Correspondence

Ciprofloxacin-resistant *Salmonella typhi*

The incidence of multidrug-resistant *Salmonella typhi* is increasing in India.[1–3] Clinicians treat non-responsive patients with either fluoroquinolones or newer cephalosporins. Some patients also have a delayed response to ciprofloxacin despite the organism being sensitive to ciprofloxacin by the routine disk diffusion method. This prompted us to determine the minimum inhibitory concentration (MIC) of this drug to local isolates of *S. typhi.*

A total of 25 strains of *S. typhi,* isolated from the blood of patients with typhoid, were tested for their sensitivity to ciprofloxacin by the Kirby–Bauer disk diffusion method and the MIC was determined by the Agar dilution technique.[4] The interpretation was as described by Murphy *et al.*[5]

All isolates of *S. typhi* were sensitive to ciprofloxacin by the disk diffusion method. However, 18 of the 25 (72%) isolates were sensitive to ciprofloxacin (MIC ≤0.125 mg/L), 4 (16%) had reduced susceptibility (MIC ≥0.25 mg/L to ≤1 mg/L) and 3 had low level resistance (MIC 2 mg/L).

Thus, it is not possible to identify *S. typhi* with low level resistance by the disk diffusion method. Patients infected with such organisms may not respond to the usual dose of ciprofloxacin. Therefore, it is important to determine the level of resistance to ciprofloxacin in each strain of *S. typhi.*

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Nalidixic acid-resistant *Salmonella typhi* in Mumbai

We read with interest the article 'Changing pattern of antibiotic sensitivity of *Salmonella typhi*' by C. Ranju *et al.*[1]

However, in Mumbai, our observations have been different.[2,3] Over a 7-month period (May–November 1998), we isolated 55 strains of *S. typhi* at our centre. Thirty-seven of these were found to be resistant on screening with nalidixic acid (NARST—Nalidixic Acid Resistant *Salmonella typhi*). These patients had a protracted course with a mean fever clearance time of 8.2 days. In 2 patients the organism was grown after 96 hours of treatment with a fluoroquinolone. The minimum inhibitory concentration (MIC) to ciprofloxacin by the E. test (AB Biodisk, Solna, Sweden) in all 37 with NARST strain ranged from 0.38 mg/ml to 1 mg/ml. The 18 NASST (nalidixic acid sensitive *S. typhi*), on the other hand, showed a much lower MIC range (0.004–0.19 mg/ml) and were associated with a mean fever clearance of 5 days with no microbiological failures. Twenty-five of the 37 NARST strain showed a block resistance to ampicillin, co-trimoxazole and chloramphenicol. We did not find any resistance *in vitro* to second- and third-generation cephalosporins in any of the 55 strains.

Quinolone resistance in bacteria is associated with mutations of the target site DNA gyrase, most commonly in the quinolone resistance determining region (QRDR) of the A subunit.[4] We believe that screening for NARST with a 30 μg nalidixic acid disc is a reliable method for detecting clinical resistance to this group and is useful to decide treatment and predict outcome.

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Massive ovarian oedema

Massive ovarian oedema, first described by Gustafson *et al.*,[1] presents with chronic, intermittent, colicky lower abdominal pain. It is a benign condition (which can be easily mistaken for malignant ovarian disease) and does not require radical excisional surgery.

A 40-year-old multipara, whose last child-birth was 17 years ago, presented to us with a diagnosis of an ovarian cyst. Physical examination showed a normal sized, anteverted, mobile uterus with a palpable 5×5 cm, ill-defined, non-tender cystic mass in the left adnexal region. Per rectal examination was normal. Transabdominal ultrasonography showed a mass with homogeneous echogenicity, posterior to the uterus measuring 4.3×5.6 cm with minimal fluid in the cul-de-sac. A diagnosis of ovarian tumour was made.

At laparotomy, an oedematous jelly-like mass 10×10 cm was seen covering the uterus and adherent to its fundus. The mass had burrowed into the mesentery of the small bowel and colon, partially obliterating the cul-de-sac. There was no free fluid in the abdomen and the right fallopian tube and ovary were normal. The left fallopian tube was normal but the left ovary was incorporated in the mass. The mass was removed along with the left ovary to which it was adherent. On incising it was found that the mass was oedematous with gelatinous fluid oozing from the cut surface. A frozen section revealed stromal oedema with normal ovarian tissue and no evidence of malignancy. The uterus, other pelvic and abdominal organs were normal. Microscopic examination of the specimen showed ovarian tissue with diffuse stromal oedema. Numerous congested blood vessels were present. In some areas, extravasated red blood cells and mast cells were seen. The postoperative course was uneventful.

Massive ovarian oedema is the result of marked enlargement of one or both ovaries caused by accumulation of fluid in the stroma leading to separation of the normal follicular structures and stromal fibromatosis. It is thought to be a consequence of incomplete intermittent torsion of the ovarian pedicle.[2,3] It has been reported in patients between 6 and 33 years of age[4] with venous and lymphatic obstruction.[2] The common clinical presentation is chronic intermittent colicky pain, menstrual irregularity or abdominal distension with an adnexal mass. It usually affects one ovary, more often the right.[3] Partial torsion may be documented in about half the patients. Ultrasonography shows a solid ovarian mass, while gross examination shows oedematous tissue. Microscopically, the features are those of ovarian oedema and fibromatosis.[5,6]

Ovarian wedge resection, ovarian suspension and hormonal treatment with oral contraceptive pills have been tried.[3] The mainstay in the diagnosis is frozen section examination which reveals a benign pathology. Awareness of the condition avoids unnecessary radical surgery in young patients.

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Cancer survival estimation: The need to correct bias due to outcome-related follow up loss

Cancer survival estimation is important to assess the overall strength of cancer care, the efficacy of a given treatment, understand the biological behaviour of tumours and plan clinical research. There are a number of methods to estimate survival such as the actuarial method[1–3] and the product–limit (K–M) method.[4] These methods provide unbiased survival estimates, when there is complete follow up information of all patients till the end of the study. The reliability of the survival estimates depends to a large extent on the completeness of follow up.

A typical problem encountered in survival studies is the subjects who are lost during follow up (LFU). In India, survival data available from various cancer registries show a high proportion of such subjects.[5–8] There are numerous problems in obtaining follow up information of cancer patients. Few hospitals have an organized system for this. Further, most patients are unaware of the need for regular hospital visits, and there are logistic, economic and socio-demographic constraints. When the proportion of LFU is large and related to various known or unknown reasons associated with the outcome event, the standard methods for estimating survival rates do not apply. This is because LFU is assumed to occur at random, i.e. it is independent of the risk of death of the patient. We have previously published two methods demonstrating the magnitude of the bias due to outcome-related LFU in survival estimates and have proposed means to eliminate this. As both papers were published in journals not easily accessible to readers in India, we have briefly outlined these in this communication.

In 1995, Ganesh[7] proposed two approaches for computing loss-adjusted survival rates (LAR). In both approaches, LFU and regularly followed up patients were stratified by prognostic factors. The expected number of deaths in the latter group in each stratum were estimated and based on these, the number of probable deaths in the corresponding stratum of the LFU group was obtained. In the first approach, LAR was estimated by stratifying the total observations studied with respect to the prognostic factors, namely age, stage, residence and treatment received. The second approach used the logistic regression model taking into consideration the same factors simultaneously. In both these, the survival rates were estimated using the actuarial method.[2] The methodology was illustrated using a cohort of 336 breast cancer patients treated at the Tata Memorial Hospital, Mumbai in 1985 and followed up for 3 years. The proportion of LFU subjects during this period was 23.8%.

The 3-year LAR adjusted for age, stage, place of residence and treatment of breast cancer patients was 56% by the stratified method and 54% by the regression method. The corresponding rate by the actuarial method unadjusted for the same factors was 61%. The two proposed approaches yielded a decrease of 4.7% and 6.7%, respectively (Table I) in the survival rates compared to actuarial-unadjusted rates. The magnitude and direction of the estimated bias was dependent on the prognostic factors of the patient group.

In 1996, Mathew[8] proposed another method to estimate LAR. The probability of death of LFU patients was estimated by a multivariate logistic regression model of patients with regular follow up. The statistically significant factors in the model were stage of disease, response to treatment and patient status at last follow up. The LAR was estimated using the Kaplan–Meier method.[4] The methodology was illustrated in a cohort of 208 ovarian cancer patients treated at the Regional Cancer Centre, Thiruvananthapuram from 1989 to 1991 and followed up till the end of 1993. The proportion of LFU patients during the 5-year period (1989–93) was 51%. The follow up information was updated by postal enquiry. The 5-year survival rate calculated by direct application of the Kaplan–Meier method under the assumption that all LFUs occurred at random was 75%. The follow up rate for the same group was improved to 63% through the simple and cost-effective method of postal enquiry. Incorporation of this information in the follow up data revised the 5-year survival estimate to 55%. The 5-year LAR estimated through the model-based probability approach was 43%. The comparison of the rates computed based on LAR and by the standard assumption for LFU revealed that LAR reduced overestimation of the true survival rate by 32% (Fig. 1).

The bias due to LFU also caused underestimation of the true survival rates. Ganesh[7] showed that LAR provided a higher survival estimate for stage I breast cancer patients as compared to the rate calculated under the normal assumption for LFU.

These two studies clearly show that LFU had an important effect on the survival estimation. While there is no doubt that LFU should be kept at its minimum and simple methods such as postal enquiry should be used to improve follow up; in situations where follow up is poor, it would not be appropriate to use standard methods for survival estimation. The use of LAR in these circumstances provides a less biased survival and more authentic survival estimate. This should be borne in mind by clinicians and researchers carrying out survival studies, particularly when the end-point of the study is survival.

TABLE I. Survival estimation by different methods[8]

Method	Survival rate (%)		
	1-year	2-year	3-year
Actuarial-unadjusted	90	74	61
LAR* by stratification	88	70	56
LAR* by regression	86	67	54

* Loss-adjusted rates adjusted for age, stage, place of residence and treatment

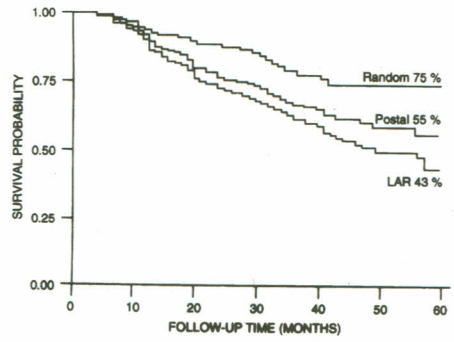

FIG 1. Cumulative survival (%) of 208 ovarian cancer patients based on random loss, postal enquiry update and LAR.
Random: survival rates based on assumption of all LFU patients occurring at random
Postal: survival rates based on improved follow up of LFU patients through postal enquiry LAR: loss-adjusted rate by model-based probability approach

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A methodology for applied medical research

In India, many institutions have well-equipped investigative research laboratories and other infrastructure which can be used for medical research. The institutions under the Indian Council for Agricultural Research are an example. They are mostly located in rural Indian townships with meagre medical facilities. However, they are equipped with modern scientific infrastructure in disciplines such as biochemistry, pathology, microbiology and molecular biology. Tissue culture and biotechnology laboratories, electron microscopes, flow photocytometer and deep freezer are among the advanced facilities available in these institutes. These institutions have a perfect network of lending and borrowing these facilities.

This infrastructure can be made use of for advanced medical research such as developing a human melanocyte culture system, standardization of herbal formulations of indigenous and tribal medicines, chromosomal studies of human genetic diseases, periodical sensitivity testing for *Neisseria gonorrhoeae,* etc. In some cases, a little upgradation may be required to suit the needs of medical research. This multifaceted utilization of laboratory infrastructure would facilitate research outside the existing medical institutions in India and may nourish original research. An 'amateur researcher' based in a rural area is likely to be guided by and to take up need-based applied research rather than trying to solve a theoretical problem. More important, multifaceted utilization provides scope for the given institution to save funds in infrastructural investment, and avoid unnecessary duplication of modern laboratory facilities.

Integration, collaboration, sharing and application of knowledge, technology and infrastructure between the national laboratories, universities and industry through a networking system is wonderful to imagine but difficult to implement. To achieve this, scientific institutions in the country should be freed from stifling bureaucratic controls, accompanied by a radical change in the mind-set of science administrators. The whole scientific community should break away from trodden and established paths in order to select specific areas of research where we could make effective global contributions. Since autonomy is not known to exist in most of these research institutions, people at the helm of affairs need to be convinced about the benefits of this method.

Patient advocacy groups, comprising people from all walks of life who can communicate with and influence the media, policy-makers, bureaucrats, governmental and non-governmental funding agencies should be formed for this purpose. They can help to create this kind of an enabling environment for science to flourish. These groups could also canvas for funds and create public opinion to support need-based research.

A multidisciplinary approach to research with this methodology can inspire fresh thinking and action, and may foster new discoveries.

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Food poisoning due to organophosphorus compounds

Food poisoning is frequently due to infection. We recently encountered a family with food poisoning secondary to the ingestion of an organophosphorous compound.

Four members of a family from a nearby village were admitted to our intensive care unit with complaints of abdominal pain, vomiting and loose stools within one hour of consumption of freshly cooked food at home. The food consumed contained pulses and *bhakar* (a kind of bread made of *jawar*). The women who had prepared the food had not consumed *bhakar* and did not have any problems. All those afflicted were taken to a primary health centre and given intravenous fluids and antibiotics but their condition deteriorated and they were referred to our institute.

The most severe manifestations were seen in a young male aged 30 years who had consumed two-and-a-half *bhakars*. He had persistent vomiting, diarrhoea, altered sensorium and excessive salivation. His pulse rate was 60 per minute and he was hypotensive. Both pupils were pinpoint but eye movements were normal. He also had one episode of tonic–clonic seizures which was controlled with injectable diazepam. The biochemical analysis was normal and electrocardiogram showed bradycardia.

The second family member afflicted was an elderly woman who had consumed one *bhakar* and complained of abdominal pain, diarrhoea and vomiting. She had bradycardia and hypotension along with pinpoint pupils. She had normal eye movements but occasional ectopic beats and twitching of her arms and chest muscles. Biochemical investigations were normal but the electrocardiogram showed occasional supraventricular ectopics. The third family member was an elderly male who had consumed one *bhakar* and had vomiting and diarrhoea. He had pinpoint pupils and bradycardia but no hypotension. The fourth was a young girl who had consumed one-and-a-half *bhakars* and had vomiting but no diarrhoea. She complained of abdominal pain and developed atrial fibrillation. She too had pinpoint pupils. The only other family member who had consumed stale food but no *bhakar* was healthy. All the afflicted family members had pinpoint pupils and bradycardia. These findings could not be explained on the basis of infectious food poisoning. Botulism was considered as a differential diagnosis. However, the pupils should have been dilated and eye movements affected by the toxin.[1] Therefore, we suspected accidental organophosphorus poisoning and contacted the Poison Information Cell located at the All India Institute of Medical Sciences, New Delhi by telephone. Based on the available information they agreed with our provisional diagnosis.

The gastric aspirate was sent for toxicological examination. All the patients were started on treatment for organophosphorus poisoning with PAM and atropine. After about 12 hours, all of them improved with complete resolution of symptoms. None of them developed the intermediate syndrome and were discharged after 72 hours. The results from the toxicology laboratory revealed the presence of an organophosphorus compound in the gastric aspirate.

On detailed questioning, we found that *jawar* was stored in jute bags in the same room where pesticides were stored. Accidental spillage of the pesticide might have been responsible for contamination of *jawar*. We were unable to obtain samples of *jawar* or the flour used to cook *bhakar* to look for presence of the poison.

The widespread use of organophosphorus compounds as pesticides have led to their easy availability. They are thus misused with suicidal and homicidal intent. The World Health Organization has reported one million accidental and two million suicidal attempts using these compounds.[2]

Accidental poisoning is usually due to exposure to pesticide during spraying in the fields and accidental inhalation or contact with skin. Accidental consumption is rare. Choudhary *et al.* reported a food-borne outbreak of organophosphorus poisoning recently.[3]

Since these compounds remain on the surface for a long time and degenerate slowly, food poisoning is possible if the contaminated foodstuff is eaten without proper washing or soon after spraying. Lack of awareness regarding the handling, storage and precautions to be taken while using such compounds results in accidents of this nature. We feel that companies marketing these compounds must provide information to consumers of the hazardous nature of these compounds as well as guidelines for their safe storage.

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