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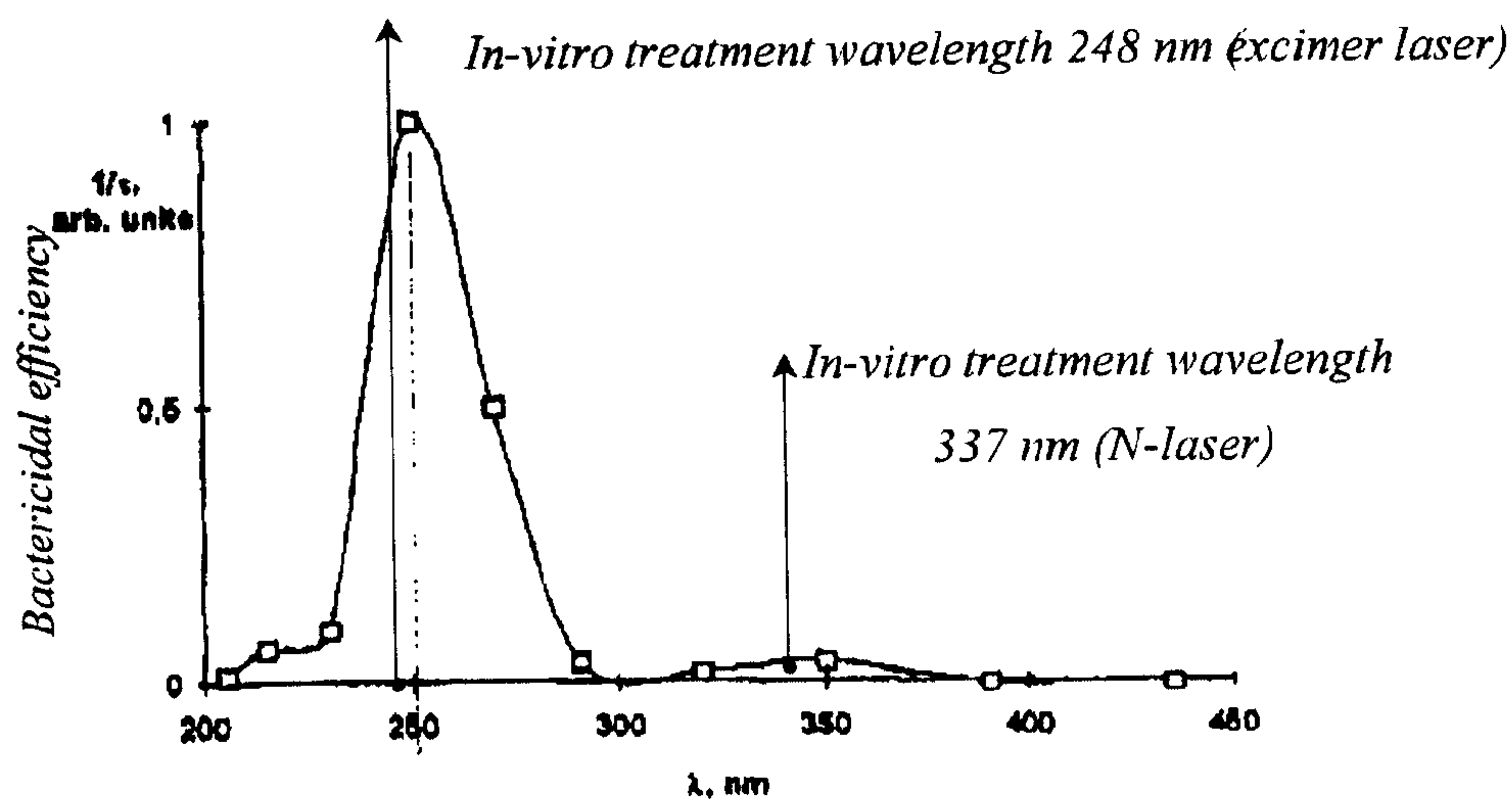
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(54) Titre : UNE METHODE ET UN DISPOSITIF LASER POUR LE TRAITEMENT D'INFECTIONS ENDOCAVITALES

(54) Title: A METHOD AND A LASER DEVICE FOR TREATMENT OF ENDO-CAVITAL INFECTIONS



Spectral peak of bactericidal efficiency for TB

(57) **Abrégé/Abstract:**

A method and an apparatus for the treatment of endo-cavital infections, particularly destructive bacterial infections and post major invasive surgery abscesses. A catheter system is used, which allows the simultaneous drainage of an endo-cavital space and irradiation of an infected locus with laser-generated pulsed ultraviolet light. The laser light wavelength is chosen so as to require radiation, which is lethal to the microorganisms causing the infection, at the lowest possible dose. Alternatively, a diode-pumped solid state Raman laser device is used which can be configured to provide in sequence a selected number of output wavelengths in the ultraviolet spectral range.

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Abstract of the Disclosure

A method and an apparatus for the treatment of endo-cavital infections, particularly destructive bacterial infections and post major invasive surgery abscesses. A catheter system is used, which allows the simultaneous drainage of an endo-cavital space and irradiation of an infected locus with laser-generated pulsed ultraviolet light. The laser light wavelength is chosen so as to require radiation, which is lethal to the microorganisms causing the infection, at the lowest possible dose. Alternatively, a diode-pumped solid state Raman laser device is used which can be configured to provide in sequence a selected number of output wavelengths in the ultraviolet spectral range.

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**A Method and a Laser Device for Treatment
of Endo-Cavital Infections.**

5 This invention relates to a method and an apparatus
for the treatment of endo-cavital infections, particularly,
abscesses such as cavernous tuberculosis, post-surgical intra-
abdominal abscesses and similar medical conditions. More
specifically, this invention relates to a system which allows
10 the simultaneous drainage of an endo-cavital space and
irradiation of an infected locus with laser-generated
ultraviolet light.

15 The use of ultraviolet light is a known and proven
technique in procedures for sterilising liquids and for
rendering drinking water safe for public consumption. For
these purposes, short wavelength, spectrally non-selective
ultraviolet light is used having a wavelength of from about
200nm to about 350nm. Within the so-called UV-C wave length
range (200-270nm), ultraviolet light is most effective in
20 destroying the microorganisms commonly found in untreated
water. Typical procedures are described by Dunn et al. in US
5,900,211; by Nesathurai in US 4,983,307; and by Wang et al. in
US 5,236,595.

25 It is generally accepted that microorganisms can be
broadly grouped into five basic families; these are bacteria,
viruses, fungi, protozoa and algae. These five families have
different properties, occur in different habitats and respond
differently to microbiocides such as antibiotics. Bacteria,
30 fungi, protozoa and algae are generally characterised as
comprising a cell wall, a cytoplasmic membrane and genetic
material which is essentially DNA material. Viruses are

somewhat different and generally have an outer coating of proteins surrounding genetic material which again is DNA material. When harsh ultraviolet light penetrates the microorganism, it causes disruption of chemical bonds within the DNA system thus preventing the DNA replication step required for reproduction of the microorganism. If a microorganism cannot reproduce itself, it is effectively dead.

However, the cells of different microorganisms are not the same: different microorganisms have different sensitivities to different wavelengths of light within the UV range; also the dose the UV light required to effect microorganism destruction varies for different microorganisms. The dose (or accumulated energy) is a product of the time for which the microorganism is exposed to the radiation, and the radiation power; most commonly, power is measured in Watts (W), and time is measured in seconds.

TABLE 1. Average lethal dose densities for different microorganisms (in mWsec/cm²) measured under a non-selective UV irradiation (a Xenon lamp with a UV band filter centered at 254 nm).

Microorganism	Dose/cm ²	Microorganism	Dose/cm ²
Bacillus anthracis	8.8	Dysentary bacilli	4.2
Shigella dysenteriae	4.3	Escherichia coli	7.0
Shigella flexneri	3.4	Streptococcus faecalis	10.0
Corynbacterium diphtheriae	6.5	Staphylococcus epidermis	5.8
Vibri commo (cholera)	6.5	Bacteriophage (E.coli)	6.5
Hepatitis	8.0	Salmonella	10.0
Influenza	6.6	Baker's yeast	8.8
Legionella pneumophilia	3.8	Mycobacterium tuberculosis	10.0
Salmonella paratyphi	6.1	Polio virus	7.0
Salmonella typhosa	7.0		

Table 1 shows that for different microorganisms, the measured lethal dose (in vitro) is not constant.

In addition to using UV light to sterilise fluids such as drinking water, lasers generating spectrally narrow-line light in ranges other than in the UV range have also had some use in medical therapy. In this context, it is relevant to distinguish between the use of non-UV lasers for surgical and other techniques and the use of UV light to treat microorganism infections. For example, in some therapeutic procedures, He-Ne or Nd-YAG lasers are used as localised heat sources, which stimulate blood supply and heat or destroy selected tissues; these laser radiation wavelengths are

generally in the red or near infrared ranges. Any microorganisms present will only be affected by the laser irradiation if the heat generated by the laser causes the temperature of the microorganism to reach or exceed about 40°C.

5 Although temperatures in this range are lethal to many microorganisms, the use of such lasers as a therapeutic tool to control microorganisms is circumscribed by the unacceptable damage this level of temperature can cause to surrounding tissues.

10 Treatments of destructive forms of endo-cavital infections, such as tuberculosis and post-surgical intra-abdominal abscesses, is a particularly difficult therapeutic area. The pathologically changed structures of cavital walls and substantial amounts of pus inside cavities prevent
15 efficient administration of antibiotics. Also, many pathogens causing endo-cavital infections have become antibiotic-resistant.

20 The procedures used at present to deal with endo-cavital infections are not as effective as is desired; a two step therapy is generally used. First, the cavity is drained to remove as much material as possible; this will include both cell debris due to the infection and to some extent the
25 microorganisms causing the infection. Second, an antibiotic medication is administered to the patient. If the antibiotic(s) are to be successful, maximal cavity drainage is essential. In order to achieve maximal drainage, a hollow catheter is inserted cutaneously into the cavity either blindly
30 or with guidance. Guidance is normally effected either by the use of an ultrasonic probe, or by the use of an endoscopic fiber-optic device included in the drainage catheter. But drainage is hampered by the flow characteristics of the fluid

and pus containing cell debris being removed from the cavity, and by the relatively small size of the catheter in comparison with the potential volume of the cavity requiring drainage. An additional problem is the unavoidable presence of
5 microorganisms both elsewhere in the cavity and on and around the catheter. As a consequence of these difficulties, in practice it is rarely possible to drain a cavity to the desirable level. It is also of importance that there is a real risk that some of the microorganisms are the so-called "super
10 bugs", which are mutant strains of common microorganisms such as staphylococcus resistant to the currently available antibiotics.

Endo-cavital infection-caused diseases, such as
15 destructive forms of tuberculosis and post-surgical intra-abdominal abscesses, present a rapidly growing concern internationally. In North America, post-surgical intra-abdominal abscesses are a major post-operative problem for a wide range of invasive surgical procedures. It has been
20 estimated that the percentage of patients, who develop post-surgical intra-abdominal abscesses, ranges from about 30% for colorectal surgery, through about 15% for pancreatic or biliary surgery to about 2% for gynecologic surgery. Patients
25 undergoing intra-abdominal surgery in North America alone, on an annual basis, number in the millions. These infections can be traced to several causes, including both airborne microorganisms and spontaneous leaks or perforations of either the biliary tract or the intestines. In other words, any
30 procedure devised to treat such infections has to accommodate the fact that the infection will almost certainly involve several strains of microorganisms; each strain will respond differently to any applied procedure.

It has been reported by Apollonov et al. in RU 2141859 (issued in 1998) that laser-generated ultraviolet light can be used in treating tuberculosis. By using a suitable fiber-optic catheter, the laser-generated UV light is used to irradiate and to destroy, within the lung cavern, the microorganisms, which are the cause of the tubercular infection. The method includes puncturing or draining the destructive cavern in the lungs, evacuating the purulent contents of the cavern and then exposing the interior surface of the cavern to ultraviolet laser radiation. This involves 10 to 12 minutes of exposure to the defocussed pulsed radiation of a solid-state laser at a wavelength from about 220nm to about 290nm, and energy density of 200 mWsec/cm² with the pulse repetition frequency controlled as a function of the degree of destruction in the lungs, to ensure irradiation with an average energy density of 10 to 15 mWsec/cm². A treatment session is concluded with a single introduction of 1.0 units of streptomycin or canamycin into the cavern. A course of treatment comprises 10 - 12 sessions of laser irradiation of the cavern.

However, there are several difficulties with the apparatus and the procedure described by Apollonov et al. These are as follows.

- (1) The need for repeated puncturing of the cavern, which increases the degree of trauma experienced by the patient.
- (2) Before the procedure is carried out, each repeated puncturing requires repeated radiological investigations, which increase the X-ray dose to which the patient is subjected.
- (3) Each treatment session is concluded with a single introduction into the cavern of a full daily dose of an anti-tubercular medication dissolved in 2 to 3 ml of a 0.5% Sol. Novocain. The introduction of a full daily dose of anti-

tubercular medication in a single dosage unit does not permit maintaining its bactericidal concentration within the cavern at a steady level throughout a period of 24 hours. In addition, because of the quantity involved, an introduction of such an amount of anti-tubercular medication at once frequently causes irritation of the mucous tissue of the bronchi draining the cavern, and this leads to a debilitating cough and expectoration in the sputum of a considerable quantity of the anti-tubercular medication that was introduced into the cavern; it also reduces the concentration of medication and lowers its bactericidal effect.

(4) To irradiate the cavern, Appolonov et al. used the emission of an available laser generating within the UV-C spectral range (266nm, the fourth harmonic of the Nd:YAG laser). While that wavelength is still capable of producing bactericidal effect on tuberculosis pathogens, it is apparently not optimal for destroying the majority of tuberculosis microorganisms. This relationship is shown graphically in Figure 1. Inspection of Figure 1 shows that the most efficient wavelength to kill tuberculosis bacteria is about 250nm, and that some UV wavelengths may not be efficient at all to treat tuberculosis. At the same time, other bacteria are more susceptible to the wavelengths efficient in the tuberculosis treatments. The use of a UV light wavelength which is not the most efficient wavelength, which is has specific value characteristic of each microorganism strain, or class of strains, means increased exposures, higher irradiation energy density and an increased risk of side effects.

Usually, patients to receive antibacterial treatment are already under a major stress, often with depressed immune systems after having undergone a major invasive surgical procedure, or suffering from a severe infection such as

tuberculosis or intra-abdominal abscess. Thus, it is very desirable that any treatment procedure to deal with such infections would expose the patient to as little further stress as possible. It is therefore a prime concern to avoid having to surgically re-enter the cavity. The traumatic levels associated with repeated cavity re-entry implies that the level of antibiotics required to control the so-called "super bugs" may be more than the weakened patient can tolerate.

This invention results from establishing the fact that the lethal dose required for a given microorganism depends on the wavelength of the irradiating ultraviolet light. By matching the wavelength of the UV light to a specific microorganism, or class of microorganisms, the lethal dose is optimized, the irradiation efficiency is increased and the risk of damaging surrounding tissues is minimized.

It was shown in the Table 1 above that the lethal doses of the UV light are not the same for different strains of microorganisms. The UV-irradiation used in the measurements summarized in Table 1 was spectrally non-selective. The results of treating (in vitro) different microorganisms with narrow band laser generated UV light, spectrally matching the most efficient bactericidal response (found by measuring curves for various bacteria similar to that of Fig. 1), are shown in Tables 2 and 3. The average lethal doses for different bacterial strains irradiated with narrow band laser light are substantially lower as compared to those shown in Table 1.

TABLE 2. Measured average lethal doses for different microorganisms (in mWsec) measured under specific laser-line irradiation

Cavern Area (cm ²)	LETHAL DOSE (mWsec)					
	Mico- bacterium tubercul- osis	St.Aureus	Klebsiella pneumonia	Entero- bacter aerogenes	Pseudomonas aeruginos	E.coli
28.3	45	85	141	198	141	141
50.3	80	151	251	352	251	251
78.5	126	236	393	550	393	393
113.1	181	339	565	792	565	565
153.9	246	462	770	1078	770	770
201.1	322	603	1005	1407	1005	1005
254.5	407	763	1272	1781	1272	1272
314.2	503	942	1571	2199	1571	1571
380.1	608	1140	1901	2661	1901	1901
452.4	724	1357	2262	3167	2262	2262
530.9	849	1593	2655	3717	2655	2655
615.8	985	1847	3079	4310	3079	3079
706.9	1131	2121	3534	4948	3534	3534

TABLE 3. Average lethal dose densities (dose/cm²) for different microorganisms measured under laser-line irradiation specific to each bacteria (based on the Table 2 data).

	AVERAGE LETHAL DOSE DENSITY (mWsec/cm ²)					
	Micro-organism					
	Mico- bacterium tuberculosi s	St.Aureu s	Klebsiella pneumonia	Entero- bacter aerogenes	Pseudomona s aeruginos	E.coli
Dose/ cm ²	1.6	3	5	7	5	5

Thus in a first broad embodiment this invention seeks to provide a method for treating endo-cavital infections comprising:

- (a) determining the spectrum of microorganisms present in the population of microorganisms in the cavity causing the infection;
- (b) determining a ranking of the relative amounts of at least the major infecting microorganisms within the population present in the cavity;
- (c) selecting an ultraviolet light wavelength at which the lethal dose in microwatt seconds/cm² is minimised for at least the highest ranking microorganism identified in step (b);
- (d) draining the infected cavity to remove debris contained therein;
- (e) irradiating the interior of the cavity with pulsed laser-generated ultraviolet light having a wavelength close to the wavelength selected in step (c); and
- (f) if required, repeating steps (d) and (e) until a desired level of microorganism destruction has been achieved.

In a second broad embodiment this invention seeks to provide an apparatus for treating an endo-cavital microorganism infection comprising in combination:

- (A) a catheter device constructed and arranged to be both insertable into and withdrawable from the cavity;
- (B) a laser generating device constructed and arranged to provide at least one output of pulsed ultraviolet light of known intensity and wavelength of from about 200nm to about 700nm; and

(C) a drainage system constructed and arranged to remove fluid debris from the cavity;

wherein:

5 (i) the catheter device includes at least one fibre optic guide constructed and arranged to deliver ultraviolet light generated by the laser device to a locus within the cavity; and

10 (ii) the laser generating device is chosen from the group consisting of a laser generating device constructed and arranged to provide a beam of ultraviolet light of a single predetermined wavelength and intensity, and a laser device
15 constructed and arranged to provide a plurality of beams of ultraviolet light each having a known wavelength and intensity.

Preferably the at least one fibre optic device constructed and arranged to provide a beam of ultraviolet light is a single use device.

20 Preferably, the laser generating device is a tunable Raman solid state laser. Conveniently, the laser generating device is a diode pumped tunable Raman solid state laser.

25 Preferably, the catheter device includes at least a fibre optic guide connectable to the laser and constructed and arranged to permit illumination of the cavity, and a separate pumpable drainage system.

30 Preferably, the catheter device additionally includes a second fibre optic system constructed to permit viewing of the interior of the cavity.

Alternatively, the catheter device also includes an ultrasonic probe system.

5 This invention derives from the discovery that, although it is known that broad spectrum ultraviolet light is lethal to a wide variety of known microorganisms, including viruses which are extremely resistant to antibiotics, hitherto it had not been fully understood that there is a "best" frequency for each microorganism at which ultraviolet light is most lethal to that microorganism. This permits the use of the lowest dose, in microwatts/cm², to kill a given microorganism. But this also raises a difficulty, which is that laser generating devices provide a laser beam with only a very narrow wavelength range: a laser provides an essentially monochromatic beam. It then follows that if a laser device is used, although such a device may be tunable to some extent to provide a wavelength either at, or at least close to, the desired most lethal wavelength, it will only provide one wavelength which will be most lethal for only one microorganism (or a group of closely similar microorganisms). But as noted above, in the typical case of major invasive abdominal surgery the infections are caused by more than one microorganism, typically a spectrum of microorganisms is present in the population of microorganisms in the cavity and the population as a whole is causing the infection. To deal with such a broad spectrum of microorganisms a plurality of laser devices will be required.

30 An alternative laser source has recently become available which overcomes these difficulties. This is the so-called diode pumped-solid state Raman laser. These are compact solid state devices which operate at a high repetition rate and can be configured to provide more than one output frequency by interposing in sequence different Raman materials into the

pulsed laser beam. These devices also operate reliably at high pulse repetition rates of the order of 0.2kHz. It is thus now possible to obtain what is effectively a tunable laser device which can be tuned to be most lethal to more than one of the microorganisms causing an infection in a bodily cavity either after major invasive surgery, or due to other causes, for example an inner ear infection. Laser devices of this type are available from Passat Ltd, Toronto, Ontario, Canada. A typical device can provide up to nine different wavelengths adjusted to the needed wavelength within the range of from about 200nm to about 1200nm. These devices are small, compact, require no dangerous gases, and are well adapted to use in a medical facility

The method provided by this invention requires as a first step an assessment of the microorganisms in a given population to identify both the members of the population and to rank them as a proportion of the population. It is then possible to assess the most lethal wavelength for each of the microorganisms, for example by means of tests carried out on microorganism samples from one of the available collections. A data bank can then be developed which will cross reference each microorganism to the most desirable irradiation frequency. As but one example, it has been determined the most lethal wavelengths for tuberculosis are at about 248nm and about 337nm, with the longer wavelength being far less effective. At the same time as establishing the most lethal wavelength it is also desirable to establish the most effective laser pulse frequency.

The next step then is to provide a laser generating device which will provide either the most desirable wavelength for the highest ranking microorganism in the population, or for

the three or four highest ranking ones. The interior of the infected space is then irradiated to provide a desired radiation dose in microwatts/cm² to the infected locality within the space. The patient is then monitored over suitable time period to assess whether the cavity needs to be irradiated a second time.

The irradiation at a selected wavelength or wavelengths can also be accompanied by conventional antibiotic therapy.

It is also contemplated that within the scope of this invention that in order to minimise patent stress a single multichannel catheter is used which will contain at least both the fibre optics required for the laser and the channels required for effective drainage and lavage. For the adequate treatment of at least some endo-cavity infections it is desirable for the medical personnel to be able to view the inside of the cavity either directly using visible light fibre optic devices or indirectly using an ultrasonic probe. Catheter devices of this type are known; typical catheters of these types including a laser capability, drainage channels, and the like are described by among others by Johnson et al. in US 5,437,660; Costello et al. in US 5,593,404 and Doiron et al. in US 5,957,404.

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We Claim:

1. A method for treating endo-cavital infections comprising:

- 5 (a) determining the spectrum of microorganisms present in the population of microorganisms in the cavity causing the infection;
- 10 (b) determining a ranking of the relative amounts of at least the major infecting microorganisms within the population present in the cavity;
- (c) selecting an ultraviolet light wavelength at which the lethal dose for at least the highest ranking microorganism identified in step (b);
- 15 (d) draining the infected cavity to remove debris contained therein;
- (e) irradiating the interior of the cavity with pulsed laser-generated ultraviolet light having a wavelength close to the wavelength selected in step (c); and
- 20 (f) if required, repeating steps (d) and (e) until a desired level of microorganism destruction has been achieved.

2. An apparatus for treating an endo-cavital microorganism infection comprising in combination:

- 25 (A) a catheter device constructed and arranged to be both insertable into and withdrawable from the cavity;
- 30 (B) a laser generating device constructed and arranged to provide at least one output of pulsed ultraviolet light of known wavelength of from about 200nm to about 700nm of known intensity; and

(C) a drainage system constructed and arranged to remove fluid debris from the cavity;

wherein:

5 (i) the catheter device includes at least one fibre optic guide constructed and arranged to deliver ultraviolet light generated by the laser device to a locus within the cavity;

10 (ii) the laser generating device is chosen from the group consisting of a laser generating device constructed and arranged to provide a beam of ultraviolet light of a single predetermined wavelength and intensity or a laser device constructed and arranged to provide a plurality of beams of ultraviolet light each having a known
15 wavelength and intensity.

3. An apparatus according to Claim 1 wherein the laser generating device is a multi-wavelength pulsed Raman solid state laser.
20

4. An apparatus according to Claim 1 wherein the catheter device includes a separate pumpable drainage system and at least one fibre optic guide to deliver ultraviolet light.
25

5. An apparatus according to Claim 1 wherein the catheter device additionally includes a second visible wavelength fibre optic system constructed and arranged to permit illumination and viewing of the interior of the cavity.
30

6. An apparatus according to Claim 1 wherein the catheter device also includes an ultrasonic probe system.

7. An apparatus according to Claim 1 wherein the at least one fibre optic device constructed and arranged to provide a beam of ultraviolet light is a single use device.

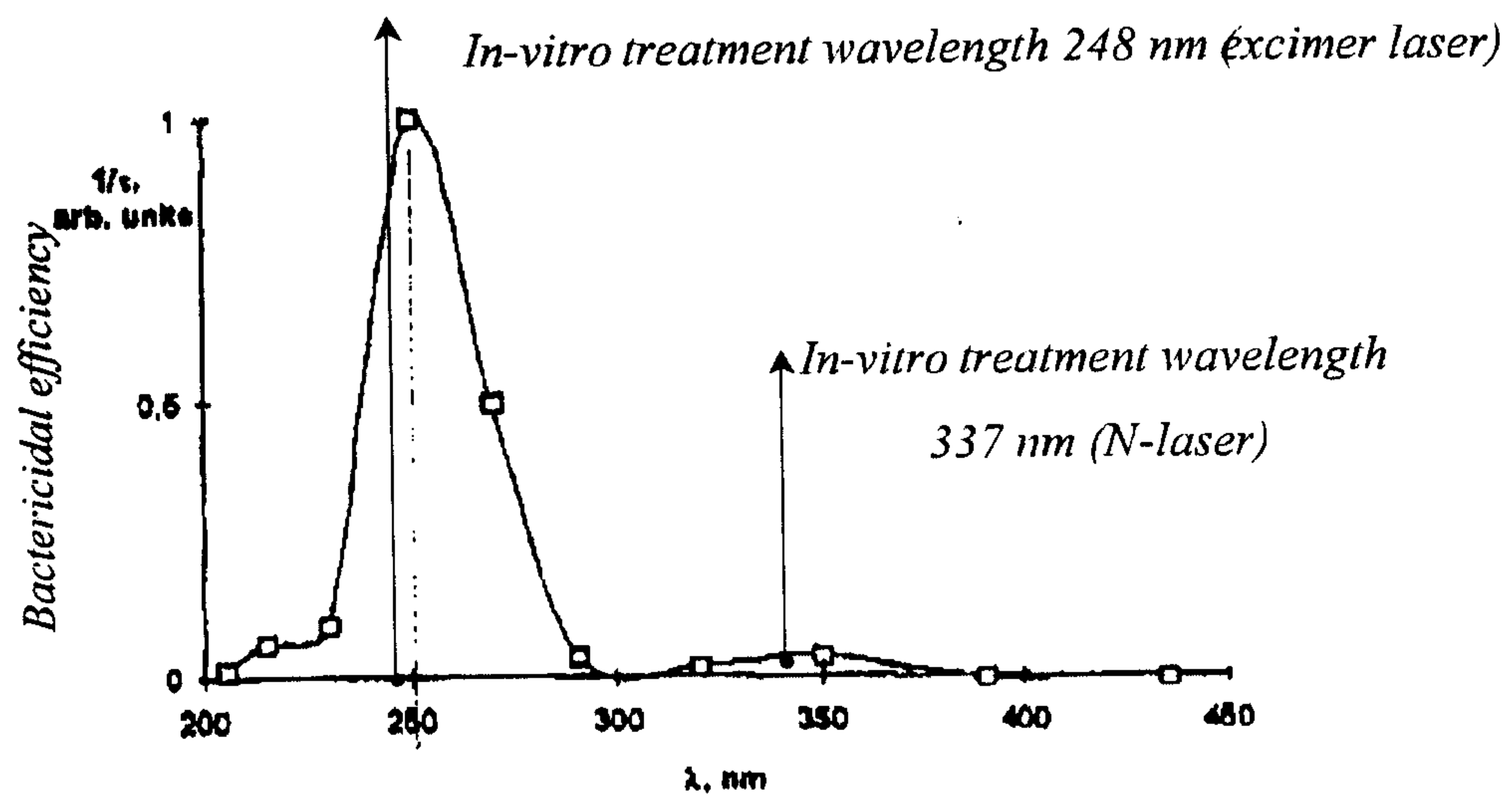
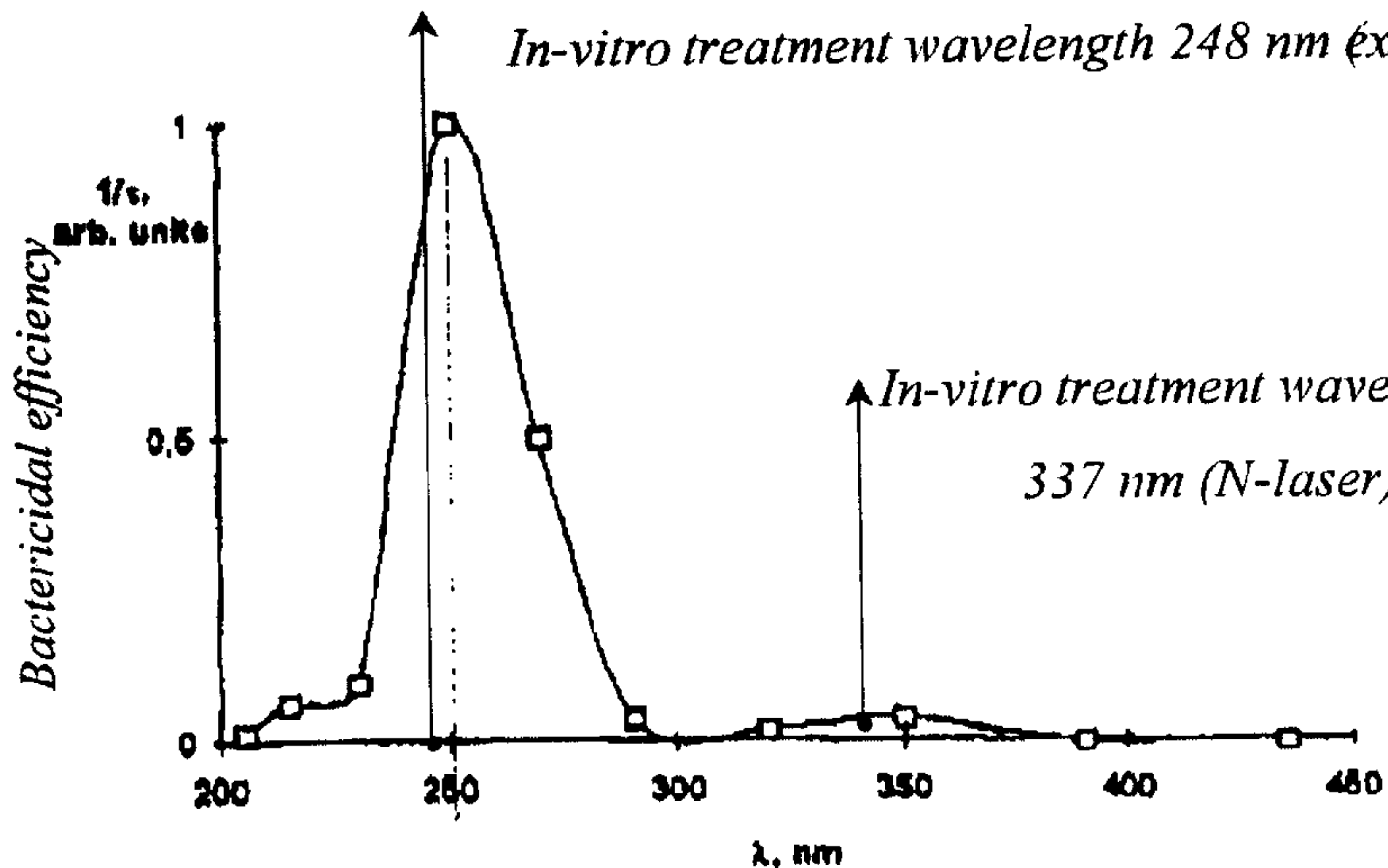


Fig. 1. Spectral peak of bactericidal efficiency for TB

In-vitro treatment wavelength 248 nm (excimer laser)



Spectral peak of bactericidal efficiency for TB