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► To cite this version:

Tanguy Davin, Benoit Lefez, Alain Guillet. Supercooling of phase change: A new modeling formulation using apparent specific heat capacity. *International Journal of Thermal Sciences*, Elsevier, 2020, 147, pp.106121. 10.1016/j.ijthermalsci.2019.106121 . hal-02329539

HAL Id: hal-02329539

<https://hal-normandie-univ.archives-ouvertes.fr/hal-02329539>

Submitted on 20 Jul 2022

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1 **Successful treatment of meningococcal bacteremia using oral doxycycline: a case report**

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17 *Keywords: meningococcal bacteremia, purpura fulminans, doxycycline*

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27 **Abstract**

28 We report the case of an 18-year old immunocompetent man who presented to the hospital
29 with fever, headaches, and arthromyalgia that progressed to an erythematous rash, with a
30 history of a tick bite 72 hours earlier. The diagnosis of rickettsial infection was suspected and a
31 course of doxycycline was initiated for a total of 5 days. Evolution was rapidly favorable under
32 treatment, with resolution of symptoms within 24 hours. Blood cultures came back positive for
33 *Neisseria meningitidis* serotype B evocative of an authentic purpura fulminans.

34 Purpura fulminans is a medical emergency, a syndrome of intravascular thrombosis
35 characterized by a very rapid evolution that requires early recognition and specific treatment. It
36 is commonly described in the young and healthy patient and has high mortality and morbidity.
37 Common bacteria mainly associated with purpura fulminans are *Meningococcus spp.*,
38 *Pneumococcus spp.*, and *Staphylococcus spp.*

39

40 **1. Case presentation**

41 An 18-year old Caucasian male, belonging to the group of men having sex with men (MSM), was
42 admitted to the hospital due to fever (40°C), headaches and arthromyalgia that evolved with an
43 erythematous rash.

44 The recent patient history revealed that 2 weeks ago he visited the South of France (French
45 Riviera) with his parents, doing trips in the forest and collecting trash. Then he returned to Paris
46 to complete his high school graduation, followed by a couple of days of wild camping with
47 friends. While camping he was bitten by a tick on the back 72 hours before his admission.

48 The day after the tick bite he noticed an erythematous and purpuric rash (**Figure 1**) on his legs
49 and pectoral area that was associated with fever and cephalalgia. Within 24 hours he presented
50 an unusual fatigue, diarrhea, nausea and vomiting. At the Emergency Room, the clinical
51 examination revealed a febrile patient, at 40°C, with hypotension (80/50 mmHg) and a
52 generalized non pruritic macular rash that disappeared in vitropression. There were no
53 neurological abnormalities.

54 Blood test showed elevated C reactive protein (150 mg/L) and neutrophilic leukocytosis,
55 absence of renal dysfunction and normal transaminase values. Serologies for hepatitis C and B
56 viruses, syphilis and HIV were negative.

57 In the hypothesis of a bacterial infection, antimicrobial therapy by 1 dose of amoxicillin-
58 clavulanate of 875/125 mg was administered intravenously and the patient was transferred to
59 our department without clinical improvement the day after.

60 The cerebrospinal fluid (CSF) was clear and colorless. The CSF cell count was 2/mm³ without
61 red blood cells, hyperglycorachia (4.7 mmol/L) and normoproteinorrachia (0.22 G/L; reference
62 value 0.20-0.40 G/L).

63 During the first hours of hospitalization, the appearance of the typical rash and the presence of
64 tick bite history, made us suspicious of rickettsiosis and the patient got started on oral
65 doxycycline 200 mg daily with rapidly a resolution of symptoms within 24 hours after his
66 admission.

67 Blood culture at 48 hours came back positive for *Neisseria meningitidis* serotype B.

68 An antimicrobial susceptibility testing was performed following the guidelines of the European
69 Committee of Antimicrobial Susceptibility Testing (EUCAST) and showed that the strain was
70 susceptible to all antibiotic tests, with the exception of a reduced susceptibility to amoxicillin
71 that also applies to amoxicillin-clavulanate: MIC (minimum inhibitory concentration) > 0.5
72 µg/ml). In addition MIC to other antibiotics were as follows: cefotaxime (MIC <0.002 µg/ml),
73 tetracycline (MIC 0.19 µg/ml), minocycline (minimum inhibitory concentration <0.064 µg/ml),
74 tigecycline, ciprofloxacin and rifampicin.

75 Considering clinical and biological resolution under treatment (decrease from 18,000 WBC and
76 a CRP level at 137 mg/L at day 0 to 4800 WBC and a CRP level at 10 mg/L at day 5), doxycycline
77 was continued for a total of 5 days. Thereafter the patient was discharged with one dose of
78 intravenous Ceftriaxone 1g administered for the eradication of pharyngeal carriage.

79 The patient was followed-up in consultation after one month for vaccination against other
80 serotypes and further investigations revealed no complementary deficiency. He was considered
81 cured with no sign of infection and normal biology. The patient declared the absence of other
82 cases of infection in his close surroundings.

83

84 **2. Discussion**

85 In this case report, the atypical clinical presentation associated with the recent history of tick
86 bite, was evocative of a potential rickettsial disease, considering the purpuric rash. So, it was
87 decided to treat the patient with doxycycline. By luck, patient's strain was susceptible to cyclins
88 which allowed full recovery.

89 *Neisseria meningitidis* is a gram-negative coccus acquired in the nasopharynx through
90 respiratory spread. The most common manifestations are related to meningitis or bacteremia,
91 but also it might result in localized infections such as arthritis or endocarditis **(1,2)**.

92 One of the clinical manifestations of the meningococcal bacteremia is purpura fulminans, a rare
93 syndrome of intravascular thrombosis which occurs due to both infectious and non-infectious
94 causes. Infectious causes include meningococcal, streptococcal and staphylococcal sepsis, but
95 the most frequent is meningococemia **(3)**. Viral and non-infectious etiologies were also
96 described (primary varicella, HHV6 infection, deficiency of protein S or C).

97 The meningococcal disease is a life-threatening, but vaccine-preventable disease. The
98 serogroups A, B, C, W, X and Y are responsible for the majority of meningococcal disease. In
99 United States, the serogroup B caused 38% of all bacteremia included 69% of cases aged 18-23
100 years **(4)**.

101 Using an alternative regimen to ceftriaxone, can be helpful in particular situations, notably in
102 patients allergic to beta-lactams. Even if ciprofloxacin is deemed to be effective, the resistance
103 of *Neisseria* group to fluoroquinolones was increased in the last decades, from 10% to almost
104 100% resistance, **(5,6)** particularly in men having sex with men (MSM). This led to other
105 therapeutic alternatives including aztreonam **(7)**. However, aztreonam's spectrum activity does
106 not include gram-positive cocci such as *Streptococcus spp.* which is why using it can be very
107 dangerous when dealing with a purpura fulminans. Also, in case of unclear anamnesis,
108 meningococcal infection can be misdiagnosed such as illustrated in our case, and doxycycline
109 might find its place in such conditions.

110 Doxycycline has been proposed for decades in the prevention of bacterial meningococcal
111 meningitis and therefore is known to be effective against *Neisseria spp.* However, the molecule
112 is not usually tested in routine antibiograms, which in our case could be helpful.

113 Moreover, doxycycline in MSM is a common regimen well validated and prescribed against STIs,
114 especially in post-exposure prophylaxis **(8)**. In the present case the patient was tested for
115 *Mycoplasma spp.* and *Neisseria spp.* even though the urinary sample was tested after he
116 received ceftriaxone and doxycycline, both came back negative. He was also negative for
117 syphilis and HIV.

118 Doxycycline is a lipophilic bacteriostatic antibiotic, which is completely absorbed after oral
119 administration but not recommended for the treatment of bacteremia, but could be considered
120 in an association. Our patient received an oral antibiotic, 2 times daily, for a total of 5 days.
121 Treating successfully bacteremia with bacteriostatic antibiotics was already described in
122 staphylococcal infections, but using Tigecycline, a derivate from doxycycline, in intravenous
123 administration **(9)**.

124 Strains resistant to penicillin have been reported from a large number of countries and in
125 France the last report stated that 30% of *Neisseria meningitidis* are resistant to amoxicillin **(10)**.
126 Overall our own experience describes an original alternative to treat *Neisseria* species.

127 The way to prevent morbidity and mortality following meningococcal disease is by vaccination.
128 Today the vaccinal recommendation includes the vaccine against A, C, W and Y serotype of
129 *Neisseria meningitidis*. Our patient was infected by a B serotype and currently there is still no
130 broad vaccine available covering all serotype B strains.

131

132 **3. Conclusions**

133 This case report highlights the risk of misdiagnosis an authentic meningococcal disease
134 presenting as a rickettsiosis. To the best of our knowledge this is the first case of meningococcal
135 bacteremia treated successfully by oral doxycycline. Our case emphasizes that doxycycline
136 could be an appropriate alternative therapy to intravenous ceftriaxone for particular non-
137 severe situation or allergy to beta-lactams after susceptibility testing.

138 **Availability of data and materials:**

139 All material and data described in the manuscript are available upon request to the
140 corresponding author of the present article.

141

142 **Consent for publication:**

143 Written informed consent was obtained from the patient for publication of this case
144 report.

145 A copy of the written consent is available for review by the Editor of this journal.

146

147 **Ethics approval and consent to participate:**

148 Not applicable.

149

150 **Conflict of interest: none.**

151

152 **Acknowledgments:**

153 SB was in charge of conceptualization, data curation, methodology, project administration,
154 resources and writing – original draft; MM supervised the work; AD visualized the manuscript;
155 SS helped for the methods; LN gave resources for the case; LA helped for resources and
156 visualization; BD supervised, validated and wrote definite version of the manuscript.

157

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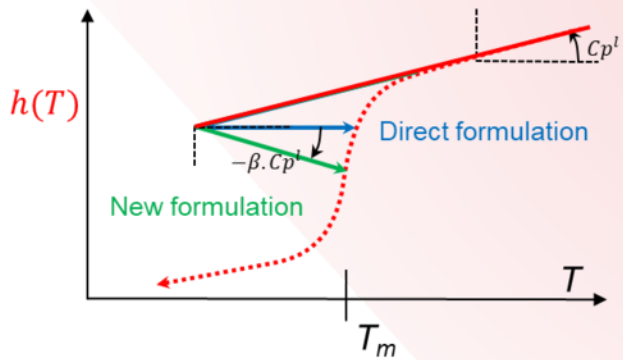
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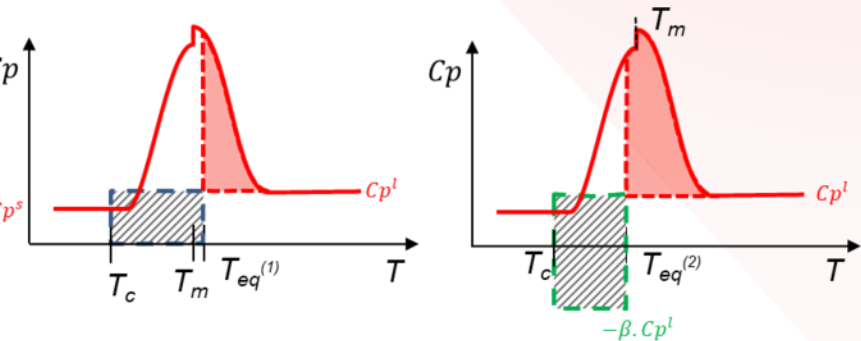
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185

Enthalpy curves $h(T)$



Equivalent $Cp(T, f_{super})$ laws



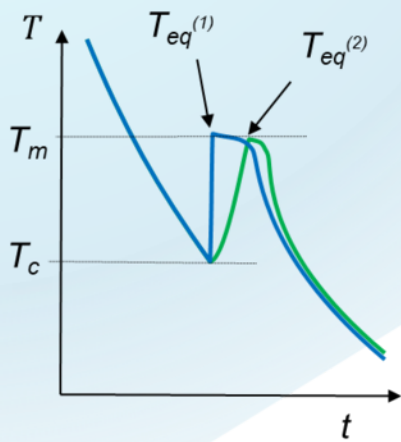
Direct formulation

New formulation

THEORY

APPLICATION

1-node example (both formulations)



Experimental/numerical comparison (new formulation)

