INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory illness with prevalence of approximately 0.75% in India. It leads to irreversible joint damage and systemic complications. It is associated with substantial morbidity and increased mortality. Patients with active RA suffer from significant decline in functional capacity. As many as 40% become work disabled within 5 years from onset of symptoms. Direct and indirect costs are also enormous.

Until recently, the highly unsatisfactory ‘pyramidal approach’ (‘go slow, go low’) was widely followed for management of patients with early RA. This approach has now become obsolete because it is proven that irreversible joint damage occurs very early in the course of RA. Further, early treatment with disease modifying anti-rheumatic drug therapy (DMARD) improves both short and long-term clinical, radiological, and functional outcomes. Delay of as little as eight or nine months in starting a DMARD can have significant adverse impact on long term outcome. Lastly, DMARD therapy is no more toxic than NSAID therapy, and benefits of DMARD therapy far outweigh the risks.

There is a ‘window of opportunity’ early in the course of RA, during which period the bulk of disease is caused by medically treatable active inflammation. Effective treatment during this phase gives the best opportunity to prevent any damage, and achieve the most optimal long-term outcome. Current best practice is, therefore, to commence DMARD therapy as soon as diagnosis of RA or ‘RA like polyarthritis’ (see below) is made.

EARLY DIAGNOSIS OF RA

To implement early treatment for all patients with RA, early diagnosis is vital. Diagnosis of RA can be delayed if features such as elevated inflammatory markers, radiographic erosions, subcutaneous nodules and positive rheumatoid factor (RF) are sought. More than 60% of patients with early RA have normal inflammatory markers, 70% do not display radiographic erosions, and 60% are seronegative for RF at the time of presentation. In the absence of these ‘hard’ diagnostic features during the early phase of disease, differential diagnosis becomes broader. In particular, patients with self-limiting arthritides such as post viral arthritis could present with polyarthritis, and mimic presentation of early RA. The American College of Rheumatology (ACR) has proposed classification criteria for RA incorporating these features but these criteria do not perform well in patients with early disease.

To overcome this difficulty for RA should be suspected in any patient who has had persistent polyarthritis, especially affecting small joints of hands and feet, for at least 12 weeks provided that other causes for similar presentation such as reactive arthritis, osteoarthritis, tuberculous arthritis, rheumatic fever or systemic lupus erythematosus have been excluded. RF predicts persistence and its presence (especially in high titre of > 50 U/ml) strengthens the diagnosis further.

Cyclic citrullinated peptide (CCP) antibody
precedes clinical symptoms of RA by many years, and predicts persistence as well as likelihood of developing radiographic erosions in patients with early, undifferentiated inflammatory arthritis. Testing for CCP antibodies is especially valuable in patients with negative RF. CCP antibodies predict persistence with high specificity of around 96%. Additional presence of RF increases specificity for diagnosis of RA to 100%. Thus, diagnosis of RA can be made earlier than 12 weeks in the presence of both these antibodies but sensitivity is only in the region of 60%.

**Management of Patients With Early Undifferentiated Inflammatory Arthritis**

Patients with early, undifferentiated inflammatory arthritis (symptom duration < 12 weeks) could remit spontaneously, remain undifferentiated, or differentiate into RA or another form of inflammatory arthritis. Obviously, diagnostic label of ‘RA’ and potentially toxic DMARD therapy are inappropriate for patients whose disease is likely to remit spontaneously.

Administration of single intramuscular injection of 120 mg of methylprednisolone or its equivalent (80 mg, if under 60 kg in weight) has been suggested as a useful approach to induce remission in this cohort of patients. Alternatively, intraarticular corticosteroids are preferable for patients with involvement of fewer joints. Failure to remit, and persistence of inflammatory joint symptoms at 12 weeks helps to differentiate RA from non-RA. This approach is currently being tested in a placebo-controlled randomised trial in Europe (SAVE, Stop Arthritis Very Early).

**Management of Patients With Persistent Inflammatory Arthritis**

All patients with persistent inflammatory arthritis (symptom duration ≥ 12 weeks) would benefit from DMARD therapy. Many patients have to be commenced on DMARD therapy even before a definite diagnosis of RA can be made (‘RA like polyarthritis’), and on the assumption that they would evolve into RA at a later date. Wherever possible, all patients with persistent arthritis should be referred to the specialist, as outcome of patients with RA managed by specialists is better than that of patients managed by non-specialists.

Common DMARDs used initially in patients with early RA include methotrexate, sulphasalazine and leflunomide. Methotrexate has higher retention rate than other DMARDs. Methotrexate is also as effective as anti-TNF monotherapy in early RA, and thus, a reasonable first choice. Hydroxychloroquine is an option for patients who refuse blood monitoring.

Pre-DMARD treatment checks

Patient education before commencing DMARD therapy is crucial. All patients should be counselled on side effects of DMARD therapy in some detail, and preferably be provided with written information. This should be reinforced during follow-up consultations as well. It is important for patients to clearly understand that

- DMARDs are not symptom relieving drugs
- It could take about 2-4 months for the DMARD to take effect
- Once commenced, DMARD therapy should be continued indefinitely even with disease remission (unless ineffective or toxic).

Complete blood counts (CBC), liver and renal function tests should be checked in all patients before commencing a DMARD. Chest X-ray serves as baseline, and also helps to detect past or present evidence of tuberculosis. For patients commencing methotrexate, excess alcohol consumption should be discouraged for fear of hepatotoxicity (up to 10 units/week permitted, but lesser the better). For patients commencing hydroxychloroquine, screening for visual acuity is mandatory.

Women in their reproductive years, who are not sterilised but sexually active, should follow a reliable method of contraception before commencing teratogenic drugs like methotrexate or leflunomide. No specific precautions are required with sulphasalazine except for folic acid supplementation before conception. Women who wish to get pregnant and men who wish to father a child should discontinue treatment with methotrexate for at least three months beforehand. Those patients on leflunomide should receive washout with 8 gm of activated charcoal four times daily for 11 days or 50 gm of activated charcoal four times daily for 11 days (without this drug clearance procedure, it could take up to 2 years for leflunomide metabolite to reach safe levels). Ideally, blood levels of leflunomide metabolite should be checked before allowing pregnancy but this test is not widely available.

**General guidance on monitoring of adverse events with DMARD therapy**

- CBC and liver enzymes should be checked regularly (Table 1). Monitoring frequency should be temporarily increased whenever dosage of DMARD is increased. In uncompliant patients, it is best not to commence DMARD therapy.
- It is important to watch for abnormal trends (e.g. gradual drop in white cell count or gradual rise in ALT) when it may be necessary to reduce dose of DMARD.
- Treatment should be withdrawn if patient develops leucopenia (< 4 X10⁹/L), neutropenia (< 1.5 X10⁹/L), thrombocytopenia (< 150 X10⁹/L), or elevation of liver enzymes to three times the upper limit of
normal. It may be possible to reintroduce treatment with the same DMARD in some patients, once blood counts pick up or liver function improves.

- In the event of allergic skin rash or pruritis (more common with sulphasalazine), treatment should be discontinued permanently.

- Patients on methotrexate complaining of persistent cough or breathlessness should have a chest X-ray ± pulmonary function studies. If methotrexate pneumonitis is diagnosed, the patient should never be re-challenged with methotrexate.

- If patients develop gastrointestinal side effects, it should be possible in most instances to continue treatment at a lower dose, or offer appropriate symptomatic treatment in addition. Those patients on methotrexate could try increasing dose of folic acid up to 3-6 times/week (avoiding the day when methotrexate is administered).

- Patients receiving hydroxychloroquine should discontinue treatment in the event of visual symptoms such as blurring or difficulty in focussing, and seek advice from optician.

**Monitoring Disease Control and Making Treatment Adjustments**

All patients on DMARD should be monitored at regular intervals to measure treatment effects by means of swollen and tender joint counts, duration of early morning stiffness, functional ability, acute phase response (anaemia, ESR, CRP), and radiographic progression. It is useful to calculate the DAS (Disease Activity score), which is a composite score incorporating swollen and tender joint score, patient’s global assessment of health, and ESR. A score of > 5.1 implies high disease activity, while score of < 2.6 implies minimal disease activity. Although DAS was mainly introduced for use in research settings, many clinicians also use it for daily clinical practice (refer to website www.das-score.nl for details and DAS calculator).

Sub-optimal disease control needs intensification of treatment. One approach would be to commence patients on oral methotrexate along with regular intramuscular corticosteroids as ‘bridging therapy’ (see later) and/or local corticosteroid injections for inflamed joints. Failure to achieve remission with this strategy should lead to rapid escalation of methotrexate doses until a dose of 20-25 mg/week is reached. If disease control is still sub-optimal, the next step would be to switch to parenteral methotrexate because bioavailability with parenteral route is close to 100%, and then to consider addition of sulphasalazine and hydroxychloroquine (‘triple therapy’), leflunomide or anti-TNF treatment.

**Role Of Combination DMARD Therapy**

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**Table 1: Common disease modifying drugs used to treat early rheumatoid arthritis**

<table>
<thead>
<tr>
<th>DMARD</th>
<th>Dose</th>
<th>Side effects</th>
<th>Monitoring requirements</th>
</tr>
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<tbody>
<tr>
<td>Sulphasalazine</td>
<td>500 mg once daily, increasing by 500 mg</td>
<td>Gastrointestinal including nausea and vomiting, allergic skin rashes,</td>
<td>Full blood count and liver function tests monthly for first three months, then three</td>
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<tr>
<td></td>
<td>every week until dose up to 2 gm/day.</td>
<td>discolouration of body fluids, reversible reduction in sperm count, bone</td>
<td>monthly thereafter. After two years, monitoring frequency could be reduced to 6-12</td>
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<tr>
<td></td>
<td>If patients with sub-optimal response,</td>
<td>marrow and liver toxicity.</td>
<td>monthly.</td>
</tr>
<tr>
<td></td>
<td>dose could be increased to maximum of</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 mg/kg/day.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Initially 7.5 to 10 mg once weekly,</td>
<td>Gastrointestinal including mouth ulcers, nausea and vomiting, bone marrow</td>
<td>Full blood count and liver function tests fortnightly for first three months, then</td>
</tr>
<tr>
<td></td>
<td>gradually increased by 2.5 to 5 mg every</td>
<td>and liver toxicity, teratogenicity, and pulmonary toxicity (‘methotrexate</td>
<td>monthly thereafter. Also periodically check blood pressure and renal function. Once</td>
</tr>
<tr>
<td></td>
<td>2-4 weeks until dose up to 15 to 20</td>
<td>pneumonitis’).</td>
<td>dose is stabilised, monitoring frequency could be reduced to two-monthly.</td>
</tr>
<tr>
<td></td>
<td>mg/week. If 20 mg is ineffective, parenteral route should be tried.</td>
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<tr>
<td></td>
<td>All patients should receive in addition, 5 mg of folic acid on the day after methotrexate to reduce gastrointestinal and bone marrow toxicity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leflunomide</td>
<td>10-20 mg/day (loading dose not preferred due to increased chance of toxicity)</td>
<td>Gastrointestinal including diarrhoea, nausea and vomiting, bone marrow and</td>
<td>Full blood count and liver function tests fortnightly for first three months, then</td>
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<tr>
<td></td>
<td></td>
<td>liver toxicity, hypertension, teratogenicity.</td>
<td>monthly thereafter. Also periodically check blood pressure and renal function. Once</td>
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<td></td>
<td>dose is stabilised, monitoring frequency could be reduced to two-monthly.</td>
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<tr>
<td>Hydroxychloroquine</td>
<td>200-400 mg/day (maximum 6.5 mg/kg/day)</td>
<td>Retinal toxicity (dose related), gastrointestinal including nausea and</td>
<td>Check visual acuity at least once every year with optician</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vomiting, headache and allergic reactions.</td>
<td></td>
</tr>
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</table>

For more detailed guidance on practical aspects of DMARD therapy, the reader is advised to consult reference 36.
Several studies in early RA have shown that combination therapy is better than monotherapy in improving short and long-term clinical, radiographic and functional outcome.\(^3\) Importantly, some trials have shown that even if combination therapy were to be used only for a short duration during early phase of the disease, joint damage is retarded for many years.\(^5\)\(^,\)\(^6\)

There are different combination treatment strategies. In the ‘step-down’ approach, the most aggressive treatment is offered at the early stage when the patient is most likely to respond to medical treatment. Once remission is achieved, individual drugs in the combination are withdrawn, and the patient is left on a maintenance agent. In the ‘step-up’ regime, aggressive therapy is offered only for those patients not responding to single DMARD therapy. Outcome is better with ‘step-down’ than with ‘step-up’ or sequential strategies. Of note, most successful ‘step-down’ combinations employed either anti-TNF or corticosteroids.

Even so, it remains unclear if combination therapy should be tried at the outset in all patients with early RA because the type of patient who would benefit most is still unknown.\(^4\)\(^8\) There is some evidence that combination therapy is more appropriate for patients with poor prognosis\(^7\) but we currently do not have a validated bedside model to differentiate patients with benign outcome from those who are likely to have a worse outcome. Until answers to these questions are clarified, there is no role for routine use of combination DMARD therapy in all patients with early RA.\(^4\)\(^8\) Recent guidelines have suggested that ‘initial DMARD monotherapy would be a reasonable course of action’.\(^3\)\(^5\)

**ROLE OF BIOLOGICAL THERAPY**

There has been increased interest with use of anti-TNF drugs for patients with early RA. Some trials have shown better clinical and radiographic outcome (including halting of radiographic progression) with the combination of anti-TNF drug and methotrexate compared to methotrexate or anti-TNF monotherapy.\(^3\)\(^,\)\(^3\)\(^4\)\(^1\)\(^1\)\(^2\) Recent evidence also suggests that it is possible to maintain disease control for as long as a year after withdrawal of infliximab, following initial combination therapy with infliximab and methotrexate.\(^4\)\(^7\)\(^,\)\(^4\)\(^9\)

It has, therefore, been proposed that anti-TNF drugs could be used as part of combination therapy, say for the first few months, for remission induction.\(^5\)\(^0\) Drugs like methotrexate could then be used for maintenance of remission. Although this idea seems sound, it is quite possible that many patients would not be able to come off anti-TNF therapy due to flare of disease. Also, the high cost of anti-TNF drugs would preclude its use in all patients with early RA, even if it were to be used only for a short duration. At the present moment, the use of anti-TNF drugs for early RA is, therefore, still limited to research studies.

### TREATMENTS USED FOR SYMPTOM CONTROL

All patients with RA should receive adequate symptom relieving treatments. Common symptoms include pain, stiffness and swelling affecting multiple joints, usually associated with loss of function, fatigue and poor sleep. Patients commonly suffer from secondary depression, fibromyalgia or anaemia, and it is important to determine their contribution to overall presentation.

**Non-steroidal anti-inflammatory drugs (NSAID)**

NSAID therapy should be considered for patients with symptoms of active inflammatory arthritis. However, benefits should be carefully weighed against risks.\(^3\)\(^1\) Increased incidence of thrombotic events, myocardial infarction and stroke with use of selective cyclooxygenase-2 inhibitors (coxibs) has been proven.\(^5\)\(^2\) This risk may also extend to non-selective cyclo-oxygenase inhibitors such as diclofenac and ibuprofen.\(^3\)\(^9\)

Current recommendations are as follows:

- Any NSAID should be used in the lowest possible dose for the shortest possible duration.
- All coxibs are contraindicated in patients with ischemic heart disease or stroke.
- Caution is required in patients with cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia and smoking history.
- In patients with both gastrointestinal and cardiovascular risk factors, it is preferable to use non-selective NSAID with proton pump inhibitor than a coxib.

NSAID are also not ideal in the presence of other risk factors such as old age (> 65 years), renal impairment, peptic ulcer disease, concomitant anticoagulant therapy, congestive heart failure, hypertension, asthma, pregnancy and breast-feeding.

**Simple analgesics**

As far as possible, simple analgesics such as paracetamol or codeine preparations should be used in preference to NSAID to control pain.

**Intraarticular corticosteroids**

When only few joints are inflamed, it is preferable to inject corticosteroids intraarticularly. It avoids systemic side effects, suppresses synovitis, and prevents development of erosions in early RA.\(^3\)\(^4\) Local injections of corticosteroids are useful for patients with carpal tunnel syndrome (if unresponsive to wrist splints), trigger finger, tenosynovitis or rotator cuff tendinitis.

Important contraindications for local steroid injection therapy include suspected septic arthritis, bleeding diathesis, and presence of prosthetic joint. Complications are few, and include introduction of infection (1:15,000), trauma to nearby nerves and vessels,
brief flare of synovitis due to presence of crystals in the
corticosteroid preparation, skin and subcutaneous tissue
atrophy (with superficial injections), and tendon rupture
(when injecting for tenosynovitis). When multiple joints
are injected, blood pressure and glycemic control could
be disturbed briefly.

It is generally not a good idea to inject more than
three joints in one sitting, and to inject the same joint
more than three or four times/year.

**Systemic corticosteroids**

Systemic corticosteroids are often used as 'bridging
therapy' (during the lag time that it takes for DMARD
therapy to take effect) to control disease activity
especially for patients with active disease in multiple
joints.\(^{55}\) Corticosteroids are very effective in rapidly
controlling inflammatory joint symptoms, and
improving mobility and function. Both high (initial
dose of 60 mg of prednisolone/day)\(^{42}\) as well as low
doses (7.5 mg of prednisolone/day)\(^{56}\) have been shown
to retard radiographic progression. Corticosteroids
are also effective in patients with extraarticular
manifestations.

Corticosteroids are not ideal for long-term use
because of their well-known side effect profile. Hence,
the use of corticosteroids should be limited to the short-
term. If long-term use is unavoidable, all patients should
receive adequate prophylaxis against steroid induced
osteoporosis.\(^{57}\) It would be prudent to obtain chest X-ray
before corticosteroid therapy is commenced, to detect
evidence of old or active tuberculosis.

Corticosteroids should always preferably be used
with a DMARD (except in the very elderly), in pregnant
patients (use < 10 mg/day), those in whom DMARD
therapy is likely to be associated with significant risks
(e.g. alcoholic patients, those with liver disease or severe
renal failure), and those in whom DMARD monitoring
is likely to be difficult.

Corticosteroids can be administered as:

- Methylprednisolone in a dose of 80-120 mg,
intramuscularly, every 4 weeks for the first 2-4
months (the usual time that it takes for DMARD to
take effect). It could also be used during periods of
high disease activity.
- Oral prednisolone, beginning with < 10-15 mg/day
and gradually tapering over several months.
- Intravenous methylprednisolone pulses,
especially if unresponsive to oral or intramuscular
corticosteroids. Up to 1000 mg is administered
with each pulse, given on alternate days up to three
pulses.

**Other drugs**

Many patients complain of poor sleep pattern,
excessive daytime tiredness, widespread body pain
that is out of proportion to joint inflammation
('fibromyalgia'), and symptoms of depression. These
symptoms need to be addressed with appropriate
therapy including low dose tricyclic anti-depressants to
improve sleep, selective serotonin reuptake inhibitors,
graded exercise program and sometimes, cognitive
behavioural therapy. In such patients, it is important
not to escalate DMARD therapy in the absence of active
ongoing inflammation.

**Benefits of Multidisciplinary Team Approach**

For patients with early RA, input of physiotherapists
and occupational therapists is particularly helpful.\(^{58,59}\)
Occupational therapists provide advice on joint
protection techniques, assistive devices, and modification
of home and work environment. They also provide
splints, disease education, and psychological support
to help the patient cope with the illness.

Physiotherapists teach exercises to maintain or
improve range of movement in joints, as well as aerobic
conditioning exercises to improve general fitness, reduce
fatigue and improve sleep. They also provide treatments
like heat/cold, laser, diathermy, ultrasound, TENS,
acupuncture, hydrotherapy, and balneotherapy (bathing
in thermal or mineral waters).

Most patients with early RA suffer with foot
problems, and it is useful to obtain advice from a
podiatrist or orthotist. In particular, many patients
benefit from modification of footwear, and placement
of appropriate insoles.

**Role of Complementary and Alternative Medicine**

Because conventional drug treatments for chronic
diseases such as RA often fail to achieve remission,
and induce side effects, many patients turn towards
complementary and alternative medicine (CAM),
especially as they are generally perceived to be safe.\(^{60,61}\)
Many patients are likely to continue with conventional
treatments as well, and it is important for the practitioner
to be aware of any potential drug interactions. Some
patients try to discontinue conventional treatments, and
it is important to emphasise to them that CAM should
not replace conventional treatments.

There is some evidence for gamma linolenic acid
(GLA, present in evening primrose oil) in improving pain
and stiffness in RA.\(^{62}\) But for most other CAM modalities
including Ayurveda, Homeopathy, acupuncture, Indian
oil massage, reflexology, yoga, copper bracelets, magnets,
glucosamine and chondroitin, vitamins, minerals, and
herbs, it is hard to offer proper evidence-based advice.
Some modalities such as yoga, meditation, reflexology
and oil massage do promote relaxation, and therefore,
make patients feel symptomatically better.\(^{31}\)

There is some evidence that a Mediterranean type diet
rich in fish, cooked vegetables and olive oil is beneficial for patients with RA. Fasting, vegetarian diets, elemental diet, and elimination of specific allergens have all been shown to be beneficial but they are difficult to sustain for too long. Fish oil supplementation has also been shown to be useful, and, has the added advantage of offering beneficial cardiovascular effects.

**Steps To Reduce Cardiovascular Risk**

Accelerated atherosclerosis is a leading cause of death among patients with RA, and arises due to multiple mechanisms including uncontrolled active inflammatory disease, therapy with corticosteroids and NSAID, and traditional risk factors such as smoking, hypertension, diabetes mellitus, dyslipidemia and obesity. The following steps should be taken to reduce cardiovascular morbidity and mortality:

- Inflammatory disease should be adequately controlled with DMARD therapy. There is some evidence that methotrexate is protective against cardiovascular mortality.
- Exposure to corticosteroids and NSAID should be minimised.
- Patients should be advised to quit smoking.
- Patients should be advised on healthy diet, exercise, and fish oil supplementation.
- Hypertension, diabetes mellitus and dyslipidemia should be appropriately controlled. Recent evidence suggests that statins might have beneficial effect on inflammatory process in addition to reducing cardiovascular risk.
- High index of suspicion for cardiac disease, and appropriate screening strategies are required, as incidence of silent ischaemia and sudden death among patients with RA is increased.

**Conclusion**

The saying, “we know all about rheumatoid arthritis except what causes it and how to treat it” may still be true, but the way we manage RA has vastly improved in the last decade. The aim of management has now moved from ‘retardation of disease progression’ to ‘total prevention of disability’. The pace at which research in early RA is currently progressing means that we would continue to see radical changes with therapeutic strategies in the coming years. Many more forms of targeted therapy are currently undergoing clinical trials, and likely to move from ‘the bench to the bedside’ in the near future.

However, the realistic goal of early management of RA could be achieved only with early patient presentation, and increased physician awareness. There are several other challenges that are more specific to under-developed and developing nations, including limited numbers of specialists with rheumatology training (especially in semi-urban and rural areas), lack of infrastructure in many places for holistic management with multi-disciplinary team approach, general neglect of rheumatology teaching in undergraduate curriculum, practical difficulties with patient education, patient non-compliance with conventional treatment, high prevalence of co-morbidity such as tuberculosis and malnutrition, problems with monitoring of adverse events secondary to DMARD therapy, and very high costs of biological therapy. All these difficulties would also need to be addressed in order to uplift care for our RA patients on par with developed nations.

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**Announcement**

**APICON 2008**

Website for APICON 2008 is www.apicon2008.org