J, White CS (2006). Acute Lung Infections in Normal and Immunocompromised Hosts. *Radiol Clin N Am* **44**: 295–315.
4. Rolston KVI (2001). The spectrum of pulmonary infections in cancer patients. *Current Opinion Oncology* **13**: 218-23.
5. Vento S, Cainelli F (2003). Infections in patients with cancer undergoing chemotherapy: aetiology, prevention, and Treatment. *Lancet Oncol* **4**: 595–604.
6. Hirschtick RE, Glassroth J, Jordan MC, *et al* (1995). Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med* **333**:845-851.
7. Rimland D, Navin TR, Lennox JL, *et al* (2002). Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. *AIDS* **16**:85-95.
8. Shankar EM, Kumarasamy N, Vignesh R, *et al* (2007). Epidemiological studies on pulmonary pathogens in HIV-positive and -negative subjects with or without community-acquired pneumonia with special emphasis on Mycoplasma pneumoniae. *Jpn J Infect Dis* **60**:337-341.
9. Mayaud C, Parrot A, Cadranel J (2002). Pyogenic bacterial lower respiratory tract infection in human immunodeficiency virus-infected patients. *Eur Respir J Suppl* **36**:28s-39s.
10. Gil Suay V, Cordero PJ, Martinez E, *et al* (1995). Parapneumonic effusions secondary to community-acquired bacterial pneumonia in human immunodeficiency virus-infected patients. *Eur Respir J* **8**:1934-1939.
11. Navin TR, Rimland D, Lennox JL, *et al* (2000). Risk factors for community-acquired pneumonia among persons infected with human immunodeficiency virus. *J Infect Dis* **181**:158-164.

12. Miguez-Burbano MJ, Ashkin D, Rodriguez A, *et al* (2005). Increased risk of Pneumocystis carinii and community-acquired pneumonia with tobacco use in HIV disease. *Int J Infect Dis* **9**:208-217.

13. Aviram G, Fishman JE, Boiselle PM (2007). Thoracic infections in human immunodeficiency virus/ acquired immune deficiency syndrome. *Semin Roentgenol* **42**:23-36.

14. da Silva RM, Teixeira PJ, Moreira Jda S (2006). The clinical utility of induced sputum for the diagnosis of bacterial community-acquired pneumonia in HIV-infected patients: a prospective cross-sectional study. *Braz J Infect Dis* **10**:89-93.

15. Nyamande K, Lalloo UG, Vawda F (2007). Comparison of plain chest radiography and high-resolution CT in human immunodeficiency virus infected patients with community-acquired pneumonia: a sub-Saharan Africa study. *Br J Radiol* **80**:302-306.

16. Marchiori E, Muller NL, Soares Souza A, Jr., *et al* (2005). Pulmonary disease in patients with AIDS: high-resolution CT and pathologic findings. *Am J Roentgenol* **184**:757-764.

17. Shanmugasundar G, Wanchu A, Gupta D, Kang M (2007). Profile of pulmonary manifestations in HIV infected patients not on HAART. (MD Thesis; Post-graduate Institute of Medical Education & Research, Chandigarh).

18. Mwachari CW, Nduba VN, Park DR, *et al* (2006). Clinical presentation among HIV-infected and non-infected adults with community acquired pneumonia in Nairobi. *Int J Tuberc Lung Dis* **10**:516-522.

19. Johnson DH, Carriere KC, Houston S, *et al* (2003). Hospitalization for community-acquired pneumonia in Alberta patients with human immunodeficiency virus infections: a case control study. *Can Respir J* **10**:265-270.

20. Christensen D, Feldman C, Rossi P, *et al* (2005). HIV infection does not influence clinical outcomes in hospitalized patients with bacterial community-acquired pneumonia: results from the CAPO international cohort study. *Clin Infect Dis* **41**:554-556.

21. Nyamande K, Lalloo UG, John M (2007). TB presenting as community-acquired pneumonia

in a setting of high TB incidence and high HIV prevalence. *Int J Tuberc Lung Dis* **11**:1308-1313.

22. Arozullah AM, Parada J, Bennett CL, *et al* (2003). A rapid staging system for predicting mortality from HIV-associated community-acquired pneumonia. *Chest* **123**:1151-1160.

23. Cordero E, Pachon J, Rivero A, *et al* (2000). Community-acquired bacterial pneumonia in human immunodeficiency virus-infected patients: validation of severity criteria. The Grupo Andaluz para el Estudio de las Enfermedades Infecciosas. *Am J Respir Crit Care Med* **162**:2063-2068.

Ann Natl Acad Med Sci (India), **45(1):** 45-65, 2009

Pneumonia in Organ Transplant Recipients

G. C. Khilnani and Vijay Hadda
Department of Medicine, All India Institute of Medical Sciences,
New Delhi-110016.

Abstract

Solid organ transplant and hematopoietic stem cell transplant is an established treatment for many malignant and non-malignant end stage diseases. With advances in understanding of immunology of transplantation, the graft survival has improved but immunosuppression is still an issue. Immunosuppression puts these patients at risk of opportunistic infections. Pneumonia is amongst one of the most common infections in this population. Microorganisms causing pneumonia vary from bacterial, mycobacterial, fungal to viral depending upon the level of immunosuppression. Therefore, management of pneumonia in this group of patients is challenging. Most of the times, isolation of the causative organism is not possible at the time of presentation making selection of antimicrobials difficult. Empirical treatment is usually guided by various factors like, age of the graft, level of immunosuppression, radiological features, prevalent local pathogens and initial response to therapy. Recently, with better understanding of immunology and antimicrobial therapy, mortality and morbidity have reduced significantly.

Key words: Solid organ transplantation, hematopoietic stem cell transplantation, immunosuppression, pneumonia.

Correspondence: Dr. G. C. Khilnani, Professor, Department of Medicine, All India Institute of Medical Sciences, New Delhi, India. Phone: +91–11-26593488; Fax: +91-11-26588663. E-mail: gckhil@hotmail.com Proceedings of the NAMS-PGI Symposium on 'Community Acquired Pneumonia', held in Chandigarh, 2007.

Introduction

Solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) represent one of the greatest medical achievements of the twentieth century. With advances in basic immunobiology and clinical care, these treatment options are offered to more patients with various malignant and non-malignant diseases. According to United Network for Organ Sharing, the number of transplants has already exceeded 25,000 per year, for last five years (http://www.UNOP.org) and worldwide, 30,000-40,000 HSCTs are performed each year. Kidney (60%) is the most common SOT and others include liver (25%), heart (10%) and lung (5%). Immunosuppressive therapy in the form of corticosteroids and other drugs is an integral part of organ transplant management. Although, with advanced understanding of immunobiology, the rejection and overall survival have improved in these patients, these techniques make them more prone to developing various infections.

Although, with introduction of more effective prophylactic strategies and refined immunosuppressive regimens, the incidence of infectious complications after transplantation has declined, it still remains a common life-threatening complication in these patients. Pneumonia is the most common infection in lung and heart transplant recipients (1, 2) and is only second to intraabdominal infection in liver transplant recipients (3). Renal transplant recipients are having the lowest risk of pneumonia reflecting the less rigorous surgical procedure and the decreased level of immunosuppression required to sustain it.

Like SOT, HSCT recipients are also at high risk for pulmonary infectious complications (4). Factors affecting susceptibility to infection are pretransplant immune status, type of conditioning regimen, degree and duration of neutropenia, and development of graft versus host disease (GVHD) (4). Allogenic transplant recipients are at greater risk than autologous transplant, and matched, unrelated-donor transplant carries maximum risk (4).

Pathophysiology

In normal person lungs are well protected from pathogens by general, innate and adaptive immune mechanisms which are intricately intertwined with overlapping signaling pathways (5). The general defenses in upper airway consist of nasal pathway, sinuses and turbinates which trap inhaled pathogens. In lower respiratory tract there are cough and sneeze reflexes, glottis to cover larynx and

mucociliary clearance to prevent entry of pathogens. Surfactant lining, alveolar macrophages and lymphatic system contain pathogens in the bronchial tree, which escaped the above defenses.

Innate immunity in the form of IgA (in conducting airway) and IgG (in alveoli) activate complement cascade in response to pathogen exposure. The respiratory mucosa also secretes cytokines and chemokines which attract leukocytes and defensins (6). The final and the most affected defense in transplant recipients against pneumonia is adaptive immunity. This consists of activation and proliferation of clonal lymphocytes specific for antigenic characteristics of the pathogen (6). Subsequently, there is a complex interaction between T-lymphocytes, antigen presenting cells (APC) and class II major histocompatiblity complex protein. It results in intracellular activation of calcineurin, upregulation of nuclear activity and interleukin-2 (IL-2) production. IL-2 stimulates immune system in many ways but the most important is self-proliferatory effect on activated T-cells. Once a specific line of "helper" T-lymphocytes (Th) is activated it will mature as Th1 (control cell mediated immunity) or Th2 (control humoral immunity). The mature T-lymphocytes travel to site of inflammation and through interactions with various cells like cytotoxic T-lymphocytes, B lymphocytes, natural killer cells and phagocytes contain infection. Once the acute infection is controlled, the lymphocyte activity subsides and few cells linger as memory cells that can be summoned in future.

In transplant recipients, exogenous immunosuppression achieved with different classes of drugs leads to T-lymphocyte suppression. Various mechanisms involved are calcineurin inhibition (cyclosporine A and tacrolimus), cell cycle inhibition (azathioprine and mycophenolate mofetil), blunting of IL-2 proliferating action on T-lymphocytes (sirolimus and everolimus) or broad-spectrum immunosuppression (corticosteroids). Drugs used for induction therapy to minimize early acute rejection, i.e. antilyphocytic antibodies or IL-2 receptor antibodies, affect lymphocyte function and overall immune response. High doses of chemotherapy with or without total body irradiation are administered to ablate the bone marrow, maximize tumor cell kill and induce immunosuppression to prevent rejection of the donor stem cells. The number of other factors like anatomic location, type of transplant and comorbid conditions like diabetes and renal failure also contribute to immunosuppression. Certain viral

infections [Epstein-Barr virus, cytomegalovirus (CMV), HIV, and hepatitis C virus], along with the factors described above, result in a net "state of immunosuppression" and put these patients at high risk of pulmonary infections (5,7).

Time Trend in Infections

Interestingly, the spectrum of microorganisms responsible for infections is similar among various organ recipients and these appear in fairly characteristic sequence in the post transplantation course (5). During first month the infectious risk is posed by surgery and intensive care, and immunosuppression has lesser role and nosocomial bacterial infections predominate, similar to that of the general surgical population. The period from 1 to 6 months, the period of maximum sustained immunosuppression, is characterized by the emergence of opportunistic pathogens. Beyond 6 months, stable allograft function permit reduction of immunosuppression in the majority of patients and common community-acquired pathogens are responsible for pneumonia during this period. Opportunistic infections occur less commonly in this later period but remain threat among subset of patients requiring augmentation of immunosuppression for treatment of chronic rejection or recurrent episodes of acute rejection. Modern prophylactic regimens using sulfonamides, azoles, and antivirals, have considerably changed the classical pattern of infections and the previous paradigm of predicting pathogens in certain time points post-transplantation is no longer applicable. Duncan *et al* (8) suggested modified timelines that account for the use of prophylactic regimens and their effect on the onset of infections post-transplantation (Figs. 1 and 2).

Etiology of Pneumonia

Bacterial Pneumonia

Although considerable overlap exists, there are significant differences in epidemiology and clinical presentation of these infections in SOT and HSCT recipients. Almost one third of nosocomial and community acquired pneumonia in SOT and 15% in HSCT are caused by pyogenic gram negative or gram positive bacteria (9).

Nosocomial pneumonia is almost exclusively a perioperative complication. Common pathogens are gram negative but *Staphylococcus aureus* and, in some centers, *Legionella* species are also encountered (8,9). Some studies have shown an increase in the prevalence of methicillin-resistant *Staphylococcus aureus* infections and this must be considered when initiating

empiric antibiotic therapy (10). Risk factors for nosocomial pneumonia are the need for prolonged postoperative mechanical ventilation, impairment of cough reflex, narrowing of the bronchial anastomosis, disruption of pulmonary lymphatics, and impairment in the mucociliary "escalator" because of ischemic injury to the bronchial mucosa. Passive transfer of occult pneumonia initially acquired by the donor is another circumstance unique to lung

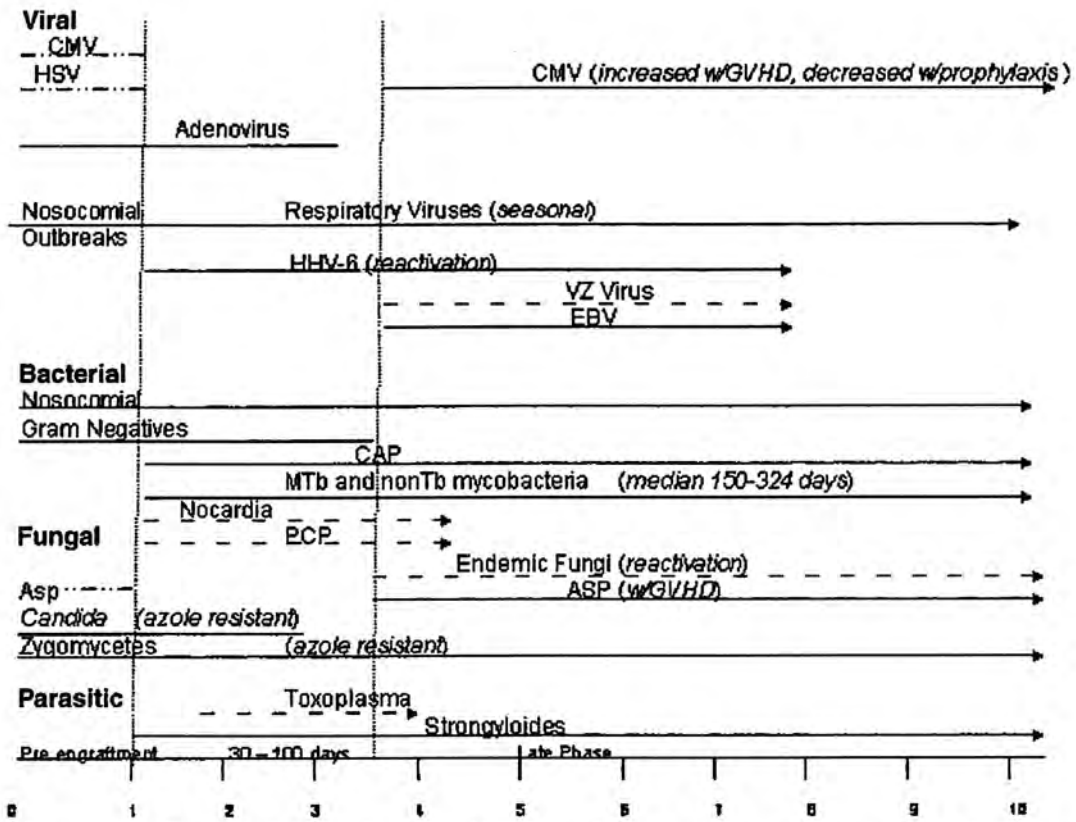

Figure 1 : Proposed infection timeline based on the use of common prophylactic antimicrobials such as sulfa, azoles, and antivirals in recipients of solid organ transplants. *Dotted lines* denote onset of infection that would occur without prophylaxis. *Solid lines* indicate the most common times to onset of infection for each pathogen. Asp = *Aspergillus*; Blasto = *Blastomyces*; CAP = community-acquired pneumonia; CMV = cytomegalovirus; Cocci = *Coccidioides*; Crypto = *Cryptococcus*; EBV = Ebstein-Barr virus; Histo = *Histoplasma*; HSV = herpes simplex virus; MTb = *Mycobacteria tuberculosis*; PCP = *Pneumocystis carinii*; Toxo = Toxoplasmosis; VZV = *Varicella zoster* virus. Zero denotes the time of transplantation. (Reproduced with permission from ATS (8))

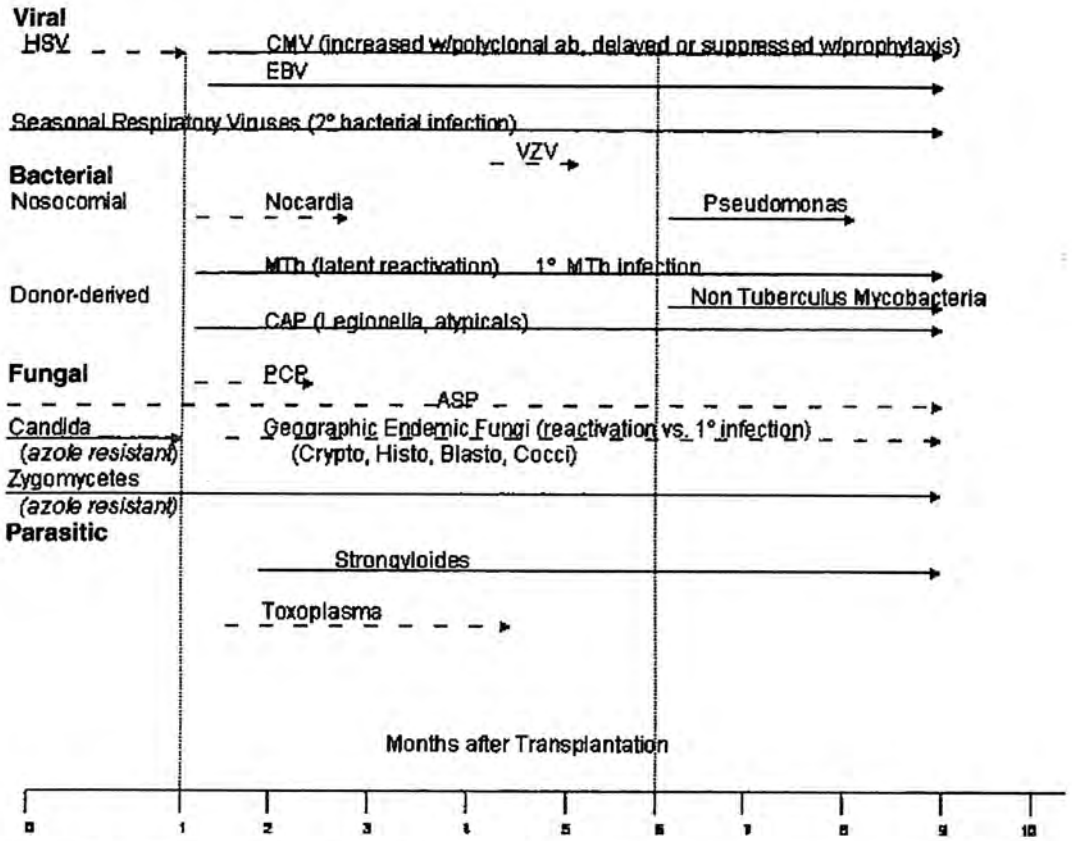

Figure 2 : Proposed infection timeline based on the use of common prophylactic antimicrobials such as sulfa, azoles, and antivirals in recipients of HSCT. *Dotted lines* denote onset of infection that would occur without prophylaxis. *Solid lines* indicate the most common times to onset of infection for each pathogen. Asp = *Aspergillus*; CAP = community-acquired pneumonia; CMV = cytomegalovirus; EBV = Ebstein-Barr virus; GVHD = graft versus host disease; HHV 6 = human herpes virus 6; HSV = herpes simplex virus; MTb = *Mycobacteria tuberculosis*; PCP = *Pneumocystis carinii*; VZV = *Varicella zoster* virus. Zero denotes the time of transplantation. (Reproduced with permission from ATS (8))

transplantation. Although the incidence of nosocomial pneumonia has declined significantly in transplant recipients (8, 9) but the mortality remains high.

Community acquired pneumonia (CAP) occurs later in the posttransplantation period. *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Legionella* species are the leading culprits responsible for CAP in these patients (7, 8). Among lung transplant recipients who have

developed bronchiolitis obliterans syndrome (BOS), *Pseudomonas aeruginosa* is identified as the etiologic agent in the majority of cases. Earlier, Nocardia infections were relatively common (11). With introduction of cyclosporine-based immunosuppressive regimens and wide spread use of sulfonamides for *Pneumocystis carinii* pneumonia (PCP) prophylaxis have reduced *Nocardia* infections markedly. Recent case series have suggested a frequency of *Nocardia* infection in the order of 0.2–2.1%. (9,12) Clinicians must remain particularly vigilant for this infection in patients in whom trimethoprim–sulfamethoxazole has either not been administered because of allergy or has been discontinued after the first year.

Mycobacterial Pneumonia

In developed countries it is relatively uncommon post transplantation infection but transplant recipients are having 30- to 100-fold higher annual risk of developing tuberculosis than that of the general population (13). In United states and Europe tuberculosis has been reported in about 0.5–2% of organ transplant recipients (13,14). In endemic areas like India it is seen in up to 15% of transplant recipients (15). Reactivation of latent infection is believed to be the predominant mechanism for development of active tuberculosis after transplantation. Other less common modes of acquisition include nosocomial outbreaks and donor transmission through infected kidney, lung, and liver allografts (13).

Nontuberculous mycobacteria like *Mycobacterium avium* complex, *M. kansasii*, *M. abscessus*, and *M. asiaticum* are commonly reported among lung transplant recipients and may be more common than *M. tuberculosis* as a cause of pulmonary infections. In the largest published series encompassing 261 patients, nontuberculous mycobacteria was documented in 16 patients (6.1%) compared with only 2 cases of pulmonary tuberculosis (0.8%) (16). Thirteen of the 16 cases were due to *M. avium* complex; *M. kansasii*, *M. abscessus*, and *M. asiaticum* each accounted for one case. Pulmonary infection tended to occur late in the post transplantation course and preexistent chronic rejection is a major risk factor.

Pulmonary infection due to nontuberculous mycobacteria species is considerably less common in other solid organ transplant populations, heart transplant recipients and renal transplant recipients (0.1%) (16,17). This is only rarely reported complication after liver transplantation. *M. kansasii* and *M. avium*

complex are the prevailing pathogens responsible for pulmonary infection in these populations (17).

Viral Pneumonia

Beyond the first months post-transplant, viral pathogens emerge as the most important group of infections affecting the transplant recipients. Among lung transplant recipients they are the second most common cause of infection, accounting for 23 to 31% of all infections, but the incidence in non-lung grafts recipients varies considerably (18). As about 50% of the adult population harbor latent virus, CMV infection is considered as the most important pathogen affecting transplant recipients. Therefore, reactivation of latent infections accounts for virtually all transplant-related CMV disease. Almost 75% of solid organ transplant patients have evidence of CMV infection (19). CMV has been implicated in chronic allograft rejection - bronchiolitis oblitrans syndrome (BOS) in lung transplant recipients, though phenomenon is not observed with other allografts.

Human stem cell transplant patients are at increased risk for CMV pneumonia due to effects related to delayed reconstitution of cytotoxic T cells and immunosuppressants. Recipients of allogeneic grafts are at greater risk (20-35%), presumably due to increased requirements for immuno-suppression as compared to autologous HSCT (1-6%). Previously CMV infection onset was usually seen during first 100 days of post-transplantion. Anti-CMV prophylaxis has changed the onset of disease from the first 100 d (decreased from 35 to 6%) to beyond the first 100 d (up from 4 to15%). (9) Patients with chronic graft versus host disease (GVHD) are particularly vulnerable to CMV due to an increased need for immunosuppression. GVHD also causes an immunodeficient state by involving mucosal surfaces, reticuloendothelial system, and bone marrow (9).

Herpes simplex virus infection is commonly seen in up to 18% of transplant recipients. It may cause severe pneumonia in up to 10% of patients and can be fatal in about 20% of cases. Community-acquired viruses like, *influenza* A and B, *Para influenza*, respiratory syncytial virus, and adenovirus often lead to significant pneumonitis (up to 66%) and respiratory failure. Of these, *Para influenza*, *adenovirus*, and *respiratory syncytial virus* have been directly linked to BOS in lung transplant patients (9, 20). Human herpes virus 6 causes idiopathic pneumonia syndrome in post HSCT patients (9).

Fungal Pathogens, Protozoa, and Parasites

The incidence of invasive fungal infection in solid organ transplantation is 5–50%. *Candida* species is the most common, occurring in the early period post-transplant but it rarely causes pneumonia. The classic opportunistic fungal infection encountered in organ transplantation is *Aspergillus* species, with an incidence of 18–22%, and has a clinical presentation similar to *Mucormycosis*. *Aspergillus* or *Mucormycosis* are strongly associated with neutropenia in patients undergoing HSCT, but can occur despite adequate numbers of circulating neutrophils in solid organ recipients. Invasive disease is usually associated with a high mortality (50–100%) and localized Aspergillus infections are associated with significant morbidity in the lung transplant patient (21,22).

Less common fungi are *Cryptococcus, Histoplasma, Coccidioides* (reactivation of latent infection) and *Blastomyces dermatitidis* (primary disease). *Pneumocystis carinii* prophylaxis that includes sulfonamides has significantly reduced the incidence of *P. carinii* pneumonia and *Toxoplasma* in all transplant recipients (9,23). *Trichoderma species, Pseudallescheria boydii, Torulopsis species, Microascus species, Penicillium species, Zygomycetes, Absidia* and *Rhizopus* are few emerging fungi (24).

Approach To A Transplant Recipient With Pneumonia

When a transplant recipient presents with symptoms suggestive of pneumonia, an aggressive initial approach with broad spectrum antibiotics and comprehensive diagnostic work up is strongly recommended. Unlike CAP no triage system is recommended for these patients. Need for hospitalization is decided by the type of antimicrobial, extent of testing, and the supportive care needed. Furthermore, as this acute illness can have profound effect on long term immunosuppression as a result of drug interactions, patients may require hospitalization for drug dose modification and drug level monitoring.

Clinical presentation of pneumonia in SOT and HSCT recipients is similar to immunocompetent patient and can be mimicked by non infectious etiologies like atelectasis and pulmonary edema in many patients. Specifically, in lung transplant recipients, it is difficult to differentiate ischemia reperfusion injury and acute rejection from infective pneumonia (25).

Radiographic image, in the form of chest X-ray, can provide useful

information during initial evaluation. It corroborates the clinical suspicion of pneumonia and type of infiltrates as diffuse versus focal can help to narrow the spectrum of pathogens (2). Bacterial pneumonia is typically associated with focal consolidation, whereas diffuse interstitial pattern is often seen in viral and PCP infections (25). Exceptions also occurs for the above generalization like lung transplant patients with severe BOS manifest pneumonia as coarse diffuse infiltrates, CMV pneumonia can present with more confluent infiltrates and *Aspergillus* may present as focal consolidation, diffuse infiltrates, or multifocal nodules with cavitation. Computer tomography (CT) scan can characterize and localize infiltrates better and additionally can be used for sampling of nodules or lymph nodes. Although radiological images are helpful but the imaging pattern is not specific enough to obviate need for microbiologic or histological confirmation of suspected pathogen.

Identification of pathogen

Various noninvasive tests are available to identify different pathogenic organisms and some times obviate need for invasive test like fibroptic bronchoscopy (FOB). Respiratory secretions i.e. sputa can be examined for gram stain, culture and acid fast staining (for bacteria, mycobacteria, nocardia, fungi and virus); for viral antigens (respiratory syncytial virus, para influenza, adenovirus) ; and direct fluoresce antibody (PCP). Serum tests are available for CMV (nucleic acid amplification or antigen (pp65) level), *Histoplasma* and *Cryptococcus* (antigen) and *Aspergillus* (galactomannan antigen). Urine can tested for presence of *Histoplasma* or *Legionella* antigen.

Role of fibroptic bronchoscopy (FOB)

Bronchoscopy is an important tool in diagnosis of pneumonia in immunocompromized patients like organ recipients. Bronchoalveolar lavage (BAL) and protected-specimen brushing samples have excellent yield of culturing various organisms in these patients (2,26,27). In patients with lung transplant showing lung infiltrates on chest X-ray FOB guided transbronchial biopsy can be used to exclude acute rejection of lung. When used with other tests, it can provide complimentary results. Large studies (27) involving 300 lung transplant patients demonstrated a direct impact of FOB on management of these patients. In our experience BAL has a high diagnostic yield (75.8%) in patients with kidney transplant (28).

Several authors have advocated different strategies for FOB with

limited experiences (9,27), but it can be deferred for an empirical treatment in cases where high likelihood of bacterial process like, focal consolidation, where noninvasive testing can identify a cause or when risk outweigh benefits of FOB. In these cases empiric therapy for bacterial pneumonia is safe with reassessment in 2-3 days. Infections with resistant nosocomial pathogens, opportunistic organisms and multiple organisms are more common during first 6 months after transplantation (2, 8, 9). Early FOB is justified more in patients with lung transplant recipients as acute graft rejection, post transplant lymphoproliferative disease, and tracheal stenosis can be confused with pneumonia. Rarely, surgical lung biopsy may be required when FOB technique do not reveal diagnosis.

Unfortunately, many patients are having poor lung functions so may not be fit for FOB. Therefore, before considering for FOB, risk-benefit should be assessed and where risks outweigh benefits conservative approach with empirical antibiotics is justified. The isolates from sputa or previous FOB specimen can help in selection of antibiotics. In absence of this information broad-spectrum therapy, particularly covering *Pseudomonas aeruginosa* should be initiated. In such cases, FOB can be done if there is no response with this therapy.

Treatment Of Pneumonia

To describe whole treatment of pneumonia is beyond the scope of this article. Therefore we have described only the salient features. For detailed treatment readers may take information from references.

Hospital acquired pneumonia

Infection control measures like standard precautions, isolation of resistant pathogens, routine intensive care unit (ICU) surveillance minimization of aspiration, avoidance of unnecessary and prolonged intubation and aggressive pulmonary toileting are recommended to prevent HAP (29,30). Empiric broad spectrum antibiotics should be started immediately in all suspected cases of HAP. Choice of antimicrobial agent depends on institutional patterns. As all bacterial pneumonia are treatable, an early, aggressive effort to achieve etiological diagnosis is recommended so that definite therapy can be administered (29,30). In patients with HSCT pneumonia may not be recognized radiologically because of blunted inflammatory response (9), but are treated similarly with broad spectrum antibiotics.

Community acquired pneumonia

For prevention of CAP pneumococcal, influenza and *H.infleunza* B (HIB) vaccines should be given to each candidate prior to SOT or HSCT (31). Although pneumococcal revaccination is recommended every 5 yearly, in patients with SOT it may be considered every 2-3 year interval. *H.infleunza* B revaccination is recommended based on the HIB antibody titres (31). In most cases, identification of organism by gram stain or cultures is not possible. So, American Thoracic Society (ATS) and Infectious Disease Society of America have provide guidelines for empiric treatment of CAP (32). Beta-lactam plus macrolide or quinolones are recommended as first choice of therapy in SOT. In patients who are at high risk like with lung transplant recipients who have cystic fibrosis or BOS should be treated using beta-lactam with anti-pseudomonal activity (32). Similar therapy is recommended for CAP in HSCT recipients.

Legionella pneumonia is a fatal disease, if treatment is delayed. Therefore, prompt empiric therapy is recommended in all patients with suspected cases of *Legionella* (31, 33). The preferred therapy for *Legionella* is azithromycin or a flouroquinolones. Erythromycin is not used routinely because of its interaction with calcineurin inhibitors. Initially, recommended duration of therapy was 21 days, but now 10-14 days is accepted as standard therapy (31,33). For *Nocardia*, trimethoprim-sulfamethoxazole (TMP-SMX) is drug of choice and the recommended dosing is 15 mg/kg/day of trimethoprim divided in 2-4 doses either orally or intravenously (34). Other drugs like sulfonamides alone, imipenem, meropenem, amikacin, minocycline, 3rd generation cephalosporins, linezolid, ciprofloxacin and amox-clavulanate are less studied options (34). HSCT recipients are also similarly treated and in cases with myelosupression or sulfa drug allergy, second line drugs can be used.

Tubercular pneumonia

The treatment of TB pneumonia is complicated by a number of factors present in the SOT patient, as both disease and its therapy have been attributed for high mortality in SOT (9). Rifamycins dramatically increase hepatic metabolism of calcineurin inhibitors and consequently lower the blood levels of these agents. This may lead to rejection and graft loss in significant number of patients receiving rifamycins (35). Isoniazid (INH) has also been reported to interact with calcineurin inhibitors. This interaction generally is not clinically significant

and should not preclude the use of INH. Drug induced hepatotoxicity remains an important side effect with INH. In liver transplant recipients, INH induced hepatotoxicity may lead to discontinuation of drugs in 41% to 83% of the patients (9).

The American Thoracic Society published guidelines for treatment of TB in SOT recipients, though many issues remain unresolved (36). In general, rifampicin either alone or in combination is not used in patients with SOT, therefore duration of therapy extends beyond the standard six month course. The patients on INH should be monitored for hepatotoxicity. Asymptomatic elevation of transaminases less than five times of normal range should prompt close monitoring rather stopping INH.

HSCT recipients are also treated similarly and rifampicin is generally not recommended because of its interactions with corticosteroids, fluconazole, analgesics and calcineurin inhibitors which are commonly used in these patients (36).

Non tubercular mycobacteria are treated with rifamycins and clarithromycin both of which have significant effects on metabolism of calcineurin inhibitors. Thus these patients require close monitoring. Other drugs like aminoglycosides which are recommended for therapy are also toxic. Initiation of treatment with two drugs and in severe cases three or more drugs are recommended (37).

CMV pneumonia

Drugs which are approved by Food and Drug Administration (FDA) are acyclovir and its valine prodrug valacyclovir; ganciclovir and its valine prodrug valgancyclovir; cidofivir and foscarnet. Leflunomide has some activity against CMV but is not approved by FDA. CMV immunoglobulins (CMVIG) are used for prevention of infection and disease.

Overall CMV therapy is more effective in SOT population than in the HSCT population. Ganciclovir is considered first line therapy for all SOT recipients and has shown benefit in renal, heart, heart-lung, and lung transplant recipients who have CMV disease and pneumonia (38-40). In lung transplant recipients, combination of ganciclovir plus intra venous immunoglobulins (IGIV) or CMVIG is associated with increased survival and is preferred therapy (40,41). Cidofivir and foscarnet, both with little experience, are associated with nephrotoxicity and dehydration and magnesium wasting, respectively.

In the HSCT population, CMV pneumonia is treated with ganciclovir

alone or in combination with foscarnet or CMVIG (42, 43). The combination of foscarnet plus ganciclovir may provide antiviral synergy but requires careful monitoring (43). Cidofivir and foscarnet are considered second line therapies because of toxicities. CMVIG either alone or ganciclovir demonstrated variable results (40,41,44).

Fungal pneumonia

The mainstay of treatment has been antifungal drugs supplemented with reversal of underlying immunosuppression, when indicated and feasible. In some cases surgery and only rarely, immune modulation is required. Various antifungal drugs against *Aspergillus* species currently available are amphotericin B (liposomal and lipid formulations), itraconazole, voriconazole, and caspofungin. Length of therapy is not standardized, but many courses continue 10 to 12 weeks or several weeks after clinical and radiographic resolution.

Amphotericin B has been the main antifungal drug in use for *Aspergillus* infection, but voriconazole is now considered a first line therapy and is being used increasingly. In one study involving 277 immunocompromised patients (including 9 HSCT and 14 solid organ transplant recipients) with confirmed or probably invasive aspergillosis, the use of voriconazole was associated with a greater complete or partial response at 12 weeks, lower mortality, and lesser need of other drugs (45). A few other small studies also indicate that voriconazole seems to be equivalent to amphotericin B (46). With availability of lipid preparation of amphotericin B (lipid complex, liposomal and colloidal dispersion amphotericin), a higher dose (5 mg/kg/d) is used as initial treatment. High doses may be more effective in select situations, but superior efficacy has not been proven. Though there are conflicting data in the transplant population but one retrospective study in 41 liver transplant recipients showed mortality benefit in patients receiving lipid forms of amphotericin (33%) compared to conventional amphotericin (86%) (47). Liposomal preparations do seem to have a more favorable side-effect profile than standard amphotericin B, particularly with respect to risk of nephrotoxicity.

Voriconazole leads to inhibition of the P-450 cytochrome system resulting in increased levels of cyclosporine, tacrolimus, or sirolimus. The interaction may be severe particularly with sirolimus so this combination is discouraged. Also, intravenous voriconazole is contraindicated in patients whose creatinine clearance is less than 50 ml/min. Itraconazole is also useful, but its oral absorption is less

reliable. Posaconazole is a newer triazole with a significant activity against *Aspergillus*.

Caspofungin is a member of the new echinocandin family of drugs. It acts on the fungal cell wall rather than the cell membrane and is approved as second-line therapy for refractory aspergillosis. HSCT and SOT recipients have shown a favourable response in approximately 45% of patients who were not responding or were intolerant to amphotericin (48,49). The drug was well tolerated in all studies. Cyclosporine resulted in increased concentration of caspofungin but no change in cyclosporine level, when used concurrently. It can reduce levels of tacrolimus and it needs to be monitored. Elevations of liver enzymes can occur, but significant hepatotoxicity is rare.

Few clinical studies showed combination of amphotericin B with capsofungin or voriconazole with capsofungin was associated with improved response (49-52). Though, there has been concern about combining azoles and amphotericin because some animal studies showed antagonism (49,52). This antagonism was assumed to be caused by alterations of the sterol composition induced by azoles that made an amphotericin less effective. With echinocandins, antagonism would not be anticipated. Some animal studies of echinocandins combined with either amphotericin or caspofungin have been very promising.

The efficacy of combination therapy using multiple antifungal agents is yet to be proved by large trials. However, limited data suggest that combination antifungal therapy may be considered in subsets of high-risk patients e.g. those on renal and replacement therapy in whom mortality rates have typically exceeded 90% (49,52).

There are anecdotal reports of immunomodulation with granulocyte transfusion from donors stimulated with granulocyte-stimulating factor and gamma interferon during treatment of invasive pulmonary aspergillosis, with some safety issues (53). Surgical resection is usually required for infection resistant to medical therapy, massive hemoptysis, and sometimes to improve outcome of medical therapy (54,55). Many studies have shown that surgical resection can be performed with acceptable mortality, but indications are not well defined (54,55).

Conclusion

Management of pneumonia in transplant recipient can not be generalized. Also, it is not possible to give algorithm for antimicrobials to be

used in all cases. Like, immunocompetent patients with pneumonia, organ transplant recipients also require aggressive investigation for microbial diagnosis. However, antimicrobial therapy should be started without delay in all cases of clinically or radiologically suspected pneumonia. Choice of antimicrobials depend on type of organ transplant, severity of illness, use of immunosuppressive agents, radiological appearance, information about local microbiology and its resistance pattern. Duration of antimicrobial therapy should be individualized depending on severity of illness, causative micro-organism and extent of lung involvement. It would always be beneficial to involve a person who is trained and interested in treatment of infections in immuno-compromised patients.

References:

1. Maurer JR, Tullis E, Grossman RF, Vellend H, Winton TL, Patterson GA (1992). Infectious complications following isolated lung transplantation. *Chest* **101**:1056–1059.
2. Cisneros JM, Munoz P, Torre-Cisneros J, *et al* (1998). Spanish Transplantation Infection Study Group. Pneumonia after heart transplantation: a multi-institutional study. *Clin Infect Dis* **27**:324–331.
3. Kusne S, Dummer JS, Singh N, *et al* (1988). Infections after liver transplantation: an analysis of 101 consecutive cases. *Medicine (Baltimore)* **67**:132–143.
4. Soubani AO, Miller KB, Hassoun PM (1996). Pulmonary complications of bone marrow transplantation. *Chest* **109(4)**:1066-77.
5. Fishman JA, Rubin RH (1998). Infection in organ-transplant recipients. *N Engl J Med* **338**:1741–1751.
6. Welsh DA, Mason CM (2001). Host defense in respiratory infections. *Med Clin North Am* **85(6)**:1329-47
7. Snydman DR (2001). Epidemiology of infections after solid-organ transplantation. *Clin Infect Dis* **33**:S5–S8.
8. Duncan MD and Wilkes DS (2005). Transplant-related immunosuppression: A review of immunosuppression and pulmonary infections. *Proc American Thoracic Society* **2**:449-455
9. Robert MK, Vivek NA, Stephen WC (2004). Pulmonary Complications of Solid Organ and Hematopoietic Stem Cell Trans-

plantation. *Am J Respir Crit Care Med* **170(1)**:22-48.

10. Singh N, Paterson DL, Chang FY, *et al* (2000). Methicillin-resistant *Staphylococcus aureus*: the other emerging resistant gram-positive coccus among liver transplant recipients. *Clin Infect Dis* **30**:322–327.
11. Chapman SW, Wilson JP (1990). Nocardiosis in transplant recipients. *Semin Respir Infect* **5**:74–79.
12. Roberts SA, Franklin JC, Mijch A, Spelman D (2000). *Nocardia* infection in heart–lung transplant recipients at Alfred Hospital, Melbourne, Australia, 1989–1998. *Clin Infect Dis* **31**:968–972.
13. Singh N, Paterson DL (1998). Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. *Clin Infect Dis* **27**:1266–77.
14. Korner MM, Hirata N, Tenderich G, *et al* (1997). Tuberculosis in heart transplant recipients. *Chest* **111**:365–369.
15. John GT, Shankar V, Abraham AM, *et al* (2001). Risk factors for post-transplant tuberculosis. *Kidney Int* **60**:1148–1153.
16. Malouf MA, Glanville AR (1999). The spectrum of mycobacterial infection after lung transplantation. *Am J Respir Crit Care Med* **160**:1611–1616.
17. Queipo JA, Broseta E, Santos M, *et al* (2003). Mycobacterial infection in a series of 1261 renal transplant recipients. *Clin Microbiol Infect* **9**:518–525.
18. Alexander BD, Tapson VF (2001). Infectious complications of lung transplantation. *Transpl Infect Dis* **3**:128–137
19. Pereyra F, Rubin RH (2004). Prevention and treatment of cytomegalovirus infection in solid organ transplant recipients. *Curr Opin Infect Dis* **17**:357–361.
20. Khalifah AP, Hachem RR, Chakinala MM, *et al* (2004). Respiratory viral infections are a distinct risk for bronchiolitis obliterans syndrome and death. *Am J Respir Crit Care Med* **170**:181–187.
21. Bag R (2003). Fungal pneumonias in transplant recipients. *Curr Opin Pulm Med* **9**:193–198.
22. Oner-Eyuboglu F, Karacan O, Akcay S, *et al* (2003). Invasive pulmonary fungal infections in solid organ transplant recipients: a four-year review. *Transplant Proc* **35**:2689–2691.
23. Fishman JA(2001). Prevention of infection caused by Pneumocystis

carinii in transplant recipients. *Clin Infect Dis* **33**:1397–1405

24. Brown JM (2004). Fungal infections in bone marrow transplant patients. *Curr Opin Infect Dis* **17**:347–352.
25. Guilinger RA, Paradis IL, Dauber JH, *et al* (1995). The importance of bronchoscopy with transbronchial biopsy and bronchoalveolar lavage in the management of lung transplant recipients. *Am J Respir Crit Care Med* **152**:2037-2043
26. Sileri P, Pursell KJ, Coady NT, *et al* (2002). A standardized protocol for treatment of severe pneumonia in kidney transplant recipients. *Clin Transplant* **16(6)**:450-54.
27. Chan CC, Abi-Saleh WJ, Arroliga AC, *et al* (1996). Diagnostic yield and impact of flexible bronchoscopy in lung transplant patients. *J Heart Lung Transplant* **15**:196-205.
28. Kalra V, Agarwal SK, Khilnani GC, *et al* (2005). Spectrum of pulmonary infections in renal transplant recipients in the tropics: A single center study. *Int Urology and Nephrology* **37(3)**:551-59.
29. American Thoracic Society. Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2005). *Am J Respir Crit Care Med* **171:** 388-416
30. Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R (2004). Healthcare Infection Control Practices Advisory Committee. Guidelines for prevention of health care associated pneumonia, 2003 : recommendation of CDC and health care advisory committee. *MMWR Recomm Rep* **53(RR-3)**:1-36.
31. Avery RK, Ljungman P (2001). Prophylactic measures in the solid organ recipient before organ transplantation. *Clin Infect Dis.* **33(Suppl 1):** S15-21.
32. Mandell LA, Bartlett JG, Dowell SF, *et al* (2003). Infectious Diseases Society of America. Update of practice guidelines for the management of community acquired pneumonia in immunocompetent adults. *Clin Infect Dis.* **37(11)**:1405-33.
33. Singh N, Stout JE, Yu VL (2004). Prevention of Legionnaires' disease in transplant recipients: recommendations for a standardized approach. *Transpl Infect Dis.* **6(2)**:58-62.

34. Nocardia infections (2004). *Am J Transplant* **4(Suppl 10)**:47-50.

35. Aguado JM, Herrero JA, Gavaldá J, *et al* (1997). Clinical presentation and outcome of tuberculosis in kidney, liver, and heart transplant recipients in Spain. Spanish Transplantation Infection Study Group, GESITRA. *Transplantation* **63(9)**:1278-86.

36. Centers for Disease Control and Prevention; Infectious Disease Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients (2000). *MMWR Recomm Rep.* **49(RR-10)**:1-125.

37. Nontuberculous mycobacteria (2004). *Am J Tranplant* **4(Suppl 10)**:42-46

38. Cerrina J, Bavoux E, Le Roy Ladurie F, *et al* (1991). Ganciclovir treatment of cytomegalovirus infection in heart-lung and double lung transplant recipients. *Transplant Proc* **23**:1174-5.

39. Hecht DW, Snydman DR, Crumpacker CS, Werner BG, Heinze-Lacey B (1988). Ganciclovir for treatment of renal transplant associated primary cytomegalovirus pneumonia. *J Infect Dis* **157**:187-90.

40. Snydman DR (2001). Historical overview of the use of cytomegalovirus hyperimmune globulin in organ transplantation. *Transpl Infect Dis* **3(Suppl 2)**:6-13.

41. Valantine HA, Luikart H, Doyle R, *et al* (2001). Impact of cytomegalovirus hyperimmune globulin on outcome after cardiothoracic transplantation: a comparative study of combined prophylaxis with CMV hyperimmune globulin plus ganciclovir versus ganciclovir alone. *Transplantation* **72**:1647-52.

42. Crumpacker CS (1996). Ganciclovir. *N Engl J Med* **335**:721-9.

43. Bacigalupo A, Bregante S, Tedone E, *et al* (1996). Combined forcarnet-ganciclovir treatment for cytomegalovirus infection after allogenic hemopoietic stem cell transplantation (HSCT). *Bone Marrow Transplant.* **18(Suppl 2)**:110-4.

44. Reed EC, Bowden RA, Dandliker PS, Gleaves CA, Meyers JD (1987). Efficacy of cytomegalovirus immunoglobulin in marrow

transplant recipients with cytomegalovirus pneumonia. *J Infect Dis* **156**:641-5.

45. Herbrecht R, Denning DW, Patterson TF, *et al* (2002). Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med.* **347(6)**:408-15.
46. Denning DW, Ribaud P, Milpied N, *et al* (2002). Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis.* **34(5)**:563-71.
47. Linden PK, Coley K, Fontes P, Fung JJ, Kusne S (2003). Invasive aspergillosis in liver transplant recipients: outcome comparison of therapy with amphotericin B lipid complex and a historical cohort treated with conventional amphotericin B. *Clin Infect Dis.* **37(1)**:17-25.
48. Maertens J, Raad I, Petrikkos G, *et al* (2004). Caspofungin Salvage Aspergillosis Study Group. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. *Clin Infect Dis.* **39(11)**:1563-71.
49. Marr KA, Boeckh M, Carter RA, Kim HW, Corey L (2004). Combination antifungal therapy for invasive aspergillosis. *Clin Infect Dis.* **39(6)**:797-802.
50. Singh N, Limaye AP, Forrest G, *et al* (2006). Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: a prospective, multicenter, observational study. *Transplantation.* **81(3)**:320-6.
51. Maertens J, Glasmacher A, Herbrecht R, *et al* (2006). Caspofungin Combination Therapy Study Group. Multicenter, noncomparative study of caspofungin in combination with other antifungals as salvage therapy in adults with invasive aspergillosis. *Cancer.* **107(12)**:2888-97.
52. Singh N, Pursell KJ (2008). Combination therapeutic approaches for the management of invasive aspergillosis in organ transplant recipients. *Mycoses.* **51(2)**:99-108.
53. Catalano L, Fontana R, Scarpato N, *et al* (1997). Combined

treatment with amphotericin-B and granulocyte transfusion from G-CSF-stimulated donors in an aplastic patient with invasive aspergillosis undergoing bone marrow transplantation. *Haematologica.* **82(1)**:71-2.

54. Habicht JM, Matt P, Passweg JR, *et al* (2001). Invasive pulmonary fungal infection in hematologic patients: is resection effective? *Hematol J.* **2(4)**:250-6.

55. Matt P, Bernet F, Habicht J, *et al* (2004). Predicting outcome after lung resection for invasive pulmonary aspergillosis in patients with neutropenia. *Chest.* **126(6)**:1783-8.